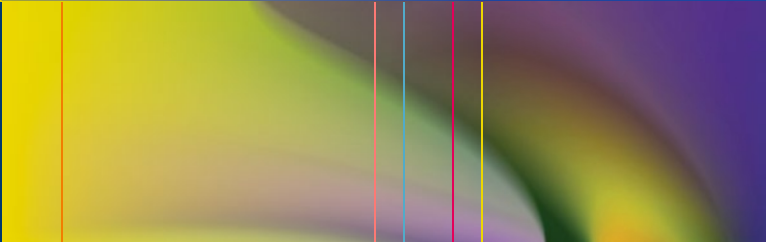Ricardo Munoz · Eduardo M. da Cruz
Carol G. Vetterly · David S. Cooper
Donald Berry *Editors*

Handbook of Pediatric Cardiovascular Drugs

Second Edition

Springer

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Editors

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Editors

Ricardo Munoz
Cardiac Intensive Care Division
The Heart Institute
Children's Hospital of
Pittsburgh of UPMC
University of Pittsburgh
Pittsburgh, PA, USA

Eduardo M. da Cruz
Pediatric Cardiac Intensive Care
Department of Pediatrics
The Heart Institute
Children's Hospital Colorado
University of Colorado Denver
School of Medicine
Aurora, CO, USA

Carol G. Vetterly
Department of Pharmacy
Services, Children's Hospital
of Pittsburgh of UPMC
Pittsburgh, PA, USA

Department of Pharmacy
and Therapeutics
University of Pittsburgh
School of Pharmacy
Pittsburgh, PA, USA

David S. Cooper
Department of Pediatrics
Cardiac Intensive Care Unit
The Heart Institute
Cincinnati Children's Hospital
Medical Center
University of Cincinnati
College of Medicine
Cincinnati, OH, USA

Donald Berry
Department of Pharmacy
Children's Hospital of
Pittsburgh of UPMC
Pittsburgh, PA, USA

Preface

In 2008, the first edition of the *Handbook of Pediatric Cardiovascular Drugs* was produced with the main purpose of providing health care practitioners with a tool to safely and consistently prescribe and administer cardiovascular drugs in children with cardiac disease. Half a decade later, this manual remains the only book of its nature, and the time has come to edit an updated version. As for the first edition, the editors have endeavored in this occasion to provide an overview of basic pediatric cardiovascular medications, in collaboration with highly reputed authors. This pocket reference handbook remains tailored to meet the daily challenges of practitioners who care for pediatric cardiac patients, from the newborn to the young adult. This book does not provide an extensive review of all cardiovascular medications, but does compile the basic information required to assist caregivers in their daily clinical practice.

We sincerely hope that this second edition of the *Handbook of Pediatric Cardiovascular Drugs* will be helpful to physicians, fellows, residents, mid levels, pharmacists, nurses and other practitioners within the multidisciplinary teams involved in the complex and high-risk care of pediatric and congenital patients with heart disease.

Pittsburgh, PA, USA	Ricardo Munoz
Aurora, CO, USA	Eduardo M. da Cruz
Pittsburgh, PA, USA	Carol G. Vetterly
Cincinnati, OH, USA	David S. Cooper
Pittsburgh, PA, USA	Donald Berry

About the Editors

Ricardo Munoz, MD, FAAP, FCCM, FACC, is Chief of the Cardiac Intensive Care Division, Director of the Cardiac Recovery Program, Medical Director for Global Business and Telemedicine at the Children's Hospital of Pittsburgh of UPMC. He is Director of International Affairs at the Children's Hospital of Pittsburgh of UPMC Heart Center, and Professor for Dr. Ricardo Munoz of Critical Care Medicine, Pediatrics and Surgery at the University of Pittsburgh, Pennsylvania, USA.

Eduardo M. da Cruz, MD, is Head of the Pediatric Cardiac Critical Care Program, the Pediatric Cardiology Inpatient Services, and Director of the Cardiac Intensive Care Unit and Cardiac Progressive Care Unit at the Children's Hospital of Colorado. He is Tenured Professor of Pediatrics, Pediatric Cardiology and Intensive Care at the University of Colorado Denver, School of Medicine, Aurora, Colorado, USA.

Carol G. Vetterly, PharmD, BCPS, is the Clinical Coordinator of Pharmacy Services and a Clinical Pharmacy Specialist in the Pediatric Intensive Care Unit at the Children's Hospital of Pittsburgh of UPMC. She is an Adjunct Assistant Professor of Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy, Pennsylvania, USA.

David S. Cooper, MD, MPH, is Chief Safety Officer in the Heart Institute, Associate Medical Director of the Cardiovascular Intensive Care Unit and Medical Director of the Cardiac ECLS Program in the Heart Institute at Cincinnati Children's Hospital Medical Center. He is Co-Director of the

Center for Acute Care Nephrology. He is Associate Professor of Pediatrics at the University of Cincinnati College of Medicine, Ohio, USA.

Donald Berry, BSPharm, is a Clinical Pharmacy Specialist within the Cardiac Intensive Care Unit at the Children's Hospital of Pittsburgh of UPMC, Pennsylvania, USA.

Contents

Contributors

Cindy Barrett, MD Pediatric Cardiac Intensive Care, Department of Pediatrics, The Heart Institute, Children's Hospital Colorado, University of Colorado Denver, School of Medicine, Aurora, CO, USA

Allyson Berg, PharmD Department of Pharmacy, Children's Hospital Colorado, Aurora, CO, USA

Donald Berry, BSPharm Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Grant Burton, MD Congenital Heart Surgery Unit (CHSU), Medical City Children's Hospital, Dallas, TX, USA

Andrea R. Chamberlain, PharmD, BCPS Division of Pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

David S. Cooper, MD, MPH Department of Pediatrics, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Kelli L. Crowley, PharmD, BCPS Department of Pharmacy Services, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA

Eduardo M. da Cruz Pediatric Cardiac Intensive Care, Department of Pediatrics, The Heart Institute, Children's Hospital Colorado, University of Colorado Denver, School of Medicine, Aurora, CO, USA

Sarah D. de Ferranti, MD, MPH Preventive Cardiology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

Jamie A. Decker, MD Division of Pediatric Cardiology, Johns Hopkins All Children's Heart Institute, South Saint Petersburg, FL, USA

Amy Donnellan, CNP Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Jennifer Eshelman, PharmD Department of Pharmacy, Children's Hospital Colorado, Aurora, CO, USA

Brian Feingold, MD, MS Department of Pediatric Cardiology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Ryan Flanagan, MD Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pediatrics, Womack Army Medical Center, Fort Bragg, NC, USA

Stuart L. Goldstein, MD Department of Pediatrics, Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Sriya Gunawardena, MBBS Division of Hematology/ Oncology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Megan Horsley, RD, LD, CSP, CNSC Department of Pediatrics, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Denise L. Howrie, PharmD University of Pittsburgh School of Pharmacy & Medicine, Pittsburgh, PA, USA

Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

David Dunbar Ivy, MD Department of Pediatrics, Children's Hospital Colorado, Pediatric Cardiology, University of Colorado School of Medicine, Aurora, CO, USA

Pediatric Cardiology, Children's Hospital Colorado, Aurora, CO, USA

Lindsey Justice, MSN, CPNP-AP Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Jonathan Kaufman, MD Pediatric Cardiac Intensive Care, Department of Pediatrics, The Heart Institute, Children's

Hospital Colorado, University of Colorado Denver, School of Medicine, Aurora, CO, USA

Traci Kazmerski, MD Division of Pulmonology, Department of Pediatrics, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Timothy K. Knilans, MD Division of Pediatrics and Pediatric Cardiology, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

David M. Kwiatkowski, MD Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Erica P. Lin, MD Cardiovascular Anesthesia, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Angela Lorts, MD Department of Pediatrics, Advanced Heart Failure, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Ryan Moore, MD Pediatric Cardiology, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Ricardo Munoz, MD, FAAP, FCCM, FACC Cardiac Intensive Care Division, The Heart Institute, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA, USA

Phuong-Tan Nguyen-Ha, PharmD Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Jaclyn E. Sawyer, PharmD Division of Pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Robert L. Poole, PharmD, FPPAG, FCSHP, FASHP Department of Pharmacy, Lucile Packard Children's Hospital Stanford, Clinical Professor of Pharmacy, University of California, San Francisco, USA

James P. Spaeth, MD Cardiovascular Anesthesia, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Shinichi Takatsuki, MD Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

Cécile Tissot, MD Division of Pediatrics-Cardiology, Department of Pediatrics, Geneva University Children's Hospital, Geneva, Switzerland

Carol G. Vetterly, PharmD, BCPS Department of Pharmacy Services, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA

Steven Webber, MBChB, MRCP Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

Chapter 1
Cardiac Physiology

Brian Feingold, Ricardo Munoz, and Ryan Flanagan

Abstract A basic understanding of cardiovascular physiology is fundamental to the comprehension of the conditions and pharmacologic mechanisms described throughout this Handbook. This chapter will provide an overview of cardiovascular physiology while highlighting the unique aspects of the neonatal and pediatric heart. While not intended to be an exhaustive review, the chapter should serve to familiarize the reader with concepts, such as cardiac structure and function, electrophysiology, shunt lesions, contractility, preload and afterload, and clinical measures of cardiac function, to be discussed in greater detail in other chapters.

B. Feingold, MD, MS
Department of Pediatric Cardiology,
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

R. Munoz, MD, FAAP, FCCM, FACC
Cardiac Intensive Care Division, The Heart Institute,
Children's Hospital of Pittsburgh of UPMC,
University of Pittsburgh, Pittsburgh, PA, USA

R. Flanagan, MD (✉)
Division of Pediatric Cardiology, Department of Pediatrics,
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pediatrics, Womack Army Medical Center,
2817 Reilly Road, Fort Bragg, NC, USA
e-mail: ryanflanagan1@yahoo.com

A basic understanding of cardiovascular physiology is fundamental to the comprehension of the conditions and pharmacologic mechanisms described throughout this Handbook. With that goal in mind, this chapter will provide an overview of cardiovascular physiology while highlighting the unique aspects of the neonatal and pediatric heart. While not intended to be an exhaustive review, the chapter should serve to familiarize the reader with concepts to be discussed in greater detail in other chapters. For those seeking further knowledge, a list of more comprehensive sources is provided at the conclusion of this chapter.

1.1   Basic Cardiac Structure and Function

The human heart is in essence two pumps connected in series, delivering blood to the pulmonary and systemic circulations. It is comprised of two atria which receive venous blood, two ventricles which pump blood, valves which prevent the backflow of blood, and a conduction system which transmits the electrical impulses that drive cardiac activity. The electrical signal is propagated and converted to mechanical activity through a series of biochemical interactions which involve stereotyped ion fluxes (mainly Na^+, Ca^{++}, K^+) through voltage-gated ion 'pores' and downstream protein interactions. While inherited or acquired defects in these components may result in cardiac disease, these same mechanisms form the basis of pharmacologic therapies.

1.2   Electrophysiology

Rhythmic and coordinated contraction of the heart is accomplished by the propagation of an electrical impulse (action potential) in a precise manner (Fig. 1.1). Each action potential
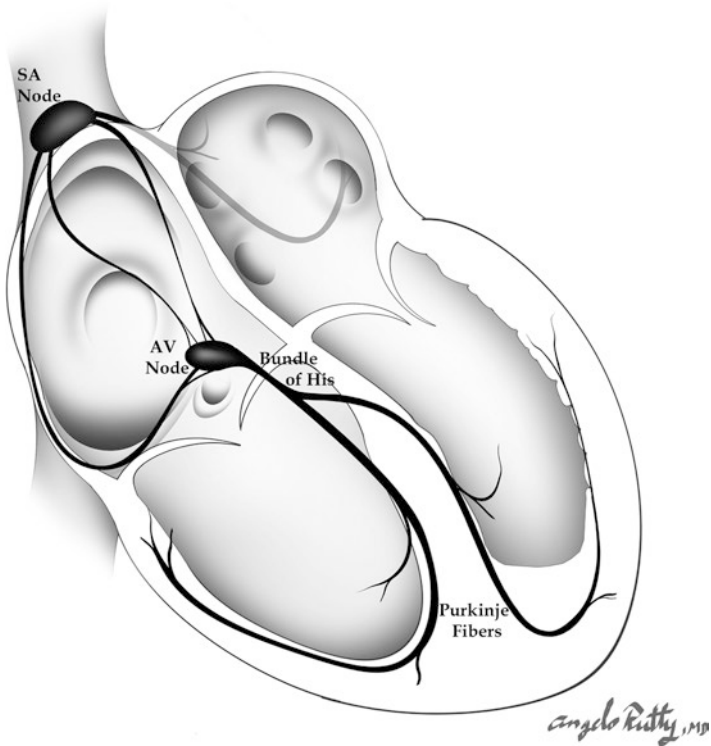
FIGURE 1.1 Diagrammatic representation of structures involved in normal cardiac conduction. *SA* sino-atrial, *AV* atrio-ventricular

is normally initiated by the sino-atrial (SA) node, a specialized group of myocardial cells in the high right atrium. These cells exhibit automaticity, meaning they spontaneously become electrically active (depolarize). The impulse then spreads to adjacent atrial myocytes via cell-to-cell connections termed gap junctions. Ultimately, the wave of depolarization reaches a second group of specialized cells at the bottom of the right atrium, near the crux of the heart, called the atrio-ventricular (AV) node. Because the atria and ventricles are electrically isolated from one another by a circumferential band of fibrous tissue at the level of the tricuspid and mitral valves, the

only path for impulse propagation is via the AV node. After a brief (approximately 0.1 s), intrinsic delay at the AV node, the action potential is propagated quickly down the bundle of His and Purkinje fibers within the ventricular myocardium. This rapidly conducting network acts as 'wiring' to convey the impulse to the apex of the heart, allowing for a coordinated, mechanically efficient contraction of the ventricles.

1.2.1   Action and Resting Potentials

At rest, cardiac myocytes maintain a net negative electrical gradient with respect to the extracellular environment (resting potential). The gradient results from the activities of ion channels and transporters within the cell membrane and is essential to the myocyte's (and heart's) ability to propagate electrical impulse. With sufficient stimulus, alterations in the myocyte's permeability to Na^+ result in a net positive electrical gradient with respect to the extracellular environment (depolarization). Further, changes in the myocyte's ion permeability to K^+, Cl^-, and Ca^{++}, result in the eventual restoration of the negative intracellular environment. When plotted against time, the changes in electrical potential are conventionally described as having five distinct phases (Fig. 1.2) which correspond to the stereotyped alterations in membrane permeability of the cardiac myocyte. Anti-arrhythmic medications exert their influence by altering membrane permeability, affecting the characteristics of the action potential. For example, class Ia agents (procainamide, disopyramide, and quinidine) affect Na^+ influx, resulting in a decreased rate of phase 0 depolarization and mild prolongation of repolarization [1].

1.2.2   Automaticity

Automaticity refers to the intrinsic ability of a cardiomyocyte or cluster of cells to spontaneously depolarize and thus initiate propagation of an action potential. Such cells are termed "pacemaker cells" and include those of the SA and AV nodes.
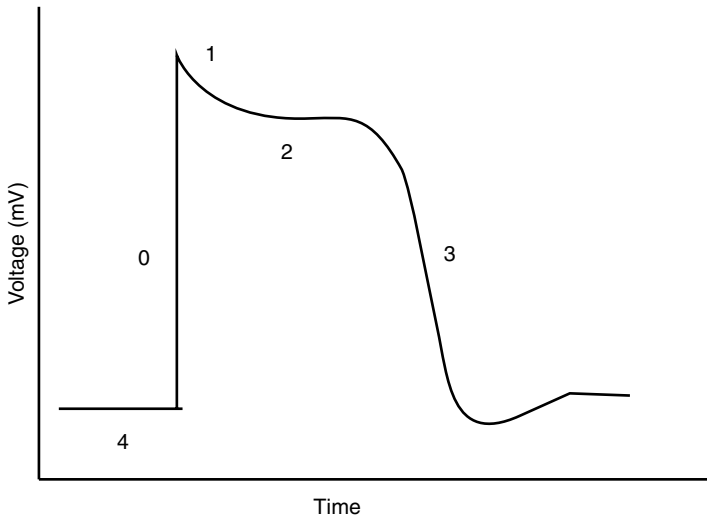
FIGURE 1.2 The action potential of a Purkinje fiber. Phase *4* is the resting state prior to electrical stimulation. Phase *0* is the rapid depolarization as a result of Na^+ influx. Phase *1* is the initial stage of repolarization due to closure of Na^+ channels and efflux of Cl^-. Phase *2*, or the plateau phase, is mediated primarily by Ca^{++} influx. Phase *3* is the rapid repolarization and is facilitated primarily by K^+ efflux. *mV* millivolts

Cells of the His-Purkinje system and even the ventricular myocardium may also spontaneously depolarize under circumstances of particularly slow cardiac rhythms (e.g., sinus node arrest, complete heart block). Because of the more rapid depolarization of the usual pacemakers, the automaticity of these cells is often not manifested during normal cardiac rhythm. Furthermore, after injury, cells which typically do not possess automaticity may acquire altered membrane conductance with resultant current leakage and spontaneous depolarization resulting in automatic tachycardias. Figure 1.3 depicts the action potential for cells of the SA and AV nodes. Notice the positively sloped phase 4, progressing toward threshold potential at which point phase 0 occurs. The slope of the phase 4 depolarization is a key determinant in the rate
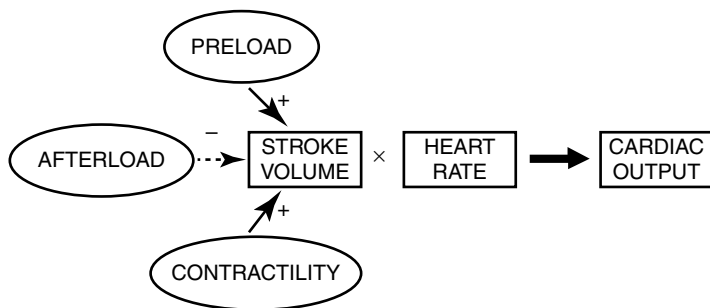
FIGURE 1.3 Preload, contractility, and afterload each impact cardiac output via their effects on stroke volume

of initiation of an action potential and thus overall heart rate. Modulation of automaticity occurs via the autonomic nervous system and may thus be affected by pharmacologic agents acting centrally (dexmedetomidine, clonidine) or those affecting the action potential initiation and propagation at the level of the myocytes (digoxin, beta-blockers). In clinical practice there is often an overlap of direct and autonomic effects with many pharmacologic agents.

1.2.3 Electromechanical Coupling

On a macroscopic level, propagation of the action potential from the high right atrium to the AV node, His-Purkinje system, and finally the ventricular myocardium allows for ordered, coordinated myocardial contraction and relaxation. On a cellular level, this is accomplished by coupling the changes in electrical environment to changes in mechanical activity (myocardial contraction and relaxation) via fluctuations of cytosolic Ca^{++} concentration. As a consequence of depolarization, cytosolic Ca^{++} concentration markedly increases via influx from the cell membrane as well as release of intracellular calcium stores within the sarcoplasmic reticulum. Ca^{++} directly enables the interaction of the contractile elements actin and myosin, the result of which is myofiber

shortening. Just as the process of myocyte contraction is reliant upon Ca^{++}, myocardial relaxation is an *active* process, requiring the expenditure of energy in the form of adenosine triphosphate (ATP) to scavenge Ca^{++} from the cytosol quickly and inhibit continued contraction [2]. The neonatal myocardium has a poorly developed calcium transport process which results in an exaggerated dependence upon extra-cellular calcium concentration to maintain cardiac contractility in neonates. For further detail on the downstream interactions between contractile elements and the process of electromechanical coupling, the reader is referred to selections referenced at the conclusion of this chapter.

1.2.4   Dysrhythmias

While an extensive review of all dysrhythmias is outside the scope of this chapter, a brief overview of the mechanisms of the basic categories of dysrhythmias is provided. On the simplest level, heart rhythm abnormalities can be divided into those that are 'too slow' (bradyarrhythmias) and those that are 'too fast' (tachyarrhythmias). Bradyarrhythmias primarily result from delay or block in conduction of the impulse from the high right atrium to AV node and His-Purkinje system, and most involve disease of the AV nodal tissue [first degree and second degree type I (Wenckebach) heart block] or of the His-Purkinje system [second degree type II (Mobitz) and third degree (complete) heart block]. Bradyarrhythmias may also result from disease of the sinus node (ineffective automaticity), such that no appropriate pacemaker is available to establish a physiologic heart rate. Tachyarrhythmias are more varied in terms of etiologies and can originate from the atria, ventricles, or AV node. However, the mechanism which underlies each can often be categorized as automatic or re-entrant. An automatic tachycardia results from a cell or cluster of cells acquiring abnormal automaticity, such that this region of the heart spontaneously depolarizes more rapidly than the sinus node, establishing the heart rate at greater than physiologic rates. The most common examples of automatic

tachycardias include ectopic atrial tachycardia, multifocal atrial tachycardia, and junctional ectopic tachycardia. Automatic tachycardias tend to exhibit a gradual 'warm-up' and/or 'cool-down' phases at onset and termination, and despite the overall rapid rate, there is subtle variability in heart rate over time. In contrast, re-entrant tachycardias result from additional, non-physiologic electrical pathways that allow conduction of an impulse to back to a region of the heart that has repolarized following the earlier conduction of the *same* impulse. Such 'short-circuits' essentially allow the same impulse to recycle itself and lead to successive depolarizations. Re-entrant tachyarrhythmias characteristically have an abrupt onset and termination and a non-varying rate during the tachycardia. The re-entrant circuit may exist exclusively within the atria (atrial flutter), ventricles (ventricular tachycardia), or AV node (AV node re-entrant tachycardia), or may be comprised of tissue that connects the atria, AV node, and/or ventricles (accessory pathway tachycardia).

1.3   Cardiovascular Physiology

Care of the patient with hemodynamic derangements remains rooted in basic physiologic concepts – preload, contractility, and afterload – first described in the late 19th century. These factors directly impact stroke volume, which along with heart rate are the key determinants of cardiac output (Fig. 1.4).

1.3.1   Preload

Preload refers to the ventricle's intrinsic ability, within a physiologic range, to alter the force of contraction based on the degree of ventricular filling just prior to contraction (end-diastolic volume/fiber length). The greater the end-diastolic volume, and thus ventricular myofiber stretch, the greater the force of contraction. This relationship of increasingly forceful contraction with increasing preload continues to correlate until the myocardial fibers are stretched to a point
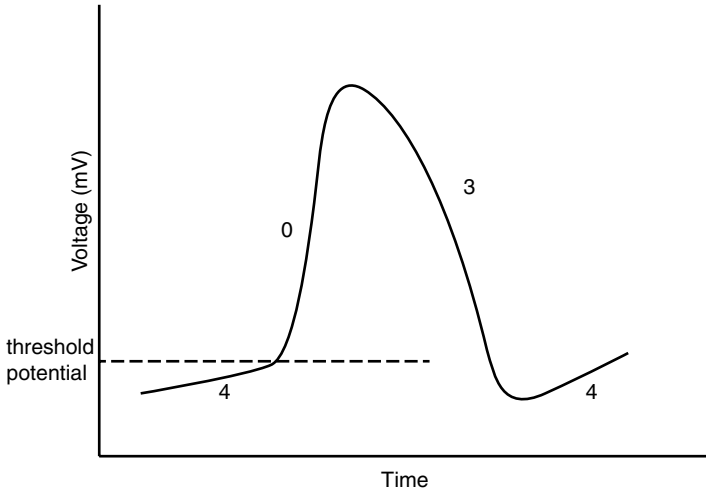
FIGURE 1.4 Diagrammatic representation of the action potential of sino-atrial or atrio-ventricular nodal cells. Phase *4* is characterized by the positive slope, indicating gradual depolarization toward threshold (termed automaticity), at which point the phase *0* upstroke is observed. *mV* millivolts. Phase *3* is repolarization phase returning the cell back to the baseline, or resting potential

that contractility actually begins to fall off. The relationship between preload and contractility is known as the Starling relationship. Conceptually, preload is most often equated with the intravascular volume status of a patient. Under conditions of relatively low volume status (e.g., dehydration), the force of myocardial contraction, and thus cardiac output, is diminished. Volume status is most often gauged clinically by measuring the central venous pressure (CVP), which is usually equivalent to the ventricular end-diastolic pressure. Assuming normal ventricular compliance (pressure-volume relationship) and absence of significant tricuspid (or mitral) stenosis, CVP is a clinically useful surrogate for preload. Caution must be used when interpreting the CVP in light of the clinical scenario (i.e., a 'normal' CVP may in fact be too low if there is a poorly compliant ventricle as occurs with diastolic dysfunction or constrictive pericarditis).
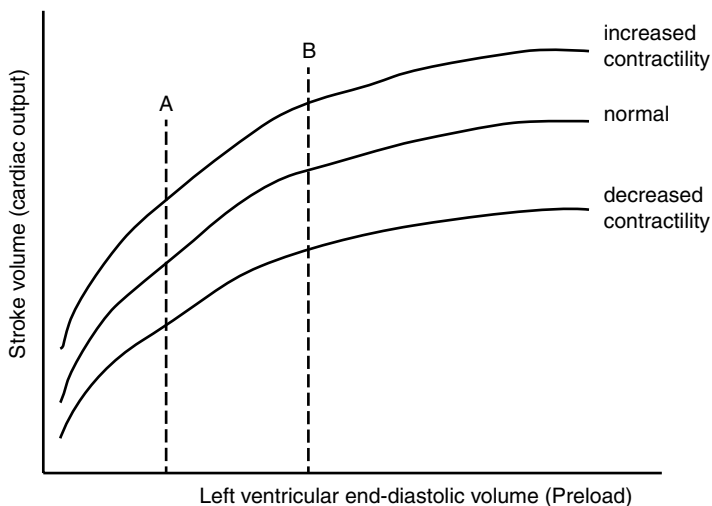
FIGURE 1.5 Frank-Starling curve illustrating the relationship between various preload, cardiac output, and inotropic states. At preload *A*, cardiac output is less than that at a greater preload *B*. However, for a given preload A or B, cardiac output is, in part, determined by the inotropic state (contractility)

1.3.2   Contractility

As already noted, within physiologic range, the greater the myofiber stretch (preload), the greater the force of contraction. However, contractility (or inotropic state) specifically refers to the magnitude of response to a given preload and can be thought of as the 'multiplication factor' for any given preload (Fig. 1.5). Contractility is an intrinsic property of the muscle fiber that is relatively independent of changes in preload or afterload. In other words, for any given preload, the force of contraction will be greater under conditions of increased inotropy (e.g., dobutamine infusion) and less under conditions of depressed inotropy (e.g., systolic dysfunction). In the setting of low cardiac output (e.g., dilated cardiomyopathy), improvement is sought by administration

of medication (e.g., dobutamine, low-dose epinephrine, milrinone, digoxin) to augment contractility. Each of these therapies has multiple effects, aside from enhanced inotropy, which may limit their therapeutic efficacy (e.g. increased myocardial oxygen consumption, excessive tachycardia, or arrhythmias).

1.3.3   Afterload

Afterload is defined as the ventricular wall stress during contraction and is often conceptualized as the load against which the ventricle contracts. In clinical practice, afterload is usually identified with systemic vascular resistance, which is primarily determined by the arteriolar resistance. However, from LaPlace's principle, wall stress is directly proportional not only to the ventricular pressure, but also to ventricular chamber diameter, while it is inversely proportional to ventricular wall thickness. Thus, for the left ventricle, the major components of afterload are peripheral vascular resistance, arterial wall stiffness, mass of the column of blood in the aorta, blood viscosity, and LV wall thickness and diameter. Similarly, for the right ventricle (RV), afterload is primarily influenced by pulmonary artery impedance, pulmonary vascular resistance, mass of the column of blood in the pulmonary circulation, viscosity of the blood, and RV chamber characteristics. Examples of clinical scenarios in which the left ventricle (LV) faces increased afterload include aortic stenosis (increased resistance), coarctation of the aorta and systemic hypertension (increased resistance and wall stiffness), and dilated cardiomyopathy (increased chamber diameter). For any given preload, greater afterload results in more limited myofiber shortening during contraction and decreased stroke volume as compared to contraction in the face of lesser afterload (see next section, SV_B vs. SV_{DA} of Fig. 1.5B). In other words, afterload determines the size of the ventricular cavity at the end of contraction, independent of the ventricular volume prior to contraction (preload).

1.3.4   Pressure-Volume Loops

Visual representations of these physiologic concepts can be helpful to appreciate best their individual characteristics and impact upon one another *in vivo*. One particularly useful way to appreciate the contributions of and interactions between preload, contractility, and afterload is by examination of pressure-volume loops. As shown in Fig. 1.6a, ventricular diastolic performance (compliance) and changes in preload are illustrated by the curve at the bottom of the graph, ventricular volume throughout the cardiac cycle is illustrated by the rectangle, and contractility is illustrated by the diagonal line at end-systolic volume (end-systolic pressure volume relationship). With the onset of systole (point A), there is an increase in pressure (isovolumic contraction) until ventricular pressure exceeds aortic pressure, at which point the aortic valve opens and blood is ejected from the ventricle (point B). As the ventricle continues to empty, there is the onset of relaxation of the ventricle with an eventual drop in pressure below that of the aorta (point C). At this point ventricular pressure falls but the volume remains unchanged (isovolumic relaxation) until the pressure drops below that of the left atrium and the mitral valve opens (point D). The ventricular volume then increases during diastole, until the cycle repeats itself with the next contraction. The area within the rectangle represents stroke work, and the distance along the x-axis between the vertical lines is the stroke volume. As illustrated in Fig. 1.6b, increased preload results in a greater stroke volume as compared to baseline, but the end-systolic volume in both instances is limited by the afterload (and contractility). With decreased afterload (dash-dot line), a lesser end-systolic volume and greater stroke volume are achieved. Conversely, increased afterload results in greater end-systolic volumes (i.e., decreased myofiber shortening) and diminished stroke volume. As shown in Fig. 1.6c, alterations in contractility (inotropic state) also affect changes in stroke volume. Finally, differences in ventricular compliance (slope and shape of curve at bottom of graphs) result in differences in end-diastolic volume (myofiber stretch) for a given preload (Fig. 1.6d), and thus also impact stroke volume.
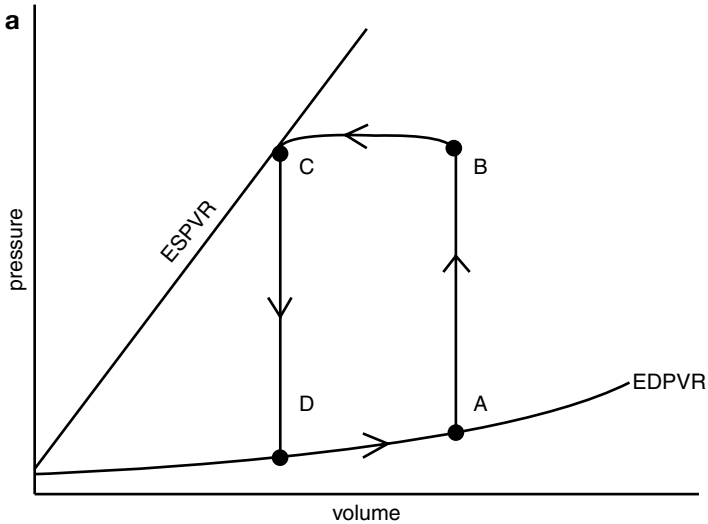
FIGURE 1.6 (**a**) Stylized pressure-volume loop. Followed in the counter-clockwise direction are end-diastolic volume and onset of systole (*A*), isovolumic contraction (*A–B*), aortic valve opening (*B*), ventricular ejection (*B–C*), aortic valve closure (*C*) and isovolumic relaxation (*C–D*), mitral valve opening (*D*) and diastolic filling of the ventricle (*D–A*). The volume difference between lines *AB* and *CD* is the stroke volume. *ESPVR* end-systolic pressure volume relationship, *EDPVR* end-diastolic pressure volume relationship. (**b**) Increased preload results in a greater stroke volume (SV_{IP}) as compared to baseline (SV_B), but the end-systolic volume in both instances is limited by the afterload (height of the PV curve) and contractility (slope of the ESPVR line). In the setting of decreased afterload, stroke volume is increased (SV_{DA}) by achieving a lower end-systolic volume. (**c**) For a given preload and afterload, stroke volume (*SV*) varies based on contractility. ESPVR lines *A*, *B*, *C* represent progressively increased inotropic states. (**d**) The impact of changes in ventricular compliance are depicted by the two EDPVR curves. In the setting of decreased compliance ($EDPVR_B$), a greater central venous pressure (CVP_B) is required to achieve the same ventricular end-diastolic volume and stroke volume (*SV*)
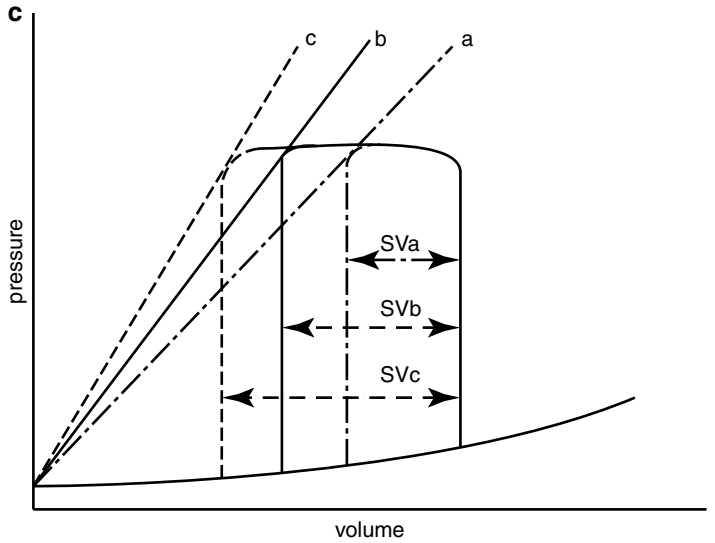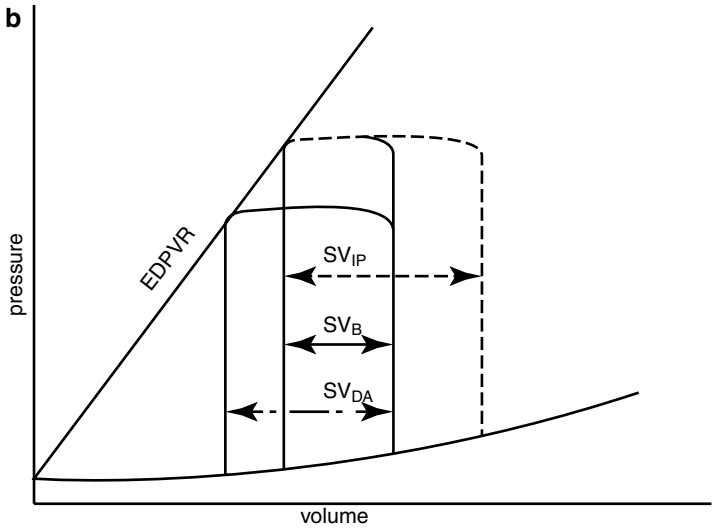
FIGURE 1.6 (continued)
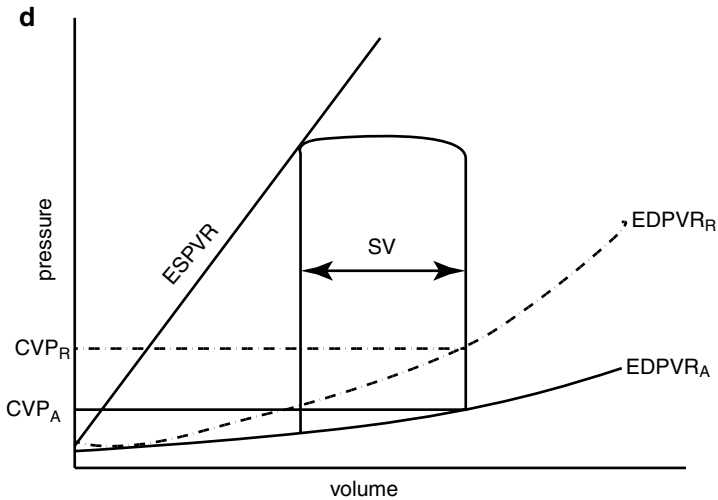
FIGURE 1.6 (continued)

1.3.5 Clinical Measures of Cardiac Function and Contractility

Bedside assessment and care of patients is driven in part by the technology available for clinical assessment. For example, while the use of impedance catheters to ascertain pressure-volume loops might best inform clinicians as to the changing cardiovascular status of their patients (and the response to therapies) during hemodynamic instability, this technology is impractical to use in most cases because they require an invasive procedure for placement and impractical levels of continuous monitoring. Thus, most clinicians rely on surrogate measures and their clinical experience to manage patients. Just as CVP is commonly used to estimate preload and systemic blood pressure to estimate afterload, echocardiographic assessments of ventricular systolic function are often relied upon to assess contractility. Specific estimators of contractility include shortening fraction (SF), ejection fraction (EF), and mean velocity of circumferential fiber shortening

(Vcfc). Both SF and EF are similar in their approach in that they measure the extent of shortening to assess LV systolic function. For EF, the end-systolic and end-diastolic parameters are estimated LV volumes (LVESV and LVEDV), whereas for SF, the parameters are linear measurements of LV cavity length or dimension (LVESD and LVEDD). The formulas for each are given below:

$$EF = (LVEDV - LVESV) / LVEDV \times 100$$

$$SF = (LVEDD - LVESD) / LVEDD \times 100$$

For EF the volumes are estimated from two dimensional echocardiography, whereas for SF the dimensions are measured using M-mode echocardiography. While both are relatively easy to ascertain and provide some quantification of LV systolic function, these measures are dependent on preload and afterload, which vary over time and are unlikely to be the same at serial evaluations. Another measure of ventricular function, mean Vcf_c, makes use of the rate of LV ejection to assess systolic function and has the advantage of being preload and heart rate independent, but still does not account for afterload.

Wall stress, the tension per unit cross-sectional area of myocardium, is thought to be the best estimator of ventricular afterload as it accounts for LV wall thickness (mass). Comparison of the mean Vcf_c to LV wall stress enables assessment of contractility free from the biases of preload, heart rate and afterload. Unfortunately, none of these measures account for ventricular diastolic function, an often underappreciated but increasingly recognized contributor to symptomatic heart failure. Indices of diastolic function are available but discussion of them is outside the scope of this chapter.

1.4   Unique Features of the Pediatric Heart

From structural, physiologic, and anatomic perspectives, the neonatal and pediatric heart differs from the adult heart. Animal studies have shown that both systolic and diastolic

cardiac function in the neonate are reduced compared to the adult. From a structural perspective, this results in large part from differences in calcium handling by the cardiomyocyte. Because the immature cardiomyocyte has less sarcoplasmic reticulum, intracellular calcium stores are limited [3]. The diminished numbers and activities of sarcoplasmic reticulum membrane transport proteins further differentiates the calcium flux of the immature heart from that of the adult heart. As a result of these differences in calcium handling, the immature cardiomyocyte has a greater reliance on extracellular calcium to enable myofibril contraction and relaxation [4]. Also contributing to the unique physiologic profile of the neonatal and infant heart are fewer numbers of contractile elements per myocyte and a greater relative proportion of non-cardiomyocytes to cardiomyocytes as compared to the mature heart. Additionally the alignment of the contractile elements of the neonatal heart is 'disorganized' when compared to the linear parallel arrangement of the contractile elements of the adult cardiomyocyte. The former likely impacts the ability to generate systolic tension, whereas the latter is thought to contribute to the relative non-compliance of the neonatal and infant heart.

Many of these structural differences impact the clinical characteristics of the neonatal and infant heart. For example, the neonatal and infant heart is exquisitely sensitive to serum calcium concentration, such that following cardiac surgery, calcium infusions are often used for inotropic support. Also, limited ventricular compliance results in the inability of neonates and young infants to augment stroke volume as a means of increasing cardiac output. Thus, the neonate, infant, and (to a lesser extent) the young child rely much more on increases in heart rate as the primary mechanism to augment cardiac output. Clinically, this explains the relatively fast heart rates of infants and young children, and the inability to tolerate heart rates that are normally observed in adults.

When evaluating a neonate, infant or young child, it is mandatory that a thorough assessment of the underlying cardiac anatomy be conducted, as significant structural lesions can go undetected prior to clinical presentation. Some of these

lesions result in heart failure from low cardiac output (e.g., left heart obstruction from coarctation of the aorta, hypoplastic left heart syndrome, or critical aortic stenosis), while others result in heart failure from pulmonary over-circulation (e.g., large left-to-right shunts from ventricular septal defects, or a patent ductus arteriosus).

1.5 Shunt Lesions and Calculations

Common to the practice of pediatric cardiology is the care of patients with structural lesions that cause shunting of blood. An explanation of the terms and calculations used to describe shunted blood flow follows. A key principle to keep in mind when considering congenital heart disease and quantification of shunts is that marked changes in systemic and pulmonary vascular resistance occur around the time of birth and continue for some time thereafter. These changes impact the direction and magnitude of shunt flow, and multiple therapeutic maneuvers (e.g., pharmacotherapy, mechanical ventilation, and inhaled gases) are often used to affect the degree and minimize the impact of shunting during the management of patients. It is also essential to appreciate the relationship that exists between cardiac output, vascular resistance, and blood pressure. This relationship is conceptualized as Ohm's Law (voltage $=$ current$\times$resistance) with the substitution of pressure (P) for voltage, cardiac output (Q), and vascular resistance (R) for current to yield the equation $\Delta P = Q \times R$.

As was noted at the onset of this chapter, the heart is in essence two pumps that are connected in series. The right heart pumps to the pulmonary circulation and the left heart to the systemic circulation. In the absence of a shunt, right heart cardiac output (Qp) is equal to left heart cardiac output (Qs), i.e., $Qp:Qs = 1$. In the setting of a net left-to-right shunt, $Qp:Qs > 1$, and in the setting of a net right-to-left shunt, $Qp:Qs < 1$. A simple rule of thumb (analogous to electrical current) is that 'blood flows down the path of least resistance'. Thus, the relative resistances

of the pulmonary and systemic circulations are a primary determinant of the net direction and magnitude of a shunt. Although this holds true for shunts at the ventricular (ventricular septal defects) and vascular levels (aortopulmonary window, patent ductus Arteriosus, and surgically created arterial shunts), the direction and magnitude of shunts at the atrial level are not determined by the downstream resistance, they are instead determined by the relative compliance of the left and right ventricles. In clinical practice, both flow and pressure are relatively easily measured, whereas resistance is usually calculated. Rearranging the equation noted above, pulmonary vascular resistance (PVR) = $\Delta P/Qp$, where ΔP is the transpulmonary gradient [mean pulmonary artery pressure – mean pulmonary vein (or left atrial) pressure]. Likewise, systemic vascular resistance (SVR) = $\Delta P/Qs$, where ΔP = transsystemic gradient [mean arterial pressure–central venous pressure].

In day–to-day practice, knowledge of the normal physiologic changes in PVR and SVR from fetus to neonate to adulthood enables clinicians to make reasonably valid assumptions about a particular patient's condition and to direct appropriate therapies. However, there are instances where the clinical picture is not entirely clear and quantification of the magnitude, or even net direction, of a shunt is necessary. Clinically, much of the information necessary to quantify a shunt or calculate resistance can be achieved at cardiac catheterization with the measurement of oxygen saturations and pressures in the various cardiac chambers and major blood vessels. Furthermore, quantification of Qp may be achieved at the bedside in the intensive care unit or at the time of catheterization with the use of a thermodilution catheter (i.e. Swann-Ganz catheter) or measurement of oxygen consumption (VO_2) and application of the Fick principle. While detailed descriptions of each of these techniques is outside the scope of this Handbook, a thermodilution catheter enables measurement of Qp and the pressures necessary to calculate PVR, whereas measurement of VO_2 and appropriateoxygen saturations enables calculation of Qp and Qs.

The reader is directed to the table at the end of this chapter for a list of commonly used formulas and to the suggested reference texts.

1.6   Hemodynamic Calculations

Example 1 – Large, unrestrictive ventricular septal defect in an 8 week old

	Pressure (mmHg)	Oxygen saturation (%)
Superior vena cava	8	68
Right ventricle	85/55	88
Pulmonary artery	70 (mean)	88
PCWP	15	98
Aorta	85/55	98

Hgb $= 13.0$ g/dL, $VO_2 = 55.8$ mL/min, and BSA $= 0.25$ m^2

Using Fick Equation:

$$Qp = VO_2 / \left[Hgb \ (g/dL) \times 13.6 \times \left(PV_{sat} - PA_{sat} \right) \right]$$
$$= 55.8 / \left[13 \times 13.6 \times (0.98 - 0.88) \right] = 3.2 \ L/min$$

$$Qs = VO_2 / \left[Hgb \ (g/dL) \times 13.6 \times \left(Ao_{sat} - MV_{sat} \right) \right]$$
$$= 55.8 / \left[13 \times 13.6 \times (0.98 - 0.68) \right] = 1.1 \ L/min$$

Thus, $Qp:Qs = 3.2/1.1 \sim 3:1$ (Alternately, since all other terms cancel out, if only saturations are known, can use $(Ao_{sat} - MV_{sat}) / (PV_{sat} - PA_{sat}) = (0.98 - 0.68) / (0.98 - 0.88) = 3:1$).

$$Qp_i = Qp / BSA = 12.6 \ L/min/m^2$$

$$PVR = TPG / Qp_i = (70 - 15 \ mmHg) / 12.6 \ L/min/m^2$$
$$= 3.97 \ \text{indexed Wood units}$$

Example 2 – Large, unrestrictive ventricular septal defect in a 5 year old

	Pressure (mmHg)	Oxygen saturation (%)
Superior vena cava	8	68
Right ventricle	85/55	73
Pulmonary artery	70 (mean)	73
PCWP	15	98
Aorta	85/55	98

Hgb = 13.0 g/dL, VO_2 = 55.8 mL/min, BSA = 0.7 m^2

$$Qp_i = 5.0 \text{ L / min/m}^2$$

$$Qp : Qs = (0.98 - 0.68)/(0.98 - 0.73) = 1.2 : 1$$

Thus, Qs_i = 5.0 L/min/m^2/1.2 = 4.2 L/min/m^2

$$PVR = TPG / Qp_i = (70 - 15 \text{ mmHg}) / 5.0 \text{ L/min/m}^2$$
$$= 11.0 \text{ indexed Wood units}$$

Example 3 – Large atrial septal defect

	Pressure (mmHg)	Oxygen saturation (%)
Superior vena cava	10	72
Right atrium	10	79
Right ventricle	32/14	83
Pulmonary artery	20 (mean)	83
PCWP	11	99
Aorta	85/55	99

Hgb = 12.6 g/dL, VO_2 = 86 mL/min, BSA = 0.7 m^2

$$Qp_i = 4.48\,L/min/m^2$$

$$Qs_i = 2.65\,L/min/m^2$$

$$Qp:Qs = 4.48\,/\,2.65 = 1.69:1$$

$$PVR = TPG\,/\,Qp_i = \left(20 - 11\ mmHg\right)/\,2.65\ L/min/m^2$$
$$= 3.4\ \text{indexed Wood units}$$

Example 4 – Tetralogy of Fallot

	Pressure (mmHg)	Oxygen saturation (%)
Right atrium	10	63
Right ventricle	85/55	63
Pulmonary artery	16 (mean)	63
PCWP	11	
Aorta	85/55	87

$Hgb = 14.2$ g/dL, $VO_2 = 62$ mL/min, $BSA = 0.3$ m^2

$$Qp_i = 2.97\,L/min/m^2$$

$$Qs_i = 4.43\,L/min/m^2$$

$$Qp:Qs = 2.97\,/\,4.43 = 0.67:1$$

$$PVR = TPG\,/\,Qp_i = \left(16 - 11\ mmHg\right)/\,2.97\ L/min/m^2$$
$$= 1.68\ \text{indexed Wood units}$$

1.7   Formulas

$$Qp:Qs = \left(\frac{\text{aortic} - \text{mixed venous saturation}}{\text{pulmonary venous} - \text{pulmonary arterial saturation}}\right)$$

$$Qp = VO_2 / [13.6 \times Hgb\ (g\,/\,dL)$$
$$\times\ (pulmonary\ venous - pulmonary\ arterial\ saturation)]$$

$$Qs = CO = VO_2 / \Big[13.6 \times Hgb\ \big(g\,/\,dL\big) \times \big(aortic - mixed\ venous\ saturation\big)\Big]$$

$$PVR = transpulmonary\ gradient\big(TPG\big) / Qp$$

$$TPG = mean\ pulmonary\ artery\ pressure$$
$$-\ pulmonary\ capillary\ wedge\big(or\ left\ atrial\big) pressure$$

$$SVR = \big[mean\ arterial\ pressure - central\ venous\ pressure\big] / Qs$$

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Chapter 2
Clinical Pharmacokinetics: Applications in Pediatric Practice

Denise L. Howrie and Carol G. Vetterly

Abstract The statement "Children are not little adults" is a foundation of pediatric drug therapy referring to well-documented differences in pharmacokinetics and pharmacodynamics existing between children and adults [1–6]. It is therefore important to understand the influence of age on drug disposition, especially in neonates and infants, and resulting effects on drug activity. This chapter will provide

D.L. Howrie, PharmD (✉)
University of Pittsburgh School of Pharmacy & Medicine, Pittsburgh, Pittsburgh, PA, USA

Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA
e-mail: howrie@pitt.edu

C.G. Vetterly, PharmD, BCPS
Department of Pharmacy Services,
Children's Hospital of Pittsburgh of UPMC,
 Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics,
University of Pittsburgh School of Pharmacy,
Pittsburgh, PA, USA
e-mail: carol.vetterly@chp.edu

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brief discussions of principles of pediatric pharmacokinetics and knowledge of the effects of disease states upon disposition of cardiovascular drugs affecting safe and effective drug therapy.

Keywords   Pediatric pharmacokinetics • Drug absorption

2.1   Pediatric Pharmacokinetics

2.1.1   Drug Absorption

Oral Administration

The rate of drug absorption is generally slowed in infancy when compared to older children and adults [1, 3]. Efficiency of absorption of drugs following oral administration may be variable, especially during infancy in the presence of prolonged gastrointestinal emptying time (6–8 h), unpredictable gastric peristalsis and delayed time to peak concentrations [1, 3]. Gastric pH values of 1–3 are achieved within 24 h after birth [1], become acid neutral by 1 week of age and slowly decline over 2–3 years to adult values [4]. These changes may result in greater absorption of basic drugs such as amoxicillin, erythromycin and penicillin G, while reducing absorption of weak acidic drugs including phenobarbital in infants [1, 3, 4].

Reduced bile acid pool and low lipase production decrease absorption of fat-soluble vitamins [1]. Irregular peristalsis may affect small intestinal drug absorption in childhood. Improvement in antral contractions occurs through the first week of life and intestinal motility through early infancy [3]. Other developmental differences include reduced glutathione-S-transferase, altered microflora and changes in splanchnic blood flow [3]. Diarrhea, as well as variation in intestinal transit, may accelerate transit with reduced and variable absorption from sustained-release products [1, 4].

2.1.2   Other Routes of Administration

Percutaneous absorption of drugs including adrenal cortico-steroids and alcohols may be increased in infancy due to greater relative body surface area, enhanced hydration of epidermis and decreased thickness of the epidermis and stratum corneum [1, 3, 4]. The ratio of total body surface area to body mass is greater in infants and children when compared to adults [3, 4].

Absorption from intramuscular injection sites may be less predictable in neonates due to variation in peripheral perfusion [1, 3, 4] and limited muscle mass. However, intramuscular absorption in neonates may be more efficient due to higher density of skeletal muscle capillaries [3].

Rectal administration of drugs such as diazepam or midazolam may result in higher serum concentrations as compared to oral administration, although this is not an age-dependent observation for these drugs [1]. Immaturity of hepatic metabolism may increase rectal drug bioavailability in neonates, although enhanced expulsion of rectal products could also reduce drug bioavailability [3].

2.1.3   Bioavailability

The amount of a drug dose that reaches the systemic circulation is the "bioavailability" of the drug. It is affected by drug absorption, metabolism in the intestinal wall (referred to as pre-systemic metabolism) and hepatic metabolism (referred to as "first pass effects"). Low bioavailability values reflect either poor absorption or high rates of metabolism.

2.2   Drug Distribution

Drug transport through body compartments occurs under the influence of factors including protein binding, body fluids, membrane transport and blood and tissue hemodynamics. Drugs generally distribute rapidly through blood to more

highly perfused organs such as liver and kidneys, then more slowly to other compartments. Drug movement occurs into and out of multiple compartments over time to maintain equilibrium, with disease states, drug lipid solubility, characteristics of body tissues, regional pH differences and protein binding as determinants.

2.2.1   Volume of Distribution

The volume of distribution (Vd) of a drug indicates the extent of drug distribution into body fluids/tissues and relates the amount of drug in the body to measured plasma concentration (Css) and is defined as:

$$Vd(L/kg) = \frac{\text{Amount of drug}(mg)}{\text{Css}(mg/L)}$$

In clinical practice, this value permits rapid calculation of "Loading Doses" to rapidly achieve therapeutic serum concentrations for drugs such as phenytoin and lidocaine by use of measured mean Vd values for the defined patient population. For example, if the average population Vd for a given drug is 1 L/kg and the desired plasma concentration is 15 mg/L, the required average "Loading Dose" would be 15 mg/kg. Drugs with extensive extra-plasma distribution appear to have large Vd values.

2.2.2   Total Body Water and Extracellular Fluid Volume

Expanded total body water values relative to body weight are observed in newborns, infants and children when compared to adults: 80 % total body weight in premature infants and 70–75 % in newborns as compared to 50–60 % in adults [1, 4]. Neonates and young infants also have a greater extracellular fluid compartment relative to body weight when compared to

adults [1, 3, 4]. For water-soluble drugs demonstrating distribution through total body water, including aminoglycosides, penicillins and cephalosporins, larger doses (expressed as mg/kg doses) will be required in infants to achieve comparable serum concentrations to those achieved in adults.

2.2.3   Total Body Fat

Preterm infants have significantly lower body fat (1 %) when compared to full-term infants (15 %) and adults (20 %). Lipid-soluble drugs such as benzodiazepines would therefore demonstrate lower Vd estimates in premature infants, leading to augmented clinical effects [1].

2.2.4   Protein Binding Effects

Drugs in plasma bind to proteins including albumin, α-1-acid-glycoprotein (α-1-AG) and lipoproteins. Albumin is the major serum protein that binds anionic drugs at two binding sites. Site I has binding sites for drugs such as warfarin, sulfonamides, phenytoin and valproate, while Site II is the binding site for penicillins and benzodiazepines. In the presence of lower concentrations of albumin in the first year of life (75–80 % of adult values [5]), the presence of fetal albumin with reduced affinity for many drugs, and endogenous competitive substances such as bilirubin and free fatty acids, higher free drug concentrations for drugs such as phenytoin, salicylates, and valproic acid may result in augmented response [3, 4]. The potential competition of drugs that are highly bound to albumin with endogenous substrates such as bilirubin that are also bound to albumin dictates cautious use of drugs such as ceftriaxone and sulfonamides in infants with or at risk of hyperbilirubinemia [4].

Although emphasis is placed upon albumin and drug binding, the role α-1-AG cannot be overlooked, as this protein binds important cationic and neutral drugs. Changes in α-1-AG in an acute phase reaction due to inflammation, as

seen after myocardial infarction, may result in lower free concentrations of drugs including lidocaine, propranolol and quinidine. Additionally, concentrations of this protein are 50 % of adult levels during infancy and increase slowly over the first year of life [4, 5].

2.3   Drug Elimination

Drug elimination from the body generally occurs via the liver or other sites of metabolism and/or the kidney through excretion of active drug or biotransformed metabolites. Total body elimination is the sum of all metabolism and excretion.

2.3.1   Metabolism

Drug metabolism occurs through biotransformation through Phase I reactions (oxidation, reduction, sulfoxidation, hydrolysis) [4] by conversion of a functional group such as hydroxyl, amine or sulfhydryl [7]. Oxidation proceeds via mixed-function oxidase systems including cytochrome P-450 reductase enzymes through hydroxylation, dealkylation and deamination. Both Phase I and II reactions mature over time [4]. Phase I reactions generally mature by 1 year of age [1]. Phase II reactions, also called synthetic or conjugation reactions, combine these byproducts with substances such as glucuronide, sulphate or glycine. After Phase II reactions, the more polar metabolites are more readily excreted via the urine [7]. Phase II processes mature at a slower rate, for example, glucuronidation activity by 3–4 years of age [1].

2.3.2   Hepatic Extraction of Drugs

Efficiency of drug removal by the liver (hepatic extraction ratio) is affected by hepatic blood flow, protein binding and intrinsic metabolic activity. Hepatic clearance of a drug (CLh) describes the volume of blood from which the drug is

completely removed per unit time, which is a function of hepatic blood flow and extraction ratio of drug as follows:

$$CLh = Q \times \frac{Ci - Co}{Ci}$$

where Q = hepatic blood flow, Ci is concentration of drug entering the liver and Co is concentration of drug leaving the liver. High clearance drugs include metoprolol, propranolol, lidocaine, nitroglycerin and verapamil. For these drugs, clearance is greatly dependent upon hepatic blood flow, necessitating dosage adjustment when diseases affect this [8].

2.3.3   Cytochrome P-450 Isoenzymes

Drug metabolism to pharmacologically-inactive or less active compounds may occur in many tissues, although the greatest sites of drug metabolism are the liver and gastrointestinal tract through activity of specific drug-metabolizing enzymes referred to as cytochrome P (CYP)-450 enzymes. These enzymes, present in highest concentrations in the liver, small intestine, kidney, lung and brain, are responsible for drug metabolism, with over 30 types of human enzymes identified thus far. CYP enzymes are classified in families and subfamilies based on amino acid sequences.

Intense interest is focused upon these pathways, as observed genetic polymorphism affects drug metabolism and, therefore, effects. Over 90 % of common medications are metabolized by seven isoenzymes: 3A4, 3A5, 1A2, 2C9, 2C19, 2D6, and 2E1 [1, 7]. Knowledge of patterns of drug metabolism through CYP-450 isoenzymes permits assessment of potential drug-drug interactions for prescribed medications.

Multiple factors affect individual CYP activity including genetics and ethnicity, environmental factors such as nicotine and ethanol, and diseases [7]. For example, in cirrhosis, reduced CYP activity occurs through loss of functional tissue. CYP activity is reduced in inflammation and infection, increasing potential toxicity risk. CYP activity can also be

affected through substances that inhibit activity either via simple competitive inhibition or as an irreversible inhibition effect. Examples of irreversible inhibitors include clarithromycin and erythromycin, isoniazid, carbamazepine, irinotecan, verapamil, midazolam, fluoxetine and grapefruit products including bergamottin [7].

The CYP3A4 isoenzyme pathway is responsible for metabolism of the greatest number of drugs commonly used in clinical care, with sites of metabolism in hepatocytes and intestinal mucosa as well as the duodenum and esophagus [6]. Approximately 40 % of CYP3A4 activity is in the small intestine [6], producing the "first pass" phenomenon of drug metabolism prior to systemic exposure and determining bioavailability of drugs including opioids, calcium channel blockers and β-blockers.

Common examples of drug substrates for the CYP3A4 family include cisapride, prednisone, cyclosporine, tacrolimus, quinidine, amiodarone, calcium channel blockers, many benzodiazepines, common "statins", lidocaine, carbamazepine and dextromethorphan [9]. Potent inhibitors of 3A4 activity include macrolide antibiotics such as erythromycin, azole antifungals, and psychotropic agents such as sertraline, fluoxetine, and nefazodone. Isoenzyme activity may be affected by potent inducing compounds including phenytoin, phenobarbital and carbamazepine as well as rifampin. Dramatic variations in CYP3A4 activity are documented, with 4-to 13-fold differences in clearance rates [6].

The CYP2D6 isoenzyme pathway, affecting approximately 25 % of drugs, demonstrates important variability based upon genetic polymorphisms, with dextromethorphan as a marker of drug-metabolizing capacity. As many as 3–10 % of the Caucasian and 0–2 % of Asian and African-American populations may demonstrate slowed rates of drug metabolism ("poor metabolizers") for substrates including opioids, tricyclic antidepressants, flecainide, fluoxetine, β-blockers and mexiletine [9]. Inhibiting drugs include cardiovascular agents such as amiodarone and quinidine, cimetidine, and psychotropic agents such as fluoxetine, paroxetine and sertraline. Again, enzyme induction is seen with concurrent use of phenytoin, phenobarbital and carbamazepine.

The CYP2C isoenzyme pathway also demonstrates significant genetic variability caused by polymorphisms, potentially affecting approximately 15 % of clinically-useful drugs. Approximately 3–5 % of Caucasians, 18–23 % of Asians and 5 % of African-Americans demonstrate reduced CYP2C19 activity, increasing the risk of delayed drug metabolism and toxicity [9]. Substrates for this isoenzyme system include omeprazole, S-warfarin, propranolol, topiramiate and diazepam. Examples of drugs that may inhibit this system include fluconazole and potentially other azole antifungals, omeprazole, sertraline, fluoxetine and isoniazid. Inducing substances include phenytoin, phenobarbital and carbamazepine as well as rifampin.

A fourth isoenzyme pathway responsible for metabolism of approximately 5 % of drugs is the CYP1A2 system, with important substrates including theophylline, R-warfarin and caffeine, and notable inhibitors including azole antifungals, macrolides including erythromycin, fluvoxamine, paroxetine and isoniazid.

2.3.4 Development of Metabolic Functionality with Age

Maturation of CYP microsomal activity occurs at different ages and rates [4–6]. CYP activity is present at 30–60 % of adult values in infancy [4, 6] and each CYP enzyme undergoes a unique maturation process. For example, CYP3A7 demonstrates greater expression in fetal liver and regression to 10 % after age 3 months and undetectable levels in adults [3, 4, 6]. CYP3A4 is reported to express at 50 % adult values between ages 6–12 months of age, with low activity *in utero* but rapid development within a week of life [3, 4, 6]. These lower levels of CYP3A4 in infancy may cause inability to clear cisapride and therefore increase drug toxicity risk [4].

CYP2C, involved in metabolism of warfarin, phenytoin, and diazepam, demonstrates 33 % of eventual activity in the first month of life [4]. Interestingly, elevated CYP2C content has been reported in Sudden Infant Death Syndrome, with a

possible role of pulmonary smooth relaxation by endogenous substances metabolized through this system [4].

CYP1A2, involved in metabolism of acetaminophen, warfarin, caffeine and theophylline, is low in neonates [1], develops in 1–3 months [3], and achieves 50 % adult activity by age 1 year [4]. N-demethylation patterns of caffeine metabolism vary by age, with N3-demethylation more prominent in infants [4]. CYP2D isoenzymes involved in metabolism of β-blockers, codeine, captopril, and ondansetron increase in activity over several years of age, achieving 66 % of adult values by that age [4]. Deficiency in infancy may contribute to adverse effects in infants of selective serotonin reuptake inhibitor (SSRI)-treated mothers [1]. CYP2E1 isoenzymes develop to 40 % values by age 1 year, with eventual adult values at 1–10 years [4].

Age-dependent increases in drug clearance in children less than 10 years of age are reported for many drugs when compared to clearance values in adults. The mechanism(s) for these observed differences have not been described [3].

Phase II reaction functions also mature over time [3], as exemplified by slowed development of acetyltransferase that limits accurate assessment of acetylation status until after several years of age [4]. Slowed glucuronidation activity may contribute to the observed toxicity of chloramphenicol in infants and may also determine detoxification of morphine in infancy [3] and in bilirubin metabolism [4]. Development of glucuronidation activity to adult values has been reported to occur over widely variable time periods from 3 months to >3 years of age [4]. Sulfate conjugation can be an alternative pathway of metabolism for morphine and acetaminophen during infancy [4].

2.3.5   Drug-Drug Interactions

Drug interactions result from physical or chemical effects, pharmacokinetic competition or as pharmacodynamic effects at receptor sites. These are considered as adverse drug effects that are usually predictable and, ideally, avoidable. Although

over 100,000 drug interactions have been documented, only a subset of these is clinically significant because of potential for harm [7]. Glintborg et al. detected 476 potential drug interactions in 63 % of a cohort of 200 elderly patients, although only 4.4 % were classified as relative contraindications for use and none resulted in adverse events documented in patient records. Patients receiving multiple medications were at greatest risk for drug-drug interactions [10]. In approximately 46 million individuals as reported by Malone et al., 2.5 million persons have been exposed to a drug-drug combination judged to be clinically important, with more women than men and more older individuals than younger individuals exposed. The highest prevalence drug-drug interaction involved an non-steroidal anti-inflammatory drug-warfarin exposure [11]. Data in pediatric populations are generally lacking, although Novak et al., reported a 3 % incidence of serious drug-drug interactions in pediatric patients receiving chronic anti-epilepsy drugs [12].

2.3.6   Implications of Cytochrome P-450 Drug-Drug Interactions of Cardiovascular Drugs

The CYP-450 system may have significant effects upon cardiovascular drug therapy. β-adrenergic blocking agents such as propranolol, metoprolol, carvedilol and timolol undergo metabolism via the CYP2D6 pathway and would be affected by "inducers" like rifampin and "inhibitors" including quinidine, amiodarone, and cimetidine. Carvedilol is a racemic mixture of both R- and S-enantiomers, with metabolism by CYP2C9, CYP1A2 and CYP3A4 as well as CYP2D6; this complex pattern of metabolism may mitigate effects of inhibitor drugs upon carvedilol [13].

Although angiotensin converting enzyme (ACE) inhibitor prodrugs may undergo metabolism via CYP enzyme systems, no significant CYP-mediated drug-drug interactions have been documented. However, inhibitor compounds such as

fluconazole and inducers such as rifampin may affect plasma concentrations of losartan which undergoes transformation via CYP2C9 to an active metabolite [13].

Calcium channel blocking drugs are substrates for CYP3A4 and are therefore subject to significant drug-drug interactions. Decreased effectiveness of verapamil and nifedipine has been noted with rifampin, while increased bioavailability and potential toxicity may be seen when CYP3A4 inhibitors like azole antifungals or quinidine are used with members of this drug class. Conversely, drugs in this class such as diltiazem and verapamil may exert clinically-significant inhibitory effects through CYP3A4 upon cyclosporine metabolism and have been proposed as means to reduce cyclosporine dose requirements for potential cost savings. Diltiazem also may reduce metabolism of triazolam, midazolam and methylprednisolone [13]. The potential risk of hypotension and shock may exist when macrolide antibiotics are administered with nonhydropyridine calcium channel blockers [14].

Antiarrhythmic agents are also subject to important drug-drug interactions involving CYP-450 enzyme pathways, and agents in this class may act as substrates, inducers or inhibitors of various isoenzymes. Quinidine, for example, undergoes metabolism through CYP3A4 pathways and may achieve higher serum levels in the presence of inhibitors including azole antifungals and cimetidine and lower levels with classic inducers such as phenytoin and phenobarbital. In addition, quinidine may reduce codeine effectiveness by inhibiting CYP2D6 conversion to morphine. Disopyramide may be affected by cytochrome inducers such as rifampin and by inhibitors including macrolides and human immunodeficiency virus (HIV) protease inhibitors [9].

In addition to documented interactions with propranolol due to hepatic blood flow, lidocaine is also affected by P-450 inducers such as rifampin and inhibitors such as HIV protease inhibitors, necessitating close monitoring of serum concentrations. Mexiletine, subject to rifampin-induced CYP2D6 metabolism, may also increase theophylline concentrations related to its inhibitory effects upon CYP1A2. Flecainide

toxicity may result from concurrent use of SSRIs that affect CYP2D6 pathways as well as amiodarone [9].

Amiodarone demonstrates complex potential drug-drug interactions related to CYP-450 effects as well as other mechanisms. Amiodarone-related inhibition of CYP2C9 may result in toxicity during concurrent phenytoin, theophylline or cyclosporine therapy, while phenytoin may decrease amiodarone concentrations and increase metabolite concentrations [9].

Furanocoumarin(s) including bergamottin contained in grapefruit may cause irreversible inhibition of intestinal CYP3A4 within 24 h of ingestion of 200–300 ml juice; ingestion of fresh grapefruit with decreased CYP3A4 activity by 47 % within several hours of ingestion [15, 16]. Although initial recommendations included timing of medications several hours post-grapefruit products, inhibitory effects may continue for up to 72 h. Variability in CYP3A4 between individual patients leads to variability in effect and lack of predictability due to this interaction. Pharmacokinetics of parenterally-administered drugs, however, are unaffected [15, 16]. High-dose consumption may also affect hepatic CYP3A4 enzymes [15]. Overall, grapefruit effects would be expected to increase oral bioavailability (and therefore effects) of drugs metabolized via CYP3A4 through decreased pre-systemic clearance.

Diverse cardiovascular agents have been documented as affected by grapefruit juice constituents. The HMG-CoA inhibitors atorvastatin, simvastatin and lovastatin have the greatest potential for enhanced bioavailability due to significant CYP3A4 intestinal metabolism, while pravastatin or fluvastatin do not rely on this pathway for metabolism. Dihydropyridines such as felodipine, nicardipine and nifedipine are examples of calcium channel blockers that may demonstrate enhanced systemic bioavailability (1.5–4-fold) producing augmented effects on blood pressure, especially significant in the elderly. The angiotensin II type 1 inhibitor losartan is metabolized via CYP3A4 and CYP2C9 to its active metabolite; grapefruit juice may reduce conversion

and therefore therapeutic effects. Other agents that may be significantly affected include amiodarone, quinidine, sildenafil and propafenone [15, 16].

2.3.7 Excretion

Drugs can be excreted through urine, bile, sweat, air or other fluids. However, the most important routes are the bile and the kidney. The kidney is the major organ responsible for elimination of parent drug and/or metabolite, with renal excretion the product of glomerular filtration, tubular secretion and tubular reabsorption. Factors affecting glomerular filtration include molecular size, protein binding and number of functional nephrons. Tubular secretion of weak organic acids or bases occurs via active transport subject to competition with other substances. Tubular reabsorption of drugs occurs via active or passive transport in the distal tubule, and may be dependent upon urine pH, urine flow rates and drug properties including ionization.

In pediatrics, glomerular filtration function is dramatically reduced in newborns [5], with greater immaturity in premature infants when compared to full-term; increases in glomerular filtration rate (GFR) occur in the first weeks of life to achieve 50–60 % of adult function by the third week of life [1, 3] and adult values by 8–12 months of age [3]. Premature infants show slower improvement of GFR when compared to full-term infants [1], with continued reduced drug clearance despite chronologic age. By 3–6 years of life, GFR values (expressed per kg) exceed adult values [1]. Therefore, drugs dependent upon glomerular filtration will show reduced drug clearance through early infancy, more evident in premature infants, and likely require dosage reduction. However, during early childhood, higher daily doses are likely when corrected for weight and in comparison to adult doses due to increased GFR.

Tubular secretion rates are also reduced in neonates [1, 3] and mature during the first year of life, reaching adult values by age 7 months [4] and maturing much later than glomerular filtration function.

The development of renal excretion pathways must be appreciated for appropriate prescribing of many drugs in infancy, especially when drugs with narrow therapeutic indices are administered such as vancomycin and aminoglycosides. The use of therapeutic drug monitoring by measuring serum concentrations is helpful in guiding drug dosing to individualize therapy in infants and children.

2.4 Alterations in Pharmacokinetics in Disease States

2.4.1 Liver Disease

Pharmacokinetic changes and the need for dosing adjustments of cardiovascular drugs in the presence of liver disease have been extensively discussed [8, 17]. Liver disease may produce significant changes in plasma protein binding, hepatic blood flow and oxidative metabolism via CYP-450 isoenzymes. The need for dosing adjustment in the presence of liver diseases is most clearly evident when cirrhosis is present due to factors including variable P-450 activity and altered blood flow to functional hepatocytes [8]. CYP-450 activity may be decreased overall, but selectivity of enzyme systems may be present, with CYP1A2 susceptible to degree of liver damage as well as variable activity of CYP3A4. Other liver diseases including chronic active hepatitis do not uniformly affect hepatic drug elimination [8]. Unfortunately, in both liver disease and congestive heart failure, liver function test values are not indicative of altered drug metabolism and thus do not aid dosing adjustments.

2.4.2 Cardiovascular Agents in Liver Disease

The angiotensin II receptor antagonists may show significant alterations in pharmacokinetics and effects in the presence of liver disease. Losartan and its active metabolites achieve

higher serum concentrations with lower plasma clearance rates (approximately 50 %) and higher bioavailability in the presence of alcoholic cirrhosis. Valsartan also demonstrates significantly increased plasma concentrations with potentiation of effects in the presence of liver dysfunction with two-fold increase in the area under the curve (AUC) [8].

ACE inhibitors, as prodrugs, may be affected in liver disease with reduced conversion to active forms in the presence of liver cirrhosis. Lisinopril, as a non-prodrug form, may be preferred in this setting [8, 17].

Anti-arrhythmic agents may also show significant alteration in pharmacokinetics in the presence of liver dysfunction, with serum concentrations useful for assessing patient-specific dosage adjustment. Dosage reduction may be required for quinidine in the presence of heart failure or cirrhosis. Serum level monitoring of procainamide is recommended due to variability in reported pharmacokinetic parameters by various investigators. Liver dysfunction may necessitate dosage alterations of lidocaine, mexilitene, disopyramide, tocainide, and flecainide. Dramatic dose reduction of propafenone by 50–80 % is recommended in cirrhosis due to increased bioavailability, prolonged half-life and increased plasma levels [8].

Propranolol, a high-extraction drug, demonstrates significant alterations in pharmacokinetics in states of altered liver blood flow, as well as impaired activity of microsomal enzymes and inhibition of its own metabolism resulting from altered hepatic flow. Cirrhosis is associated with prolonged drug clearance rates. Additionally, propranolol has also been reported to reduce lidocaine clearance by 40–50 % [8].

Carvedilol demonstrates increased bioavailability, reduced drug clearance rates and increased Vd (280 %) in the presence of cirrhosis, with initial dose reductions and careful monitoring recommended [8].

Calcium channel blockers generally require dosage adjustments and close monitoring in the presence of cirrhotic liver disease due to multiple factors including increased bioavailability, altered protein binding, prolonged drug half-lives and

decreased drug clearances. Verapamil, amlodipine, felodipine, isradipine, nimodipine and nicardipine are examples of drugs in this class affected by liver disease [17].

2.4.3   Renal Disease

The kidney is of great importance in excretion of drugs, both parent drug or metabolites, which may also possess significant pharmacologic activity. Drug elimination may be dramatically altered in the presence of severe renal dysfunction and during supportive renal replacement therapies.

Although dosing guidelines may have been developed from studies in adults, pediatric-specific dosing adjustment data are generally unavailable. In these situations, dosage adjustments must be extrapolated from adult pharmacokinetic studies and patient-specific estimates of creatinine clearance using age-appropriate formulas. However, age-related differences in GFR, Vd estimates and plasma protein concentrations, and drug affinity in infants and children limit our ability to rely on data from adult populations [18, 19].

Other changes in pharmacokinetic parameters exist that determine dosing regimens in the setting of renal dysfunction. Drug absorption may be reduced via oral administration routes through changes in gastric pH, use of phosphate binders and other antacids, and enhanced bioavailability due to reduced pre-systemic clearance in the intestine through decreased CYP-450 activity and altered P-glycoprotein drug transport [20].

Drug distribution may be altered through decreased plasma protein binding capacity due to reduced plasma albumin concentrations, reduced albumin affinity or the presence of compounds competing for drug binding sites, as well as elevations in α-1-AG. Changes in Vd may also be present due to fluctuations in body water, muscle mass and adipose tissue [20].

Although often overlooked in renal dysfunction, changes in drug metabolism in chronic renal disease exert important effects on drug clearance. Phase I hydrolysis and reduction

reactions are decreased, as well as reduced activity of CYP-450, 2C9, 3A4 and 2D6. Phase II reactions through acetylation, sulfation and methylation are also slowed. Renal metabolism can be significant, as renal tissue contains 15 % of the metabolic activity of the liver and is involved in metabolism of acetaminophen, imipenem, insulin, isoproterenol, morphine, vasopressin and other drugs [20].

Renal dysfunction obviously reduces clearance of drugs that rely upon glomerular filtration, tubular secretion or both processes and produces prolonged elimination rates. Also important is the role of delayed renal clearance of drug metabolites with pharmacologic activity such as allopurinol, cefotaxime, meperidine, midazolam, morphine and propranolol [20].

2.4.4   Drug Elimination During Dialysis Procedures

Drug removal during dialysis is influenced by many factors including molecular weight, protein binding, Vd, water solubility, as well as technical influences of equipment (filter properties) and technique (blood flow, dialysate flow, ultrafiltration rates). In patients receiving therapy with intermittent hemodialysis, estimation of residual renal function is important to avoid underestimation of dosing requirements. Pediatric-specific dosing guidelines should be used as a basis for estimating supplemental doses for drugs removed via hemodialysis [18].

In continuous renal replacement therapies (CRRT) in children, dosage determination is best based upon estimation of total drug clearance reflecting residual renal function, non-renal clearance and clearance via the CRRT circuit. Veltri et al. utilized pharmacokinetic data from previous investigators and/or extrapolated data to develop extensive guidelines for dosing of commonly-used medications for pediatric patients with renal dysfunction or when undergoing intermittent hemodialysis or other CRRT therapies [18].

2.4.5   Cardiovascular Drugs in Renal Disease

There are numerous drugs that demonstrate significant alterations in pharmacokinetics and/or pharmacodynamics in the setting of renal dysfunction. ACE inhibitors undergo significant renal clearance, with dosage adjustments required. However, fosinopril is an exception. Careful monitoring of serum electrolytes, especially potassium, and renal function is required. β-blockers may also require dosage adjustment: atenolol, nadolol, sotalol, and acebutolol. Other antihypertensive agents and/or active metabolites may also accumulate in renal disease: methyldopa, reserpine, and prazosin [20].

Other cardiovascular drugs also require dosage adjustment. Digoxin demonstrates altered Vd (approximately 50 % of normal) and both the loading dose and maintenance dose should be reduced with decreased renal clearance. Procainamide and its active metabolite n-acetyl-procainamide will accumulate to toxic concentrations in the presence of renal disease, necessitating dosage adjustment and close monitoring of serum concentrations of both anti-arrhythmic agents [20].

2.4.6   Congestive Heart Failure (CHF)

In CHF hypoperfusion of the liver and passive congestion of liver sinusoids can affect drug metabolism. Total hepatic blood flow is reduced proportional to cardiac output, with significant effects upon high extraction drugs such as lidocaine. Additionally, depression of P-450 activity also has been reported in the presence of CHF, with improvement following effective treatment. As in liver disease, liver function test values are not indicative of altered drug metabolism and thus do not aid in dosing adjustments [8].

Cardiovascular Drugs in CHF

Sokol et al. have also summarized the effects of CHF upon important cardiovascular drug classes, although only limited data are available. ACE inhibitors such as ramipril

may show higher peak concentrations and prolonged half-lives in the presence of severe CHF, although no significant changes are reported with lisinopril, captopril or fosinopril [8].

Anti-arrhythmic agents may be affected in the presence of CHF. Close monitoring of serum levels of quinidine is recommended, as lower doses may be required due to reduced plasma clearance and higher serum concentrations. Variability in pharmacokinetics may occur also with procainamide, and close monitoring of serum procainamide and n-acetyl-procainamide concentrations and QTc is also recommended [8].

As previously described, congestive failure may greatly affect lidocaine pharmacokinetics, with reduction in drug clearance correlated with cardiac output. Dosage reduction by 40–50 % has been advocated, with close monitoring of serum levels. Reduction in loading doses associated with decreased Vd is also recommended. Doses of mexilitene, tocainide, flecainide and amiodarone may also require adjustment in CHF [8].

2.4.7   Critical Care Settings

Absorption

Redistribution of blood flow to central organs in shock states may reduce oral, sublingual, intramuscular, or subcutaneous absorption profiles of drugs. Additionally, use of vasoactive drug infusions may also affect drug absorption profiles indirectly through perfusion changes. Use of enteral feedings may result in altered absorption of drugs, as demonstrated for phenytoin, quinolones and fluconazole [21].

Distribution

Theoretically, changes in pH may alter drug ionization and affect tissue penetration. Changes in body fluid concentrations and shifts can more dramatically affect those drugs that demonstrate distribution through total body water

such as aminoglycosides, with expanded Vd values in fluid overload or "third spacing" of fluids (e.g., ascites or effusions) and contracted Vd with fluid depletion (e.g., with diuretics) [21]. Increased cardiac output may also result in increased clearance of drugs. Plasma protein binding changes, including decreased production of albumin and increased production of α-1-AG, may affect "free" (unbound) drug concentrations with increased "free" concentrations of acidic drugs such as phenytoin and reduced "free" concentrations of basic drugs such as meperidine and lidocaine. Other drugs affected by protein binding changes include fentanyl, nicardipine, verapamil, milrinone and propofol.

Metabolism

Sepsis, hemorrhage, mechanical ventilation and acute heart failure may affect drug metabolism through effects upon hepatic blood flow and impact high extraction drugs including midazolam [22] and morphine. Additionally, drugs such as vasopressin and alpha-agonists may detrimentally affect hepatic blood flow during critical care support. Phase I reactions via CYP-450 enzymes in drug metabolism may also be reduced in the presence of inflammatory mediators in acute stress [21].

Excretion

The frequency of renal dysfunction in the critical care setting results in significant pharmacokinetic changes and dosage adjustments. Delayed renal clearance with resulting risk of toxicity necessitates careful assessment of renal function and resulting dosage adjustments using the many sources of dosing guidelines available from manufacturers, scientific literature and drug dosing tables, as discussed above.

Pharmacogenomics

Pharmacogenomics is the study of inherited variation in drug disposition and response, and focuses on genetic polymorphisms. This new field in pharmaceutical science holds the promise of improved drug design and selection based upon unique individual genetic patterns of drug

disposition, improved drug dosing and avoidance of unnecessary drug toxicity. Examples of applications of pharmacogenomics as described by Hines and McCarver include polymorphism of CYP2D6 and response to β-blockers, codeine and antidepressants, thiopurine methyltransferase and use of chemotherapeutic agents for pediatric leukemias, and response to corticosteroids and other drugs in pediatric asthma. Many issues remain in this field including the ethics of genetic screening, validity of phenotype screening and associations, ethnicity, conduct of clinical trials, reasonable cost, patient autonomy and practicality in clinical practice [23].

2.5   Conclusion

Pharmacokinetic variations in drug handling between adults and infants and children are important determinants of effective and safe drug dosing and use. Knowledge of age-related differences in drug absorption, distribution, metabolism and excretion may assist in anticipating potential differences to improve drug use and monitoring. It is particularly important to review the role of the cytochrome P-450 enzyme system in metabolism for many common drugs used in pediatric therapy so as to anticipate possible changes in drug clearance due to drug-disease or drug-drug interactions. There is, unfortunately, limited published experience describing pharmacokinetics of major cardiovascular drugs or the influence of liver or renal dysfunction or congestive heart failure in children, necessitating continued study and vigilance in drug use. However, knowledge of alterations of pharmacokinetics of major cardiovascular drug classes in adults in the setting of hepatic and renal disease and in the presence of congestive heart failure may assist rationale drug use in pediatrics. Finally, the field of pharmacogenomics holds promise as a science to enhance drug selection and safety in pediatric practice.

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Chapter 3
Pharmacogenomics

Jaclyn E. Sawyer, Andrea R. Chamberlain, and David S. Cooper

Abstract Pharmacogenomics is the study of inherited variation in drug disposition and response which focuses on associated genetic polymorphisms. This is an emerging field with great potential to lead to individualized medicine, optimizing therapeutic outcomes, and avoidance of unnecessary drug toxicity. Many barriers remain in this field limiting its clinical applicability. Current cardiovascular related medications with pharmacogenomic labeling are limited but include clopidogrel, warfarin, and drugs from the β-blocker and statin classes of medications. There is lack of pediatric focused research in this area which is necessary given developmental differences that additionally affect drug metabolism and response.

Keywords Pharmacogenomics • Pharmacogenetics • Polymorphism • Pediatrics • Metabolizing enzyme • Drug response • Adverse effect • Genetic testing • Labeling

J.E. Sawyer, PharmD (✉) • A.R. Chamberlain, PharmD, BCPS
Division of Pharmacy, Cincinnati Children's
Hospital Medical Center, 3333 Burnet Ave,
ML 15010, Cincinnati, OH 45229, USA
e-mail: jaclyn.sawyer@cchmc.org

D.S. Cooper, MD, MPH
Department of Pediatrics, Cardiac Intensive Care Unit, The Heart
Institute, Cincinnati Children's Hospital Medical Center, University
of Cincinnati College of Medicine, Cincinnati, OH, USA

3.1   Pharmacogenomics

The human genome project has led to great anticipation of altering the practice of medicine to individualize therapy in the form of medication administration. The excitement inferred the ability to optimize medication regimens while avoiding the potential toxicities that inevitably occur. The current approach to managing a patient's medication regimen is based upon the patient's size, assumed organ function and available evidence from clinical studies or guidelines from expert consensus panels. Knowledge of the pharmacokinetics (how the body affects the drug: absorption, distribution, metabolism and excretion) and pharmacodynamics (how the drug affects the body) is very useful when determining appropriate regimens for patients, especially the ever developing pediatric patient. These strategies do not account for inter-patient variability. The same dose in what seem like similar patients can achieve different therapeutic and toxicity profiles. General explanations that are made to account for this variability include race, age, concomitant diseases, interacting medications, nutritional variations (supplement interactions, food interactions), organ function or mechanical differences in delivery (enteral tubes, inhaled devices, etc.) [1–3]. Genetic variations are thought to play an important role in response to medications as well. This being "pharmacogenomics", was introduced in the 1950s but not until the past decade has the research surrounding such an important factor really start to explode. The availability of the complete human genome sequence and the HapMap project, which maps out genetic variations in a variety of ethnic backgrounds, has aided in the research of investigating variability in drug response based on genetic factors [4, 5]. Pharmacogenomics can be utilized to target new drug development or to individualize therapies for patients. Translation and application into clinical practice is limited. There are over 120 drugs that currently have FDA approved labeling accounting for pharmacogenomic variables but only a few have specific recommendations for alteration in the normal dosing regimen [6]. Cardiovascular

medicine is one of the areas where data suggests that pharmacogenomics contributes to the differences in therapeutic and toxic responses seen between patients [6]. There is yet to be any specific recommendations for pediatric patients regarding pharmacogenomics.

The basis for pharmacogenomics is the genetic contribution to variable drug distribution and response. The terms pharmacogenetics and pharmacogenomics are used interchangeably with the difference being the effect on drug response of a single gene versus multiple genes, respectively [6]. Pharmacogenomic variability related to pharmacokinetics occurs most commonly within the drug metabolizing enzymes and drug transporting pathways versus the pharmacodynamic drug targets. Drug metabolizing enzymes can have altered functionality based on genetic variations. Medications requiring biotransformation through an enzyme based metabolizing pathway can have metabolites that have no pharmacologic activity, more pharmacologic activity or the same activity. If, for example, a drug is a pro-drug and requires metabolism to become the active form of the drug, and the enzyme pathway responsible for this conversion has an inactive mutation leading to a disabled protein (polymorphism), the concentration of the inactive drug would be higher than desired and the active drug much lower than desired potentially leading to therapeutic failure. In adverse to this, if an active drug requires an enzymatic pathway to be converted to an inactive form of the drug or a compound that is able to be excreted from the body and a polymorphism exists in its pathway, this could lead to higher levels of the drug in the body ultimately potentiating clinical response and therefore causing toxic responses or adverse drug events. Many cardiovascular medications have the potential to have polymorphisms related to enzymatic pathways, particularly the cytochrome P450 (CYP-450) pathway. Similarly, if a polymorphism exists in relation to a drug transporter, distribution and elimination of specific compounds can be altered therefore disrupting the normal therapeutic and adverse reaction profile of particular medications. Polymorphisms affecting

the drug target activity also alter the response to the drug. Genetic variants may be more prominent in certain ethnicities, therefore leading to altered therapeutic response or toxicity profiles more common in this subpopulation [5]. Specific examples of polymorphisms will be discussed in this chapter.

When interpreting pharmacogenomics in the pediatric population, it is important to recognize they can be complicated by developmental differences in the activity and expression of drug metabolizing enzyme pathways and transporters [5, 7].

3.2   Warfarin

There are several indications in the pediatric population for the treatment and prevention of thromboembolism using the most commonly prescribed anticoagulant, warfarin. Warfarin's narrow therapeutic index makes it difficult to manage a patient's therapy while accounting for several confounding variables such as diet, drug interactions, age and concomitant disease states. In addition to this, warfarin response is also affected by genetic factors. Warfarin acts by inhibition of vitamin K reductase reaction (VKOR). Inhibition of this pathway ultimately decreases the amount of vitamin K used for conversion of Factors II, VII, IX and X to their active forms, thereby decreasing blood coagulation. Genetic variations in the VKOR complex 1, VKORC1-1639G>A, has been shown in adults to be responsible for variations in dosing requirements of warfarin. The enzymatic pathway CYP2C9 is responsible for the inactivation of the more active enantiomer, (S)-warfarin, and also has genetic variants which can be ethnicity dependent. Specific known variants, CYP2C9*2 and CYP2C9*3, are associated with decreased enzymatic activity. These individuals would require lower dosages to achieve a therapeutic response and would be at higher risk for bleeding events using standard dosing regimens. A polymorphism involving CYP4F2 has been associated with decreased metabolism of vitamin K resulting in elevated levels of vitamin K requiring higher doses of warfarin for therapeutic

effects. Together the CYP2C9 alles and VKORC1 genotype account for variability in warfarin dosing in adults anywhere from ~30–60 % of the population dependent upon ethnicity (Caucasians greater than African Americans). Product labeling has been modified to include adult dosing recommendations for specific genotypes. Validated dosing algorithms for adults are also available [1, 3–5].

Application of the pharmacogenomics of warfarin to the pediatric population is unknown at this time. Available data suggests the most significant factor in determining the dose of warfarin to be age; accounting for 28 % of the variation. Impact of pharmacogenomics in this same data set revealed only a 3.7 and 0.4 % role for VKORC1 and CYP2C9 genotypes respectively. Knowledge of the developmental changes of CYP2C9 and VKORC1 and their effect on warfarin response are limited [5].

3.3   Clopidogrel

Clopidogrel has been used more frequently over the past decade in the pediatric population to prevent thrombotic events particularly in patients with congenital heart disease after interventional catheterization or surgical procedures. In adults, variable antiplatelet response has been documented and potentially accounts for up to 40 % of subtherapeutic antiplatelet response. As a prodrug, clopidogrel is converted to an active thiol metabolite via primarily the CYP2C19 as well as CYP1A2, CYP2B6, CYPC9 and CYP3A4/5. This active metabolite irreversibly binds to $P2Y_{12}$, a fibrinogen receptor on platelets which results in inhibition of platelet aggregation. Inconsistent findings have been reported associated with variants in the P2Y12 receptor. Polymorphisms in CYP2C19 have been identified and specific loss of function alleles (CYP2C19*2) have been associated with significantly decreased concentrations of the active metabolite increasing the risk of thrombosis or adverse cardiovascular events. Clopidogrel labeling for adults includes a boxed warning in CYP2C19*2 carriers to consider alternative antiplatelet therapy [3–5].

Like adults, interpatient variability in clopidogrel anti-platelet response has been reported in the pediatric population using age and dose matched patients. Clopidogrel pharmacogenomics in the pediatric population has yet to be studied and is more of a complex interaction given the developmental variability of the CYP2C19, CYP1A2, CYP2B6, CYPC9 and CYP3A4/5 enzymatic pathways [5].

3.4   Beta-Adrenergic Blockers

Beta-adrenergic blockers (β-blockers) are used for the treatment of hypertension and heart failure in the pediatric population. They have also been used for their antiarrhythmic potential. Adrenergic receptors β1 and β2 encode the ADRB1 and ADRB2 genes respectively. Specific polymorphisms and variants of these genes have been associated with alterations in enzyme function or regulation (ADRB1 with Ser49Gly and Arg389Gly; ADRB2 with Gly16Arg and Glu27Glu). Variable therapeutic outcomes have been reported and most commonly associated with the ADRB1 Arg389Gly polymorphism. Although the data is inconsistent, one study with metoprolol and carvedilol associated this variant with greater left ventricular ejection fraction improvement, lower mortality and better antihypertensive response. Other data suggests there is no genetic association on antihypertensive effect with several of the other β-blockers, including atenolol. Many of the β-blockers utilize the CYP-450 pathway for metabolism, specifically for metoprolol, CYP2D6 is responsible for 60–70 % of its metabolism [3–5]. Polymorphisms associated with this enzyme have been associated with five times more adverse effects as well as enhanced antihypertensive effects. Other evaluations of the impact of CYP-450 metabolic variants have not been as conclusive with metoprolol or any of the other β-blockers [3, 5].

Pharmacogenomic effects on β-blockers have made it to the labeling of metoprolol, propranolol and carvedilol remarking on drug interactions, clinical pharmacology and

warnings/precautions. Specific dosage adjustments or recommendations in adults require further investigation. The applicability of this information to the pediatric population has yet to be studied [5].

3.5 Renin-Angiotensin-Aldosterone System Inhibitors

The renin angiotensin aldosterone system (RAAS) plays a vital role in regulation of electrolytes and blood pressure, mostly arising from the actions of angiotensin II. Angiotensin I is converted to angiotensin II by the angiotensin converting enzyme (ACE). Inhibition of this enzyme gives rise to many therapeutic pathways in adults and pediatrics, including hypertension, heart failure and renal disease. Several pharmacogenomic variants involving RAAS inhibition have been investigated and the results are inconclusive. There have not been consistent effects as a result of pharmacogenomic variants on blood pressure, mortality or myocardial infarction risk for ACE-inhibitors or angiotensin receptor blockers in any sort of reproducible form [5].

3.6 HMG-CoA Reductase Inhibitors: Statins

HMG-CoA reductase inhibitors (statins) are used in the adult population for primary and secondary prevention of cardiovascular disease. Two genes, HMGCR and LDLR, have been associated with pharmacodynamic variations in LDL response to statins. A polymorphism associated with KIF6 has also been identified and account for only small percentage differences in LDL response. Genetic variants involving the CYP-450 metabolic pathway of some of the statins, specifically CYP3A4/5, are associated with some of the variability in response. Variants of CYP 3A4 and SLCO1B1 have been investigated to determine their impact on the statin-related myotoxicity. Only the SLCO1B1 genotype has been

associated with myotoxicity risk with high dose simvastatin but the clinical utility of this remains unknown [3, 4]. The limited use of statins in the pediatric populations limits the ability for this to be studied and at this time has minimal applicability.

3.7 Drug Induced Prolong Qt Syndrome

Drugs with the propensity to cause QT prolongation (cardio-vascular and noncardiovascular medications) may have enhanced capabilities of this if the patient carries polymorphisms associated with metabolic pathways of that particular medication. Many of the medications that cause drug induced prolonged QT syndrome are metabolized through the CYP2D6 and CYP3A4/5 pathways. Similar to drug interactions that inhibit these metabolic pathways and lead to increased serum concentrations of the offending agent, genetic variations affecting these pathways can also lead to prolonged QT syndrome [3–5]. For pediatrics specifically, the developmental stages of the CYP450 pathway may alone be a more important variable to drug induced prolonged QT syndrome and requires further investigation of associated risk of genetic variants [5].

3.8 Application of Pharmacogenomics

The clinical relevance of pharmacogenomics is impacted by the frequency of use of the involved drug, the therapeutic index of the drug, alternative clearance pathways of the drug, alternative therapies, and the differences in activity or toxicity between the parent drug and the metabolite [1]. Factors affecting the introduction of pharmacogenomics into clinical practice largely rely on accessibility of resources. Availability of testing, financial support or reimbursement for testing, and interpretation of results are all important components to enable application of pharmacogenomics [6]. Drug labeling includes classification of testing by "test required," "test recommended" or "information only" [6]. Table 3.1 depicts the current FDA approved drugs with pharmacogenomic biomarkers on drug labels [8].

TABLE 3.1 Current FDA approved drugs with pharmacogenomic biomarkers on drug labels [8]

Drug	Biomarker	Label section
Atorvastatin	LDL receptor	Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Carvedilol	CYP2D6	Drug Interactions, Clinical Pharmacology
Clopidogrel	CYP2C19	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology
Isosorbide and Hydralazine	NAT1; NAT2	Clinical Pharmacology
Metoprolol	CYP2D6	Precautions, Clinical Pharmacology
Prasugrel	CYP2C19	Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Pravastatin	ApoE2	Clinical Studies, Use in Specific Populations
Propafenone	CYP2D6	Clinical Pharmacology
Propranolol	CYP2D6	Precautions, Drug Interactions, Clinical Pharmacology
Ticagrelor	CYP2C19	Clinical Studies
Warfarin	CYP2C9 VKORC1	Dosage and Administration, Precautions, Clinical Pharmacology

3.9   Conclusion

Pharmacogenomics is a rapidly emerging area of medicine that has made significant progress over the past decade. Optimizing therapeutic outcomes and minimizing adverse events associated with medication use is the future of pharmacogenomics with much needed research and development. The challenges are discovery, delineation of clinical

application, economic benefit and analysis of outcomes [3]. The majority of pharmacogenomics has been investigated in adults. Applying these findings to the pediatric population directly is not always appropriate as developmental differences and other pharmacokinetic and pharmacodynamic variables may have more significance in determining the optimal dosing regimen. The pediatric warfarin pharmacogenomic study is an example of this finding and displays the importance for pediatric focused pharmacogenomic studies [5].

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Chapter 4
Pharmacoeconomics

**Andrea R. Chamberlain, Jaclyn E. Sawyer,
and David S. Cooper**

Abstract Pharmacoeconomics is the description and analysis of the costs and outcomes associated with drug therapies and pharmaceutical services to health care systems, society, and individuals. Due to the changes in private and public insurance reimbursement, this has become an area of increased interest for both payers and care providers. There is a lack of pediatric data in this area of research, but by combining clinical knowledge of the treatment of pediatric cardiovascular disease with pharmacoeconomic analyses performed in adult patients this information can be used to help make cost efficient choices in the care of pediatric patients.

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J.E. Sawyer, PharmD • A.R. Chamberlain, PharmD, BCPS (✉)
Division of Pharmacy, Cincinnati Children's Hospital
Medical Center, 3333 Burnet Ave, ML 15010,
Cincinnati, OH 45229, USA
e-mail: andrea.chamberlain@cchmc.org

D.S. Cooper, MD, MPH
Department of Pediatrics, Cardiac Intensive Care Unit,
The Heart Institute, Cincinnati Children's Hospital
Medical Center, University of Cincinnati College of Medicine,
Cincinnati, OH, USA

4.1   Pharmacoeconomics

Due to the changes in healthcare reimbursement, it is important that practitioners think about the improvement in patient outcomes expected secondary to treatment. The effect of the treatment on morbidity and mortality should be considered and compared to the cost of the intervention to the patient and insurance. Pharmacoeconomic analysis provides this necessary information and helps to answer the following questions: What drugs should be added to formulary? Will patient quality of life be improved by a particular drug therapy? What is the best drug for this particular disease? [1]

Pharmacoeconomics is the description and analysis of the costs and outcomes associated with drug therapies and pharmaceutical services to health care systems, society, and individuals. Pharmacoeconomic research identifies, measures, and compares the costs and consequences of pharmaceutical products and services. The research methods for pharmacoeconomic research includes cost-minimization, cost-effectiveness, cost-benefit, cost-of-illness, cost-utility, cost-consequences, and decision analysis as well as taking into account quality-of-life and humanistic assessments. Pharmacoeconomic analysis examines the impact of alternative drug therapies and other medical interventions to help guide health care providers to the lowest cost therapeutic option with the most benefit [1, 2] (Table 4.1).

4.1.1   Direct and Indirect Costs

Direct and indirect costs must be taken into consideration when performing pharmacoeconomic analyses. Below are the different types of cost that can be assessed (Table 4.2).

The health economic outcomes model is a continuous process. Using data from pharmacoeconomic and clinical research, standardized treatment protocols and quality standards should be implemented with the goal being to achieve pre-set outcomes or endpoints. Treatment protocols should

TABLE 4.1 Economic and humanistic pharmacoeconomic evaluations

Quantitative analysis tool	Description	Notes
Cost of illness	Identify which diseases and health problems should be targeted and help categorize direct and indirect costs	Have been performed on most common disease states such as asthma and cardiovascular disease to determine cost
Cost minimization	Compare costs of available treatments with the same clinical efficacy	Find the least expensive way to attain the same therapeutic endpoint
Cost benefit	Measures cost and benefits of treatment alternatives in dollars or monetary units	Difficult due to monetary figures being placed on parameters such as decrease in diastolic blood pressure or time to reach therapeutic endpoint
Cost effectiveness	Measures relationship of cost in dollars/ monetary units to therapeutic objectives or effectiveness	Comparing the cost of different drugs to their percent reduction in systolic blood pressure
Cost utility	Measures costs in monetary units and outcomes as patient preferences or quality of life	The costs of blood pressure management would be adjusted by the number of years of life gained and the patient's quality of life

Table created with information included in Bootman et al. [2] and Bungay and Sanchez [3]

be designed using clinical and economic information from randomized-controlled trials when possible. Individual patient monitoring is imperative when implementing new protocols or interventions to properly measure the patients'

TABLE 4.2 Types of costs used in pharmacoeconomic evaluations

Type of cost	Definition
Direct medical costs	Costs incurred for medical products and services used to prevent, detect, and treat a disease
Direct non-medical costs	Costs of non-medical services that are a result of illness but do not involve medical services
Indirect medical costs	Costs of morbidity and mortality resulting from illness or disease
Intangible costs	Costs associated with pain and suffering and other non-medical outcomes of disease
Opportunity costs	Money spent on resources that cannot be spent for other things

Table created with information included in Bungay and Sanchez [3]

clinical and economic outcomes. After individualized data is gathered, analysis of the patient outcomes should be completed. The final and most important step is to continuously analyze and translate the data and feedback to improve procedures, protocols, and guidelines [2].

4.2   Cardiovascular Pharmacoeconomics

Cardiovascular disease remains the leading cause of death in the United States with a high economic burden, so there is a large focus on primary and secondary prevention and the pharmacoeconomics of such interventions. The total direct and indirect cost of cardiovascular disease (CVD) and stroke in the United States for 2008 was estimated to be $297.7 billion [4]. CVD costs more than any other diagnostic group including cancer. An estimated 82,600,000 American adults (>1 in 3) have 1 or more types of CVD (hypertension or coronary heart disease including stroke, heart failure, angina, congenital heart disease, or MI). Of these, 40,400,000 are estimated to be ≥60 years of age [4].

It is estimated that congenital cardiovascular defects make up 650,000–1,300,000 of those with CVD [4]. Congenital cardiovascular defects are the most common type of birth defect and cause more deaths in the first year of life than any other congenital defect [5]. The medications used for care of pediatric patients with cardiovascular disease are predominantly extrapolated from the wealth of knowledge in adult patients, case studies, or small scale trials. There are limited pharmacoeconomic analyses specifically targeting drug therapy in pediatric patients or in those with congenital heart disease. Since most pediatric patients have more potential years of life than certain adults with CVD, the economic impact and increased quality adjusted life years could be greater in this particular group. By combining clinical knowledge of the treatment of pediatric cardiovascular disease with the multitude of pharmacoeconomic analyses performed in adult patients, this information can be used to help make cost efficient choices in the care of pediatric patients.

4.2.1   Hypercholesterolemia

When long term effects of cholesterol control were first analyzed for secondary prevention, cholestyramine was the drug most commonly used. Cholestyramine use resulted in high costs due to its poor efficacy. Cholesterol is now a major target for secondary prevention post-myocardial infarction (MI) and with the introduction of highly effective β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors as part of standard therapy, costs have decreased compared to the increased efficacy.

HMG Co-A reductase inhibitors (statins) have proven survival benefits in adults based on several large scale placebo-controlled trials. The Scandinavian Simvastatin Survival Study demonstrated that the lipid lowering properties of simvastatin also decreased morbidity and mortality in patients with coronary artery disease [6]. The West of Scotland Coronary Prevention Study used pravastatin in men with no history of myocardial infarction but moderate

hypercholesterolemia for prevention of coronary events. The investigators found a 30 % reduction in fatal and nonfatal coronary events compared to placebo with coronary angiography and revascularization also being lower [7].

Data for statin therapy shows that with generic statin availability, they may be cost-effective for more of the population. Statins are very cost-effective and even more so now that simvastatin and pravastatin became available as generic in 2006 and lovastatin in 1999 [8]. An analysis found that generic simvastatin 40 mg daily would cost less than $1,350 per life year gained for those with an annual risk of major vascular events of 1 % or more, regardless of their age when simvastatin was started [9].

Goldman et al. evaluated the cost-effectiveness of HMG-CoA reductase inhibitors in primary and secondary prevention of coronary heart disease (CHD). They used a computer simulation model to estimate the incidence of heart disease based on risk factors and the risk of recurrent coronary events in people with pre-existing coronary disease. They used the model to estimate the cost effectiveness of lovastatin among population subsets. They found that the use of lovastatin for primary prevention was cost-effective for men 35–44 years old with hypertension, smokers, and those >13 % over ideal body weight. They concluded that lovastatin is most cost-effective for men, older patients, and patients at higher risk for CHD [10].

4.2.2   Heart Failure

Heart failure is a significant source of health care spending and is an important disease for cost-effectiveness analysis [11]. Multiple studies in adults have shown a decrease in all-cause and cardiovascular mortality with angiotensin converting enzyme (ACE) inhibitors, and they are also cost saving and cost effective compared with standard congestive heart failure (CHF) treatment with digoxin and diuretics. Prior to the data for ACE inhibitors, cost savings had only been documented

for beta-blockers [12]. ACE inhibitors are a mainstay and first line therapy in patients with heart failure. ACE inhibitors in combination with hydralazine and a nitrate have been shown to prolong life [13–15] and enalapril delays the development of CHF and decreases hospitalization in patients with left ventricular dysfunction [16]. Captopril prevents the development of CHF post myocardial infarction [17]. Fosinopril has shown a reduction in hospitalizations and better exercise tolerance in patients with CHF [18, 19].

ACE inhibitors cost-effectiveness in the treatment of heart failure has been evaluated in a number of large-scale clinical trials, including the Survival and Ventricular Enlargement (SAVE) study [20, 21] and the Veterans Administration Cooperative Vasodilator Heart Failure Trials (V-HeFT II) [15]. The SAVE study was a double blind placebo controlled trial of 2,231 patients with left ventricular dysfunction and ejection fraction ≤40 % without overt symptoms of heart failure [17]. Patient received either captopril or placebo post-MI. In the captopril group, there was reduced overall mortality, death from cardiovascular causes, development of CHF, and recurrent MI. A cost-effective analysis was done examining captopril post-MI by the German Statutory Insurance Fund. They demonstrated a cost-effectiveness ratio of $1,160 USD per life-year gained [21]. A study that extrapolated data from the SAVE trial assuming the same benefit persisted concluded that the cost-effectiveness of captopril therapy depends on the age of the patient when therapy is initiated [20].

In the V-HeFT-II trial (Veterans Administration Cooperative Vasodilator Heart Failure Trial), compared the effects of hydralazine and isosorbide dinitrate with enalapril in men with CHF receiving digoxin and diuretics [15]. Mortality was lower after 2 years in the group receiving enalapril (18 % vs. 25 %) [15]. An evaluation of the cost-effectiveness comparing these therapies found an incremental expense for isosorbide dinitrate-hydralazine of $5,600 USD/year of life saved compared to $9,700 USD/year of life saved for enalapril [21]. The authors concluded that, although more expensive, therapy with enalapril may be justified

based on the number of lives saved [21]. Angiotensin receptor blockers have not been proven more efficacious than ACE inhibitors and although not officially studied, are unlikely to be cost-effective without generic alternatives [22].

4.2.3   Hypertension

Hypertension is the most common cardiovascular condition in the United States and it has increased over the past two decades in the pediatric population potentially related to the increase in childhood obesity [23, 24]. Effective blood pressure control reduces cardiovascular risk and prevents later complications. It is important to ensure that the best treatment option is in use for patients with the lowest cost to the health care system. The cost-effectiveness of anti-hypertensives is directly related to the cost of the drug itself [25]. Older, less expensive medications such as diuretics and beta-blockers are more cost-effective [26]. Hoerger et al. found that the combination of hydrochlorothiazide with bisoprolol was more cost effective than a calcium-channel blocker or ACE-inhibitor. They estimated that the acquisition cost of enalapril would have to decrease by ~58 % and amlodipine by ~51 % to equal the cost-effectiveness of bisoprolol plus hydrochlorothiazide [25]. Chlorthalidone has been shown to be more effective than an ACE-inhibitor in lowering blood pressure and at least as effective as calcium channel blockers and ACE inhibitors in preventing cardiovascular events. However, JNC7 guidelines recommend initial choice of antihypertensive medication(s) be based on other compelling indications when present and the severity of hypertension, so the cost-effectiveness of diuretics does not make them ideal in all clinical situations [27]. Patients who should be started on thiazide diuretics as first line treatment include those without history of stroke, myocardial infarction, diabetes, chronic kidney disease, systolic heart failure, or those with high CVD risk [27]. Beta-blockers and thiazide diuretics are the most cost effective options for hypertension and should be considered as first line therapy when clinically appropriate.

4.2.4   Venous Thromboembolism

Venous thromboembolism is a significant problem that affects one million people in the United States every year. Of those events 100,000–200,000 events are fatal [28–30]. Approximately two thirds of all symptomatic venous thromboembolic events occur in the hospital with some surgical and general medical patients being at comparable risk based on risk factors [30–33]. The treatment of venous thromboembolism has an estimated cost to the health care system of $1.5 billion/year [34].

The incidence of hospital acquired venous thromboembolism is lower in pediatric patients, but it is not uncommon in post-pubescent critically ill adolescents and is costly when it occurs [35]. The cost of managing an initial episode of deep vein thrombosis is estimated at $7,712–10,804 and for an initial pulmonary embolism event $9,566–16,644 which increase with co-morbidities [36, 37]. Although much of the costs of venous thromboembolism are associated with managing the acute event, there are also significant costs associated with its long-term complications such as recurrent venous thromboembolism, post-thrombotic syndrome, and pulmonary hypertension [37, 38]. It is clear based on numerous clinical trials that appropriate prophylaxis or VTE can prevent the majority of these events from occurring.

There have been studies conducted based off of the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial data that determined that thromboprophylaxis with unfractionated or low molecular weight heparin was cost effective compared to no prophylaxis with the cost of prophylaxis of $1,249–3,088/venous thromboembolic event avoided [33, 39–41]. A low-molecular weight heparin thromboprophylaxis regimen was more cost-effective when the incremental cost for each thromboembolic event was taken into consideration and due to the lower incidence of heparin induced thrombocytopenia [41, 42].

Despite guidelines for the use of thromboembolism prophylaxis, adherence to these guidelines is poor [43]. Because

of changes in hospital reimbursement, hospitals have been required to develop the necessary documentation to show appropriate venous thromboembolism prophylaxis protocols for both surgical and medical patients. There is both a clinical and economic impact to not using thromboprophylaxis appropriately and the Joint Commission and National Quality Forum have identified this as an area in hospitals in need of improvement [44].

4.3   Conclusion

The impact and treatment of cardiovascular disease can be measured in both economic and humanistic terms. With direct and indirect costs being such a large portion of health care expenditures, it is important to use the available pharmacoeconomic data to make cost efficient and evidence based treatment regimens. Cost-effectiveness analyses are the most commonly performed pharmacoeconomic analyses for formulary decisions, and the application of these results can help to guide therapeutic choices. Since there is a lack of pediatric data in this area of research, it is important for providers to combine their clinical knowledge of the treatment of pediatric cardiovascular disease with pharmacoeconomic analyses performed in adult patients to make cost efficient choices in the care of pediatric patients.

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Chapter 5
Vasoactive Drugs in Acute Care

Eduardo M. da Cruz, Jonathan Kaufman, Grant Burton, Jennifer Eshelman, Cécile Tissot, and Cindy Barrett

E.M. da Cruz (✉) • J. Kaufman, MD • C. Barrett, MD
Pediatric Cardiac Intensive Care, Department of Pediatrics,
The Heart Institute, Children's Hospital Colorado,
University of Colorado Denver, School of Medicine,
Aurora, CO, USA
e-mail: eduardo.dacruz@childrenscolorado.org

G. Burton, MD
Congenital Heart Surgery Unit (CHSU),
Medical City Children's Hospital, Dallas, TX, USA

J. Eshelman, PharmD
Department of Pharmacy,
Children's Hospital Colorado,
Aurora, CO, USA

C. Tissot, MD
Division of Pediatrics-Cardiology,
Department of Pediatrics, Geneva University Children's Hospital,
Geneva, Switzerland

Abstract Cardiovascular dysfunction is a common feature of pediatric critical illness. Infants and children with congenital or with acquired cardiovascular diseases may exhibit compromised hemodynamics that require careful consideration when deciding which medications to select or combine. Vasoactive drugs are a cornerstone in the therapy of medical or post-operative patients with cardiovascular dysfunction. This chapter provides an overview of the most commonly used vasoactive drugs.

5.1 Introduction

Cardiovascular dysfunction is a common feature of pediatric critical illness [1]. Infants and children with congenital or with acquired cardiovascular diseases may exhibit compromised hemodynamics [2–4] that require careful consideration when deciding which medications to select or combine. Vasoactive drugs are a cornerstone in the therapy of medical or post-operative patients with cardiovascular dysfunction. In the context of cardiac surgery, the low cardiac output syndrome (LCOS) and dysregulation of the vascular tone remain one of the most important causes of morbidity and mortality in the immediate postoperative phase [5, 6], particularly in newborns

and infants. This population is particularly vulnerable due to variable and developmental differences in pulmonary and systemic vascular tone. It is not surprising that there is a paucity of consensus and evidence based guidelines in the use of vasoactive drugs in this population. As is the case in much of pediatrics there is a need to pursue collaborative, multi-center studies in order to determine what the best practice may be.

5.1.1   Brief Clinical Background and Decision-making Notions

Regardless of the etiology of cardiovascular dysfunction in the pediatric population, medical treatment must be based upon a comprehensive hemodynamic and pathophysiological appraisal [7–13], and utilizing tools that evaluate the final objective of the cardiovascular system: *adequate tissue perfusion* and not necessarily or exclusively systemic arterial pressure as measured invasively or non-invasively. All therapies and interventions must identify adequate tissue perfusion as the goal. Thus, patients on vasoactive drugs require a comprehensive hemodynamic monitoring in the intensive or intermediate care setting.

Vasoactive medications are usually administered with the perspective that short to medium-term clinical recovery will be facilitated by enhancement of cardiac output or vascular tone that has been severely compromised, whilst trying to preserve myocardial reserves and integrity of peripheral receptors [14]. No single agent is universally superior and polypharmacy, a combination of multiple vasoactive agents, is almost always employed.

The main physiological factors related to cardiac performance to be assessed are *heart rate*, *contractility*, *preload* and *afterload*. These entities may be clinically assessed and measured by non-invasive and invasive techniques. It is also crucial to keep in perspective the importance of the evaluation and the ratio between *systemic and pulmonary resistances*, the appraisal of both *right and left-sided cardiac function* and without obviating the importance of *diastolic* disturbances. Particular attention ought to be made to *cardiopulmonary and interventricular interactions*. Other factors to evaluate include aspects related to *oxygenation transport*, *extraction*

and consumption. Markers of *tissue perfusion* remain an expression of the ultimate therapeutic goal.

Pharmacological management of cardio-circulatory dysfunction is complex and targets two main receptor sites, firstly, the myocardial receptors and secondly the systemic and pulmonary vascular receptors. Vasoactive drugs are characterized as vasopressors, vasodilators, chronotropes, inotropes, and lusotropes. Most vasoactives have multiple effects and often influence the myocardium and the vascular endothelium [15–18].

Inotropic drugs mainly include sympathomimetics, phosphodiesterase inhibitors, digoxin, and probably calcium-sensitizers, and play a vital role on the myocardial and vascular performance [6, 9, 10, 18, 19]. Different issues have to be considered in order to select the proper inotropes that might be used alone or in association with drugs that target systemic or pulmonary vascular receptors. Selection criteria include a wide array of aspects related to pathophysiology of the cardiac or circulatory dysfunction and should be balanced against the potential adverse effects and drug interactions that might be deleterious or even life-threatening. It is essential to distinguish between the drug properties that support the heart and those that involve peripheral circulation.

The use of these drugs may be limited by significant increases in myocardial oxygen consumption, pro-arrhythmogenic effects or neuro-hormonal activation. Also, adrenergic receptors can be desensitized and down-regulation may occur in certain conditions [20]. Caregivers ought to consider that beta receptor-down-regulation phenomenon may arise particularly with prolonged use of catecholamines. Last but not least, the relative binding affinities of individual inotropes and vasopressors to adrenergic receptors can be altered by temperature, hypoxia or acidosis [21–25].

A solid clinical and physiological knowledge is required to choose effective drug combinations and obtain maximal effects with minimal efficient doses, and with the lowest risks possible for deleterious side-effects or interactions.

V*asodilators* are pharmacologic agents that produce relaxation of smooth muscle in the wall of blood vessels, leading to reduced vascular resistance and the potential for increased blood flow. Some vasodilators act on arterial vessels, others on

venous vessels, and a third group on both arteries and veins. Vasodilators can be classified according to their predominant site of action or by their mechanism of action. Pharmacologic reduction of afterload or systemic vascular resistance (SVR) has become increasingly important in the management of pediatric cardiac patients, just as it has for adult cardiac patients. Specifically, the principal groups of pediatric patients with cardiovascular disease who may benefit from afterload reduction therapies include the following:

1. Patients with normal cardiac anatomy and myocardial function who have systemic hypertension;
2. Patients with normal cardiac anatomy but impaired myocardial function, either due to primary myocardial disease (e.g., familial cardiomyopathy), or acquired myocardial disease (e.g., dilated cardiomyopathy secondary to viral myocarditis);
3. Patients with congenital heart disease (CHD) who have undergone palliative (e.g., the modified Norwood procedure for hypoplastic left heart syndrome) or reparative surgery and developed myocardial dysfunction;
4. Patients with CHD who develop myocardial dysfunction immediately or early after cardiac surgery, especially with cardiopulmonary bypass surgery.

Lusitropic drugs are medications that improve diastolic relaxation. The only widely clinically available and most studied lusitropic medications are phosphodiesterase inhibitors, particularly milrinone that combines inotropic, vasodilator and lusitropic effects. Levosimendan is another drug with similar effects, although it still ought to be further studied in the pediatric population.

Vasoconstrictors are drugs that target peripheral systemic and/or pulmonary circulation with more or less specific effects. Some of these drugs have an inotropic action and others act specifically in peripheral receptors. In the cardiovascular intensive care scenario, these drugs are mainly used for situations of severe vasoplegia or to antagonize a marked vasodilator effect of other drugs or to modulate vascular tone.

A combination of inotropic and vasoconstrictor drugs may be required in such circumstances.

5.2   Inotropic Drugs

5.2.1   Digoxin

Indication:

Digoxin is the oldest cardiac medication used in contemporary medicine [26]. It is a cardiac glycoside employed in the therapy of congestive cardiac failure and as an anti-arrhythmic agent that decreases ventricular rate in cases of tachyarrhythmia, including in fetal patients [27–29]. Although still widely used, few clinical trials have provided evidence for a consistent clinical efficacy in the pediatric population. Taking into account the potential for toxicity and the lack of evidence-based data supporting its use, this drug has fallen out of favor [30–33] and is not currently first line therapy for heart failure in children. Paradoxically, digoxin is the most widely prescribed anti-arrhythmic and inotropic agent.

Its popularity and reliance on (in some populations) may be due to the fact that it is one of the few oral heart failure (or inotropic) medications.

Mechanisms of action:

Digoxin has a miscellaneous action, with hemodynamic, sympatholytic and electrophysiologic effects [34]. There are both direct (due to binding to the Na^+-K^+ ATPase transport complex) and indirect (autonomic effects mediated by the parasympathetic nervous system) properties. Firstly, by inhibition of the sodium and potassium ion motion across the myocardial membrane, it increases the influx of calcium ions from the extracellular to the intracellular cytoplasm. Secondarily, it potentializes the myocardial activity and contractile force by an inotropic effect. Secondly, it inhibits ATPase and decreases the conduction through the sinus and the atrioventricular nodes. Thirdly, it increases the parasympathetic cardiac and arterial baroreceptor activity which decrease central sympathetic outflow exerting a favorable neurohormonal effect. However, evidence of

increased contractility does not consistently correlate with clinical improvement.

Dosing:

The doses described below are recommended for patients with normal renal function [35–37]. Digoxin may be considered as a non-identified high-alert medication for Safe Medications Practices list [38], which should raise the level of caution when administered. As a matter of fact, digoxin is classified as a high risk drug related to cardiovascular medication errors in children [39]. Loading doses should be administered in three divided doses. One half of the total loading dose should be administered first, then one quarter of the total loading dose should be given every 6-8 hours for two additional doses. Maintenance doses should be divided twice daily in children less than 10 years of age and given once daily in children 10 years and older. Parenteral administration is preferred in the intensive care setting since oral absorption may be erratic due to congestive heart failure and to the systematic use of antacids (Table 5.1).

TABLE 5.1 Digoxin dosing

Age group	Oral		Intravenous	
	Loading dose	Maintenance dose	Loading dose	Maintenance dose
Neonates:				
Preterm:	20 µg/kg	5–8 µg /kg/day	15 µg/kg	3–4 µg/kg/day
Term:	30 µg /kg	6–10 µg /kg/day	20 µg/kg	5–8 µg/kg/day
Infants/Children:				
1 month-2 years:	40–60 µg /kg	10–12 µg /kg/day	30–40 µg/kg	7.5–12 µg/kg/day
2–5 years:	30–40 µg /kg	7.5–10 µg /kg/day	20–30 µg/kg	6–9 µg/kg/day
5–10 years:	20–30 µg /kg	5–10 µg /kg/day	15–30 µg/kg	4–8 µg/kg/day
>10 years:	10–15 µg /kg	2.5–5 µg /kg/day	6–12 µg/kg	2–3 µg/kg/day
Adults:	0.75–1.5 mg	0.125–0.5 mg/day	0.5–1 mg	0.1–0.4 mg/day

Patients with renal failure require close monitoring of serum concentration. Loading dose is to be reduced by 50 % and maintenance dose should be adapted to creatinine clearance: if between 10 and 50 ml/min, administer 25–50 % of daily dose at normal intervals or administer normal dose every 36 h; if below 10 ml/min, administer 10–25 % of normal daily dose given at normal intervals or administer normal dose every 48 h.

Pharmacokinetics:

Onset of action: Oral: 0.5–2 h; I.V.: 5–30 min

Bioavailability:

I.V.: 100 %
Capsules: 90 %
Elixir: 80 %
Tablets: 70 %

Onset of action: I.V.: 5–30 min; Oral: 0.5–2 h
Distribution phase: 6–8 h
Maximum effect: Oral: 2–8 h; I.V.: 1–4 h
Protein binding: 20–30 %.
Metabolism: most of the drug is eliminated unchanged by the kidney
Half-life: Preterm neonates: 60–170 h; Full-term neonates: 35–45 h; Toddlers: 18–25 h; Children: 35 h; Adults: 38–48 h
Elimination: 50–90 % of renal excretion. **Digoxin is not dialyzable**.

Drug interactions:

Drugs that may increase digoxin concentration or effect	Drugs that may decrease digoxin concentration or effect
Diuretics:	
Furosemide, spironolactone, amiloride, triamterene	Rifampicin
Antiarrhythmics:	Liquid antacids
Verapamil, quinidine, amiodarone, propafenone	Cholestyramine

Drugs that may increase digoxin concentration or effect	Drugs that may decrease digoxin concentration or effect
	Neomycin
Calcium antagonists:	Colestipol
Verapamil, nifedipine, diltiazem	Penicillamine
HMG CoA reductase inhibitors:	Phenytoin
Atorvastatin, simvastatin	Sulafasalazine
Antibiotics:	Thyroid hormone
Erythromycin, clarithromycin, roxithromycin, tetracyclines	
Benzodiazepines:	
Alprazolam	
Other:	
Ketoconazole, itroconazole, cyclosporine, indomethacin, Diphenoxylate, NSAIDs	

Adverse effects:

>   Digoxin has a complex pharmacokinetic profile and narrow therapeutic index and dosing may need to be adapted to patient-specific factors (i.e., age, lean body weight, renal function) in order to minimize drug toxicity and side effects [1, 40].
>   **Cardiovascular**: dysrhythmias especially induction of ectopic pacemakers and impaired conduction, sinus bradycardia, atrioventricular block, sinus block, atrial ectopic beats, bi and trigeminy, atrial tachycardia with AV block, ventricular arrhythmias.
>   **Gastrointestinal**: nausea, vomiting, diarrhea, abdominal pain, lack of appetite or intolerance to feeding
>   **Metabolic**: hyperkalemia with toxicity
>   **Central nervous system**: fatigue, somnolence, drowsiness, vertigo, disorientation, asthenia
>   **Neuromuscular & skeletal**: neuralgia, myalgia

Ophtalmologic: blurred vision, photophobia, diplopia, flashing lights, aberrations of color vision
Other: gynecomastia

Contraindications:

Digoxin is contraindicated in patients with subaortic obstruction, hypertrophic cardiomyopathy and in patients with severe electrolyte or acid-base disturbances (hypokalemia, alkalosis) or metabolic disorders (hypothyroidism). Acute rheumatic fever with pancarditis is a relative contraindication as well.

Poisoning information:

Digoxin therapeutic levels should be monitored in the following circumstances: suspicion of toxicity, therapeutic failure, lack of compliance with the drug intake, renal dysfunction and association of drugs that might modify digoxin concentrations. Levels should be drawn at least 6 hours after a dose or just prior to a dose [41–43].

Conditions predisposing to toxicity: high dose, high serum digoxin levels, decreased renal function, hypothyroidism, drug interactions, increased myocardial sensitivity, myocarditis, myocardial ischemia, hypokalemia, hypomagnesemia, hypernatremia, acidosis, catecholamines, immediate cardiac postoperative period [36, 44].

Clinical signs of poisoning: weakness, fatigue, lack of appetite, nausea, vomiting, diarrhea, visual disturbances, headache, confusion, somnolence, agitation or delirium, hallucinations, neuropathic pain, seizures, arrhythmias, palpitations, syncope, dyspnea

EKG signs of toxicity: premature ventricular contractions, ventricular bigeminy, atrioventricular block, supraventricular tachycardia, junctional tachycardia, ventricular arrhythmias

Laboratory: serum potassium, calcium and magnesium levels and renal function should be immediately monitored. Digoxin serum concentrations: usually, toxicity

is associated with levels >2 ng/ml (normal therapeutic range: 0.8–2 ng/ml).

Treatment: suspicion of poisoning justifies immediate admission to hospital for specific antidote therapy with *Digoxin Immune Fab* in selected patients: in case of life threatening arrhythmias (ventricular dysrhythmia, supraventricular bradyarrhythmia unresponsive to atropine), hyperkalemia, hypotension or acute ingestion of toxic doses of the drug.

Dose of Digoxin immune Fab: *serum digoxin (nmol/ml) × kg × 0.3, or mg ingested × 55 (if ingestion >0.3 mg/kg)*

Close monitoring of potassium levels (risk of hypokalemia) and of hemodynamic parameters is recommended. Digoxin serum levels might acutely rise but it will be almost entirely bound to Fab fragments, thus unable to react with receptors and this might be a *misleading laboratory information*. Digoxin and Fab complexes will be slowly eliminated over around a week.

Other measures include:

1. Ipecac, charcoal even several hours after ingestion of oral digoxin
2. If digoxin Fab are not immediately available and in case of dysrhythmia:
3. Ventricular tachyarrhythmia: consider using phenytoin, lidocaine or bretylium
4. Ventricular and supraventricular tachydysrhythmia: use propranolol
5. Sinus bradycardia or AV block: use atropine or phenytoin
6. Consider transvenous pacing and cardioversion if necessary

Compatible diluents:

Oral digoxin should ideally be administered 1 h before or 2 h after meals, in order to avoid erratic absorption secondary to diets rich in high fiber or pectin content.

Attention must drawn to other drugs that might affect digoxin absorption.

I.V. digoxin may be administered undiluted or diluted in normal saline or in dextrose solutions, over 10 min. Rapid administration might be hemodynamically deleterious.

Standard concentrations:

Elixir (**Pediatric**): 50 μg/ml (2.5, 5 and 60 ml)
Capsules: 50, 100 and 200 μg
Tablets: 125, 250 and 500 μg
Injection solution:

Pediatric ampoules: 100 μg/ml (1 ml)
Adult ampoules: 250 μg/ml (1 and 2 ml)

Generic/Brand® **Names**:

Yes/Lanoxin®, Lanoxicaps®, Digitek®, Digoxine Nativelle®, Novo-Digoxin®, Digoxine-Streuli®, Digoxine-Sandoz®

5.2.2   Dobutamine

Indication:

Dobutamine is a synthetic adrenergic agonist, or sympathomimetic agent, indicated for the treatment of low cardiac output and heart failure [45]. According to the 2008 Surviving Sepsis Campaign, initiation of dobutamine is also recommended for patients with septic shock and myocardial dysfunction, or those who have not achieved an $ScvO_2$ greater than 70 % or an SvO_2 greater than 65 % following fluid resuscitation [46–48]. Dobutamine has potent β_1 activity and mild effects on β_2 and α_1 receptors that increase myocardial contractility, cardiac output, and stroke volume. Dobutamine increases blood pressure with strong inotropic effects and can cause mild systemic and pulmonary vasodilation. The β_2 receptor mediated vasodilation may be greater with dobutamine than dopamine, while the

chronotropic effects of dobutamine may be less [49, 50]. In preterm infants, dobutamine has been shown to be less effective at increasing MAP than dopamine [51, 52].

Mechanisms of action:

Dobutamine stimulates β_1-adrenergic receptors causing increased contractility and some increase in heart rate. It has less β_2 than β_1 activity and minimal α_1 effects. The cardiovascular effects of dobutamine are mediated by direct β-adrenergic activity without norepinephrine release [5]. Dobutamine also lowers central venous pressure and pulmonary capillary wedge pressure, but has no selective effect on pulmonary vascular resistances [53]. Dobutamine may improve diastolic function and when used after adequate fluid replacement it often increases urine output secondary to increased cardiac output and renal perfusion [18, 53, 54].

Dosing:

Dobutamine is administered as a continuous infusion and titrated within the therapeutic range to the minimal efficient dose necessary to achieve the desired response. It should be administered under comprehensive hemodynamic monitoring and should be avoided in hypovolemic patients. Dobutamine is contraindicated in patients with idiopathic hypertrophic subaortic stenosis [55].

Neonates: 2–20 μg/kg/min

Infants/Children: 2–20 μg/kg/min; may be increased to a maximum of 40 μg/kg/min in some circumstances

Adults: 2–20 μg/kg/min; may be increased to a maximum of 40 μg/kg/min in some circumstances

Pharmacokinetics:

Onset of action: 1–10 min

Maximum effect: 10–20 min

Metabolism: in tissues and the liver to inactive metabolites by cathecol-ortho-methyltransferase (COMT) followed by glucuronidation

Half-life: 2 min

Elimination: Renal excretion primarily with some excretion in the bile and feces

Drug interactions:

Beta-adrenergic blocking agents and calcium products may diminish the therapeutic effects of dobutamine

Adverse effects:

Cardiovascular: sinus tachycardia, ectopic beats, palpitations, hypertension, chest pain, premature ventricular contractions, ventricular arrhythmias
Gastrointestinal: nausea
Respiratory: dyspnea
Neuromuscular: paresthesia, cramps
Central Nervous System: headache
Cutaneous/peripheral: dermal necrosis (extravasation), local inflammation, phlebitis

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of dobutamine may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability). In case of extravasation, local administration of phentolamine may be indicated.

Compatible diluents:

Dobutamine is a stable product in various solutions unless alkaline, for 24 h. It is recommended to dilute it with normal saline or dextrose, with a maximal concentration of 5 mg/ml. It should be administered into a central vein, except for transient and/or urgent scenarios and should be administered using an infusion device allowing proper and reliable titration. Avoid administration into the same IV line as sodium bicarbonate, heparin, loop diuretics, and some antibiotics including cephalosporins and penicillins.

Standard concentrations:

Injection solution (**hydrochloride**): 12.5 mg/ml (20 and 40 ml vials). Also exists in premixed solutions (with 5 % dextrose) of 1, 2 and 4 mg/ml.

Generic/Brand® Names:

Yes/Dobutrex®, Dobutamine Liquid Fresenius®

5.2.3 Dopamine

Indication:

Dopamine is an adrenergic agonist, or sympathomimetic agent, with dose dependent effects indicated for the treatment of low cardiac output, heart failure, and cardiogenic or septic shock. Dopamine has moderate α_1 and β_1 receptor agonist activity with mild effects on β_2 and dopaminergic DA_1 and DA_2 receptors. The clinical effects of dopamine include increased cardiac contractility and output, heart rate, blood pressure, and in animal models it has been shown to be superior to other agents at improving mesenteric blood flow [49, 56, 57]. When used with adequate fluid replacement it may increase urine output, however the use of "renal dose" dopamine to improve renal function at low doses remains unproven [58, 59]. In preterm infants, dopamine has been shown to be more effective than dobutamine, colloid fluid, or hydrocortisone alone at increasing mean arterial blood pressure [60].

Mechanisms of action:

Dopamine is a precursor of norepinephrine that directly stimulates adrenergic and dopaminergic receptors and causes release of norepinephrine from nerve terminals. The clinical effects have been found to be dose-dependant: at *low doses* it exerts an effect on the dopaminergic receptors which produces renal, cerebral, coronary, and mesenteric vasodilation; at *intermediate*

doses it also stimulates β_1-adrenergic receptors increasing heart rate and cardiac output and stimulates indirect release of norepinephrine; at *high-doses* it activates alpha-adrenergic receptors inducing systemic and pulmonary vasoconstriction, increased heart rate, and increased blood pressure [61].

Dosing:

Dopamine is administered as a continuous infusion and is titrated within the therapeutic range to the minimal efficient dose necessary to achieve the desired response. It should be administered under comprehensive hemodynamic monitoring and avoided in hypovolemic patients [61].

The hemodynamic effects are dose-dependent and may overlap dosing ranges:

1–5 μg/kg/min (**low dosage**): increased renal and mesenteric blood flow; increased urine output

5–15 μg/kg/min (**intermediate dosage**): increased renal blood flow, heart rate, cardiac contractility, and cardiac output

>**15 μg/kg/min** (**high dosage**): systemic vasoconstriction and increased blood pressure

If doses >20 μg/kg/min are needed, and depending on the clinical requirements, more specific vasoactive medications (epinephrine, norepinephrine, vasopressin, phenylephrine, nitroprusside, phentolamine) should be considered in order to avoid marked undesirable side-effects.

Doses

Neonates: 1–20 μg/kg/min

Infants/Children: 1–20 μg/kg/min, upward titration to a maximum dose of 50 μg/kg/min may be necessary in specific and exceptional scenarios

Adults: 1–20 μg/kg/min, upward titration to a maximum dose of 50 μg/kg/min may be necessary in specific and exceptional scenarios

Pharmacokinetics:

Onset of action: 5 min

Duration: less than 10 min

Metabolism: 75 % in plasma, kidneys and liver (to inactive metabolites by monoamine oxidase and cathecol-ortho-methyltransferase) and 25 % in sympathetic nerve-endings (transformed to norepinephrine).

Half-life: 2 min

Clearance: Approximately 80 % of dopamine is excreted as homovanillic acid and norepinephrine metabolites in the urine with a small portion of the drug excreted unchanged. Dopamine clearance seems to be age and dose-related and varies significantly in children, especially in the neonatal period. It may have nonlinear kinetics in children and the kinetics seem to be altered by concomitant administration of dobutamine [62, 63]. Clearance may be prolonged by renal and hepatic dysfunction.

Drug interactions: [61]
(Table 5.2)

Adverse effects:

Endocrinological: dopamine may have some untoward neuro-endocrine effects such as alteration of prolactin, Thyrotropin-Releasing Hormone, and other pituitary hormones [64, 65]

Cardiovascular: sinus tachycardia, ectopic beats, peripheral or pulmonary vasoconstriction (*must be used cautiously in patients with elevated pulmonary artery pressure or resistances* [50]), widened QRS complexes, atrioventricular conductive abnormalities, ventricular arrhythmias, systemic hypertension (*contraindicated in patients with pheocromocytoma*), palpitations

Respiratory: dyspnea

Central nervous system: headache, anxiety

Gastrointestinal: nausea, vomiting

Renal: azotemia

Ocular: midriasis

TABLE 5.2 Dopamine drug interactions

Drugs that *antagonize* the effect of dopamine:	Drugs that *potentiate* the effect of dopamine:	Miscellaneous Interactions
Beta-blocking agents	Monoamine oxidase inhibitors	Phenytoin
	Reduce dopamine dose to 1/10th of the usual starting dose in patients who have received an MAOI in the past 2-3 weeks	Administration with dopamine can lead to significant hypotension and bradycardia
Alpha-adrenergic blocking agents	Tricyclic antidepressants	Cyclopropane or Hydrogenated hydrocarbon anesthetics
		Increase autonomic irritability and risk of serious cardiac arrhythmias
Haloperidol-may reduce the effect of renal and mesenteric vasodilation with low dose dopamine	Alpha and beta-adrenergic agonists	
	Ergonovine or Oxytocic drugs	

- **Cutaneous & peripheral**: inflammatory changes, dermal necrosis (extravasation), gangrene (high vasoconstrictive doses), piloerection

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of dopamine may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the dopamine infusion and treat

symptomatically. In case of extravasation, local administration of phentolamine may be indicated.

Compatible diluents:

Dopamine is to be infused diluted in dextrose with a maximal concentration of 3.2 mg/ml. It must be administered into a large vein, preferably a central venous catheter, with an infusion device allowing proper and reliable titration. Administration into an umbilical arterial catheter is not recommended. Dopamine must be protected from light for storage. Solutions that are darker than usual (slightly yellow) should not be used. Dopamine is incompatible with alkaline solutions and the dopamine may be rendered inactive. It may be administered with other vasoactive drugs and lidocaine.

Standard concentrations:

Injection solution (**hydrochloride**): 40, 80, and 160 mg/ml vials and prefilled syringes. Also available in premixed solutions (with 5 % dextrose) at concentrations of 0.8, 1.6, and 3.2 mg/ml.

Generic/Brand® Names:

Yes/-

5.2.4   Dopexamine

Indication:

Dopexamine hydrochloride is a catecholamine, structurally related to dopamine, with marked intrinsic agonist activity at β_2-adrenergic receptors and mild agonist activity the DA_1 and DA_2-dopaminergic receptors [66, 67]. Dopexamine also stimulates the β_1-adrenergic receptors indirectly through an inhibitory action on neuronal catecholamine uptake [68]. It reduces afterload through pronounced arterial and renal vasodilatation and evokes mild cardiac stimulation through direct and indirect β-adrenergic agonism. Some studies have shown dopexamine may improve mesenteric blood flow, but to a lesser degree than dopamine and it could be superior to

other dopaminergic agents in patients at risk for splanchnic hypoperfusion [56, 69]. Dopexamine displays beneficial hemodynamic effects in adult patients with acute heart failure and those requiring hemodynamic support following cardiac surgery [70]. In pediatric patients post-cardiac surgery, dopexamine has been shown to increase cardiac index and reduce systemic vascular resistance with little change in mean arterial pressure, however a study in preterm neonates with respiratory failure, dopexamine was shown to increase blood pressure and urine output [71–73].

Mechanisms of action:

Dopexamine reduces afterload and increases cardiac output through its agonist activity at β_2 and DA_1 receptors. Additional activation at the β_2-adrenergic receptors and inhibition of norepinephrine reuptake in nerve terminals leads to increased inotropy and blood flow to renal and mesenteric vascular beds [74]. Dopexamine is not an α-adrenergic agonist and does not cause vasoconstriction.

Dosing:

Dopexamine is administered as a continuous infusion and is titrated within the therapeutic range and to the minimal efficient dose necessary to achieve the desired response. It should be administered under comprehensive hemodynamic monitoring and avoided in hypovolemic patients.

Neonates, **Infants & Children**: 0.5–6 µg/kg/min, continuous IV infusion

Adults: 0.5–6 µg/kg/min, continuous IV infusion

Pharmacokinetics

Half-life: 7–11 min

Metabolism: extensively metabolized in the liver by *O*-methylation and *O*-sulfation

Elimination: in urine and in feces

Contraindications:

> Hypersensitivity to dopexamine or its components
> Left ventricular outflow obstruction (aortic stenosis or hypertrophic obstructive cardiomyopathy)
> Use with monoamine oxidase inhibitors
> Pheochromocytoma
> Tachyarrhythmias

Drug interactions:

> Dopexamine may enhance the effects of norepinephrine or other exogenous catecholamines

Adverse effects:

> **Cardiovascular**: sinus tachycardia, ventricular ectopy, arrhythmogenic potential, angina, chest pain, palpitations. Use caution in patients with ischemic heart disease
> **Central nervous system**: tremor, headache
> **Gastrointestinal**: nausea, vomiting
> **Metabolic**: hyperglycemia, hypokalemia; *cautious use in patients with hyperglycemia or hypokalemia*
> **Cutaneous**: phlebitis (extravasation)
> **Other**: reversible reduction in neutrophil and platelet counts

Poisoning information:

> Adverse effects due to excessive doses or altered pharmacokinetics of dopexamine may be observed. These effects are likely to be of short duration and it is recommended to transiently decrease or even withdraw the dopexamine infusion, and treat symptomatically. In case of extravasation, local administration of phentolamine may be indicated.

Compatible diluents:

Dopexamine should be diluted for infusion in normal saline, dextrose, or Ringer's solutions, with a maximal concentration of 1 mg/ml for large peripheral veins and 4 mg/ml for central venous catheter administration. It must be administered with an infusion device allowing proper and reliable titration. Dopexamine may turn slightly pink in prepared solutions, but does not lose potency with this change. Ampoules should be discarded if contents are discolored prior to dilution. Dopexamine should not be added to sodium bicarbonate, or other strongly alkaline solutions, and must not be mixed with other active agents prior to administration.

Standard concentrations:

Injection solution (hydrochloride 1 %): 10 mg/ml (5 ml vials)

Generic/Brand® Names:

No/Dopacard®

5.2.5   Epinephrine (Adrenaline)

Indication:

Epinephrine or adrenaline is an alpha and beta adrenergic-agonist agent with multiple actions ranging from being a sympathomimetic, bronchodilator, nasal decongestant and antidote for hypersensitivity reactions. Thus, it is used in the treatment of multiple diagnoses including: open-angle glaucoma, topical nasal decongestant, upper airway obstruction and viral croup, hemodynamic compromise including decreased cardiac contractility and chronotropy (low cardiac output syndrome, severe hypotension and bradycardia, myocardial dysfunction), anaphylactic reactions, anaphylactic or septic shock and cardiac arrest. This chapter concentrates on the hemodynamic and respiratory effects of the drug.

Mechanisms of action:

Epinephrine, the end product of endogenous catechol-amine synthesis, is a potent stimulator of alpha 1, beta 1 and beta 2–adrenergic receptors resulting in relaxation of smooth muscle of the bronchial tree, cardiac stimulation and dilatation of skeletal muscle vasculature. It effects are dose dependent: at *low doses* it can cause vasodilatation (beta 2-receptors); at *high doses* it may however produce vasoconstriction (alpha receptors) of skeletal and vascular smooth muscle with a subsequent increase of myocardial oxygen consumption. Moreover, it has marked metabolic effects particularly in the glucose homeostasis (hypergly-cemia) and it may induce leukocytosis.

Dosing:

Via parenteral, intra-osseous or endotracheal administra-tion, epinephrine may be used as a bolus or as a con-tinuous infusion. Epinephrine dosing has to be titrated within the therapeutic range for its indication and loca-tion of administration and preferably used at the mini-mal efficient dose, until the desired response. Endotracheal administration may require larger doses, up to tenfold the IV doses, in order to be effective in case of cardiac arrest. Epinephrine should be adminis-tered under comprehensive hemodynamic monitoring and should be avoided in hypovolemic patients.

Medication errors in dosing epinephrine have occurred secondary to incorrect administration of available concentrations:

For intramuscular or subcutaneous administration: 1:1,000 [1 mg/ml] solution is used

For intravenous or intraosseous administration: 1:10,000 [0.1 mg/ml] solution is used

Neonates:

Endotracheal: (IV or IO are the preferred routes) 0.05 mg to 0.1 mg/kg (0.5–1 mL/kg **1**:**10**,**000** solution) via the endotracheal tube every 3–5 min while other venous or IO access is being obtained

IV or IO: 0.01 mg/kg of a **1**:**10**,**000** solution [0.1 mg/mL] every 3–5 min

Infants/**Children**:

Anaphylactic/Hypersensitivity reaction

IM or SC (anaphylactic reaction, asthma): 0.01 mg/kg (maximum 0.3 mg) of a **1**:**1**,**000** solution every 5–15 min. IV or continuous infusion may be needed for severe anaphylactic reactions

Self-administration for severe allergic reactions: 1 dose every 10–20 min until arrival at an emergency medical facility

Autoinjector (EpiPen Jr®, EpiPen®, Twinject®) given IM per Manufacturer recommendations

15–29 kg: 0.15 mg IM per dose via autoinjector; if anaphylactic symptoms persist, repeat dose every 5–15 min while obtaining emergency medical care

≥ 30 Kg: 0.3 mg IM per dose via autoinjector; if anaphylactic symptoms persist, repeat dose every 5–15 min while obtaining emergency medical care

Bronchodilation/**Laryngotracheobronchitis** (**Croup**)

SC: 0.01 mg/kg (0.01 ml/kg of a **1**:**1**,**000** [1 mg/mL] solution) (maximum single dose of 0.5 mg) every 20 min for 3 doses

Nebulization (racemic epinephrine – 2.25 % solution or equivalent dose of L-epinephrine (10 mg of racemic epinephrine = 5 mg of L-epinephrine) for croup (laryngotracheobronchitis)

Infants, children and adolescents with croup: 0.05 ml/kg to 0.1 ml/kg (maximum 0.5 ml) of 2.25 % solution diluted in 2 mL of normal saline, deliver over 15 min every 20 min as needed; Use lower end of the dosing range for younger infants

Bronchiolitis:

Nebulization (racemic epinephrine – 2.25 % solution) in combination with dexamethasone reduced the rate of hospital admission, decreased the length of hospital stay for those patients admitted to the hospital and decreased the length of time that it took for the infant to resume quiet breathing and normal feeding [75].

Bradycardia or Pulseless Arrest

Endotracheal: (**preferred route is via IO or IV if available**) endotracheal increase dosage to 0.1 mg/kg (0.1 ml/kg) of a **1**:**1**,**000** solution and repeat as required every 3–5 min until IV or IO access is established. Flush with 5 mL normal saline immediately after administration. Use bag mask ventilation following saline administration to disperse medication.

IV or IO: 0.01 mg/kg (0.1 ml/kg) of a **1**:**10**,**000** solution, to be repeated as required every 3–5 min. The maximum single dose is 1 mg [76]. "High" dose epinephrine (0.1 mg/kg) has not been shown to improve outcome [77]

Continuous IV infusion (shock): 0.1–1 μg/kg/min

Adults:

IM or SC (anaphylactic reaction, asthma): 0.1–0.5 mg every 5–10 min

Cardiac Arrest ACLS guidelines

Endotracheal: (**preferred route is IV or IO**) 2–2.5 mg every 3–5 min [78].

IV or IO: 1 mg every 3–5 min as required; Higher doses may be indicated to treat specific problems such as beta-blocker or calcium channel blocker overdose [78].

Continuous IV infusion: 1–10 μg/min

Pharmacokinetics:

Onset of action:

IV: less than 1 min

Inhalation: within 1 min

SC: within 20–40 min with varying levels of absorption [79]

IM: within 5–10 min, more complete and rapid absorption if injected into the anterolateral thigh (vastus lateralus) [80, 81]

Absorption: active concentrations are not achieved by oral ingestion

Duration: very short, requiring a continuous infusion

Metabolism: hepatic (extensive) and renal (to a lesser degree) metabolism by the enzymes cathecol-ortho-methyltransferase and monoamine oxidase.

Half-life: 2–3 min.

Clearance: renal, once metabolized by hepatic glucuronidation and sulfation.

Drug interactions:

Drugs that may enhance vasopressor and cardiac effects of epinephrine
Beta-blocking agents (propanolol, atenolol, esmolol)
Alpha-blocking agents (phentolamine, phenoxybenzamine, some phenothiazides)
Alpha and beta-blocking agents (labetalol)
Tricyclic antidepressants
Halogenated anesthetic gases

Adverse effects: : [82]

Cardiovascular: sinus tachycardia, hypertension, cardiac arrhythmias, angina, sudden death. Carefully use in case of myocardial ischemia since it may increase myocardial oxygen consumption

Respiratory: rebound broncho or laryngospasm, rebound nasal congestion

Central nervous system: headache, apprehension, restlessness, cerebral hemorrhage (rare)

Gastrointestinal: nausea, abdominal pain; decreased appetite, mesenteric vasoconstriction at high doses

Genitourinary: acute bladder retention

Renal: decreased renal blood flow

Neuromuscular & skeletal: tremor, weakness

Ocular: exacerbation of acute glaucoma

Metabolic: hyperglycemia (careful use in diabetic patients) thyroid disturbances

Cutaneous: tissue necrosis (extravasation), vasoconstriction of peripheral vasculature

Other: leukocytosis

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of epinephrine may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability). In case of extravasation, local administration of phentolamine or papaverine should be indicated.

Compatible diluents:

Epinephrine should be protected from light and air. Oxidation turns the drug pink and then a brown color. It is incompatible with alkaline solutions and may be administered with other vasoactive drugs and muscle relaxants. It must be administered into a central vein, except and transiently in urgent scenarios, with an infusion device allowing proper and reliable titration. Do not use if solution is discolored or if it contains precipitants. Store between 15 °C to 25 °C (68 °F to 86 °F); do not freeze or refrigerate.

Dilutions:

Inhalation/nebulization: racemic epinephrine (2.25 %) 0.5 ml with normal saline to a total of 3–5 ml

Endotracheal: The concentration of epinephrine differs depending on if it is being administered to neonates or children and adults. See dose administration for concentrations. Each dose of epinephrine given endotracheally should be followed with normal saline to a total volume of 3–5 ml, followed by several positive pressure ventilations.

IM: use 1:200 or 1:1,000 undiluted solutions

Parenteral:

IV or IO injection: maximum concentration of 100 μg/ml (undiluted 1:10,000 solution).

Continuous IV or IO infusion: dilute in normal saline or dextrose

Standard concentrations:

Injection solution (L-epinephrine; hydrochloride): 0.1 mg/ml (1:10,000 y 10 ml), 1 mg/ml (1:1,000 × 1 ml)

Racemic epinephrine: 2.25 % solution (0.5 ml, 15 ml)

Generic/Brand® Names:

Yes/Adrenalin®, Adrénaline Sintetica®, EpiPen®, Primatene® Mist, Epifrin® Twinject®, S2®

5.2.6   Isoproterenol/Isoprenaline

Indication:

Isoproterenol is a beta 1 and beta 2 adrenergic-agonist agent that exerts a sympathomimetic and bronchodilator effect. It has a positive inotropic and chronotropic effect and a non-selective pulmonary and systemic vasodilator effect. It is used to treat bronchospasm, ventricular dysrrhythmias due to atrioventricular nodal block, bradyarrhythmias and atropine-resistant bradycardia, third-degree atrioventricular block until insertion of a pacemaker (it increases the spontaneous ventricular rate), pulmonary hypertension, right ventricular myocardial dysfunction with low cardiac output and vasoconstrictive shock status [83–87].

Isoprenaline is also used during Tilt tests, used to rule out cardiac or neurologic causes of syncope and confirm the diagnosis of vaso-vagal syncope. The supine position causes redistribution of blood with pooling of venous blood in the lower extremities. This decreases the left ventricular size and preload which stimulates catecholamine secretion with subsequent increase in ventricular

contraction (intropic effect) and heart rate (chronotropic effect). C-myocardial fibers act as mechanoreceptors and transmit this information to the vasomotor regulatory center which stimulate the vagal nerve with secondary inhibition of the adrenergic stimulation. Vaso-vagal syncope represents an exaggerated response to this phenomen with low blood pressure and bradycardia. Isoprenaline infusion is used as a sensibilization agent during Tilt test [88, 89].

Mechanisms of action:

Isoproterenol stimulates beta 1 and beta 2 receptors resulting in relaxation of bronchial, gastrointestinal and uterine muscle. In the heart, it activates β_1-receptors and consequently it increases heart rate (chronotropic and dromotropic) and contractility (inotropic). It also activates β_2 receptors on skeletal muscle arterioles and it causes vasodilatation of peripheral and pulmonary vasculature. Its inotropic and chronotropic effects tends to elevate systolic blood pressure, while its vasodilatory effects tend to lower diastolic blood pressure [90–94].

Dosing:

Isoproterenol is administered as a continuous infusion and has to be titrated within the therapeutic range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring. Isoproterenol should be avoided in hypovolemic patients. Tachyphylaxis may occur with prolonged use, thus withdrawal must be slow to prevent rebound phenomenon.

Neonates: 0.05–5 μg/kg/min
Infants/Children: 0.05–5 μg/kg/min
Adults: 2–20 μg/min

Pharmacokinetics: [95]

Onset of action: immediate
Duration: a few minutes

Metabolism: by cathecol-ortho-methyltransferase followed by conjugation in the liver, the kidneys, the lungs and various other tissues

Half-life: 2–5 min

Clearance: mostly in urine as sulfate conjugates

Drug interactions:

Enhanced effects or cardiotoxicity may be observed when administered with other sympathomimetic drugs. Beta-adrenergic blocking agents may decrease isoproterenol effectiveness. Isoproterenol may increase theophylline elimination.

Adverse effects:

Cardiovascular: flushing, ventricular arrhythmias, sinus tachycardia, hypotension, hypertension, palpitations, chest pain; it is *contraindicated in case of digoxin intoxication and should be avoided in patients with low diastolic pressures due to "diastolic steal", unrepaired Tetralogy of Fallot patients and patients subaortic obstruction*

Central nervous system: restlessness, anxiety, nervousness, headache, dizziness, insomnia, vertigo

Endocrine & metabolic: parotid gland swelling, careful use in patients with diabetes and hyperthyroidism

Gastrointestinal: heartburns, nausea, vomiting, dyspepsia, dry mouth and throat, xerostomia

Neuromuscular & skeletal: weakness, tremor

Others: diaphoresis, exacerbation of an acute glaucoma, urine retention in case of prostatic hypertrophy

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of isoproterenol may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability).

Compatible diluents:

Isoproterenol may be diluted in normal saline or in dextrose to a maximal concentration of 20 μg/ml. It should be administered into a central vein whenever possible, with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solution (hydrochloride): 0.02 mg/ml (10 ml vials) and 0.2 mg/ml (1 and 5 ml vials)

Generic/Brand® Names:

Yes/Isuprel®

5.2.7   Norepinephrine (Noradrenaline)

Indication:

Norepinephrine or noradrenaline is an adrenergic-agonist agent with potent alpha-adrenergic and weaker sympathomimetic (beta 1) action. Norepinephrine has long been used in sepsis as a treatment for vasodilatory shock, and is now the initial vasopressor of choice in all adults and in children refractory to dopamine alone [66, 78, 96–102]. It is used for the treatment of persistent vasoplegic (distributive) shock in combination with dobutamine, dopamine or epinephrine. A recent study in septic adults indicates that norepinephrine may cause venoconstriction via alpha receptors, effectively increasing preload and thus increasing cardiac index [100]. This same study, however, also revealed an increase in end-diastolic volume, likely as a result of increased afterload. This afterload, while tolerated by these septic patients, may place patients at risk if myocardial failure is the etiology of their low cardiac output. Despite this generally-accepted risk associated with the use of norepinephrine, a recent

survey of European pediatric cardiac intensivists revealed that norepinephrine is commonly administered for the treatment of low cardiac output syndrome and low systemic vascular resistance [102].

Similarly, norepinephrine may induce such peripheral vasoconstriction that it may lead to ischemia [78, 101]. There are numerous reports of tissue necrosis, particularly of the digits, associated with prolonged infusions of norepinephrine.

Mechanisms of action:

Norepinephrine, a precursor of epinephrine, stimulates alpha-adrenergic (strong action) and beta 1 (mild action) receptors inducing a strong systemic vasoconstriction, which might increase systemic arterial pressure and thus coronary perfusion. Alpha effects predominate over beta effects, with more intense vasoconstriction than inotropic or chronotropic action, which explains a mild effect on cardiac contractility, and heart rate, or cardiac output.

Dosing:

Norepinephrine is to be used as a continuous infusion and has to be titrated within the therapeutic range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring. Norepinephrine should be avoided in hypovolemic patients.

Neonates: 0.05–2 µg/kg/min
Infants/Children: 0.05–2 µg/kg/min
Adults: 0.5–10 µg/min; may be increased up to 30 µg/min in refractory cases

Pharmacokinetics:

Onset of action: almost immediate

Duration: very short, requiring a continuous infusion

Metabolism: rapidly metabolized by cathecol-ortho-methyltransferase and monoamine oxidase

Half-life: 1–2 min

Clearance: by renal excretion (80–95 % as inactive epinephrine metabolites)

Drug interactions:

Drugs that may enhance the effects of norepinephrine
Anti-histaminic drugs
Atropine sulphate
Carbonic Anhydrase Inhibitors
Catechol-o-methyltransferase inhibitor (e.g., entacapone)
Ergot alkaloids
Guanethidine
MAO inhibitors
Methyldopa
Tricyclic antidepressant drugs

Adverse effects:

Cardiovascular: palpitations, sinus tachycardia, reflex bradycardia, cardiac arrhythmias, hypertension, chest pain

Respiratory: dyspnea

Central nervous systems: headache, anxiety

Endocrine & metabolic: hyperglycemia, uterine contractions

Gastrointestinal: nausea, vomiting; may induce mesenteric vasoconstriction

Cutaneous & peripheral: inflammatory changes, dermal necrosis (extravasation)

Others: diaphoresis

Poisoning information:

Adverse effects due to excessive doses or altered pharma-cokinetics of norepinephrine may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability). In case of extravasation, local administration of phentolamine or papaverine should be indicated.

Compatible diluents:

Norepinephrine is unstable in alkaline solutions and should therefore be diluted in dextrose or at least in half-saline solution (D5W/NS) with a maximal concentration between 4 and 16 μg/ml (in case of severe fluid restriction). It must be administered into a central vein, except and transiently in urgent scenarios, with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solution (bitartrate): 1 mg/ml (4 ml vials)

Generic/Brand® Names:

Yes/Levophed®, Arterenol®

5.3   Phosphodiesterase Inhibitors

5.3.1   Inamrinone/Amrinone

Indication:

Inamrinone or amrinone is a type III Phosphodiesterase Enzyme (PDE) Inhibitor used for the treatment of low cardiac output status [86, 103–106] (i.e., myocardial dysfunction after cardiopulmonary bypass, cardiomyopathy) particularly useful in patients who have been refractory to conventional inotropic and vasodilator therapy. It may also be used as an adjunctive therapy for pulmonary hypertension.

Mechanisms of action:

Inamrinone is a bipyrade derivate that inhibits Phosphoediesterase III, thus increasing cyclic Adenosine Monophosphate (cAMP), cAMP-specific PDE and cAMP protein-kinase, which potentiates delivery of calcium to myocardial contractile units resulting in a positive inotropic effect; however, it may produce negative inotropic effect in the neonatal myocardium [107]. Moreover, PDE III inhibition results in relaxation of vascular smooth muscle inducing vasodilatation while concomitantly reducing myocardial oxygen consumption.

Dosing:

Inamrinone may be used as a bolus followed by a continuous infusion and ought to be titrated within the therapeutic range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring. Inamrinone should be avoided in hypovolemic patients.

Hypotension may occur with the loading dose and many practitioners do not systematically administer the bolus dose in order to avoid such complication; in case of hypotension it is recommended to administer 5–10 ml/kg of normal saline and to position the patient head down; if hypotension persists a systemic vasopressor may be required, and stopping the loading dose infusion is indicated. Total daily dose should not exceed 10 mg/kg. *Pharmacokinetic studies are not conclusive in order to define dosing guidelines in pediatric patients. There is no evidence-based data documenting neither safety nor effectiveness of long-term treatment (> 48 h) with this drug.*

Neonates: IV bolus of 0.75 mg/kg over 3 min (may be necessary to repeat it after 30 min); loading dose may be increased up to 1 mg/kg over 5 min and repeated up to 2 times; IV continuous maintenance dose of 3–5 μg/kg/min.

Infants/Children: IV bolus of 0.75 mg/kg over 3 min (may be necessary to repeat it after 30 min); loading dose

may be increased up to 1 mg/kg over 5 min and repeated up to 2 times; IV continuous maintenance dose of 5–10 μg/kg/min.

Adults: IV bolus of 0.75 mg/kg over 3 min (may be necessary to repeat it after 30 min); loading dose may be increased up to 1 mg/kg over 5 min and repeated up to 2 times; IV continuous maintenance dose of 5–10 μg/kg/min.

Pharmacokinetics: [108, 109]

Onset of action: 2–5 min

Maximum effect: within 10 min

Duration: 30 min to 2 h (dose-dependent)

Distribution: V_d: Neonates: 1.8 L/kg; Infants % Children: 1.6 L/kg; Adults: 1.2 L/kg

Protein-binding: 10–50 %

Metabolism: in the liver onto several metabolites by glucuronidation, acetylation or conjugation (glutathione, N-acetate, N-glycolil, N-glucuronide, O-glucuronide)

Half-life: Neonates <1 week: 12 h; Neonates 1–2 weeks: 22 h; Infants <38 weeks: 6.8 h; Children: 2.2–10 h; Adults: 6 h

Drug interactions:

Dosage reduction of diuretics (significant hypovolemia) and of dysopyramide (hypotension) might be required.

Adverse effects:

Cardiovascular: hypotension, ventricular and supraventricular arrhythmias (reported mostly in adults); inamrinone may exacerbate a pre-existing ventricular ectopy or myocardial ischemia

Gastrointestinal: nausea, vomiting, abdominal pain, anorexia

Hematological: reversible dose-related thrombocytopenia in around 2.5 % of patients [110]. This is more likely to occur in patients with a higher total dose, longer duration of infusion, high plasma concentrations of N-acetylamrinone (inamrinone metabolite) and higher plasma rations of N-acetylamrinone to inamrinone.

Eosinophyllia (idiosyncratic hypersensitivity reaction) may also occur

Hepatic: hepatotoxicity; inamrinone should be discontinued if a significant increase in liver enzymes is documented

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of inamrinone may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability).

Compatible diluents:

Inamrinone should be administered into a central vein, except and transiently in urgent scenarios, with an infusion device allowing proper and reliable titration. It must be diluted only with normal saline or half-saline (1–3 mg/ml); although incompatible with dextrose-containing solutions, it may be administered into a Y-site via with dextrose infusions. It is also incompatible with sodium bicarbonate and furosemide.

Standard concentrations:

Injection solution (lactate): 5 mg/ml (20 ml vials)

Generic/Brand® Names:

-/Inocor®

5.3.2 Milrinone

Indications:

Milrinone is a type III Phosphodiesterase Enzyme inhibitor mainly utilized for the short-term treatment of acute cardiac failure [111] and post-operative low cardiac output syndrome [86, 106, 112–115]. It may also be indicated as a co-therapy of pulmonary arterial hyperten-

sion [116–119], and septic shock [120] although there is no evidence-based data to support the latter, and as a mid to long term therapy for patients with chronic cardiac failure awaiting heart transplant [111].

Mechanisms of action:

Milrinone is an analogue of inamrinone that inhibits Phosphodiesterase III, thus increasing cyclic adenosine monophosphate (cAMP) which potentiates the delivery of calcium to myocardial contractile units resulting in a positive inotropic effect, including in newborns. Milrinone has been demonstrated to improve cardiac index and to lower filling pressures, systemic and pulmonary arterial pressures and resistances in the neonatal population. It induces an increase in cardiac output and it seems to preserve normal myocardial oxygen consumption. It may also produce diastolic relaxation (lusitropic effect) and reduce ventricular preload. Moreover, it results in relaxation of vascular smooth muscle producing vasodilatation, predominantly systemic.

Dosing:

Milrinone may be used as a bolus or as a continuous infusion and requires titration within the therapeutic range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring. Hypotension may occur with the loading dose and some caregivers do not systematically administer the bolus dose in order to avoid such complication. If significant hypotension occurs while administering the loading dose, fill the patient with 5–10 ml/kg of normal saline and reduce the infusion rate. Shall the hypotension persist, suspend the loading bolus and consider giving one dose of a vasopressor. Meticulous attention ought to be taken in patients after cardiopulmonary bypass, particularly in patients with hypoplastic left heart syndrome, as postoperative milrinone clearance may be significantly

impaired during the first few days in this population [121].

Neonates, **Infants & Children**: I.V. loading dose of 50 µg/kg over a period of 15 min, followed by a continuous maintenance dose of 0.25–1 µg/kg/min.

Adults: I.V. loading dose of 50 µg/kg over a period of 10–15 min, followed by a continuous maintenance dose of 0.375–0.75 µg/kg/min; maximum daily dose of 1.13 mg/kg.

Renal impairment: *doses must be adjusted to creatinine clearance as follows*:

Cl_{cr} 50 ml/min/1.73 m^2: 0.43 µg/kg/min.
Cl_{cr} 40 ml/min/1.73 m^2: 0.38 µg/kg/min.
Cl_{cr} 30 ml/min/1.73 m^2: 0.33 µg/kg/min.
Cl_{cr} 20 ml/min/1.73 m^2: 0.28 µg/kg/min.
Cl_{cr} 10 ml/min/1.73 m^2: 0.23 µg/kg/min.
Cl_{cr} 5 ml/min/1.73 m^2: 0.2 µg/kg/min.

Pharmacokinetics: [109, 122, 123]

Onset of action: 5–15 min
Maximum effect: within 20 min
Half-life: 3 h
Duration: 30 min to 2 h (dose-dependent)
Distribution: V_d Beta: Neonates: unknown; Infants: 0.9 ± 0.4 L/kg (after cardiac surgery); Children: 0.7 ± 0.2 L/kg (after cardiac surgery); Adults: 0.3 ± 0.1 L/kg
Protein-binding: 70 %
Metabolism: milrinone is excreted unchanged
Half-life (prolonged in case of renal impairment): Infants: 3.1 ± 2 h (after cardiac surgery); Children: 1.86 ± 2 h (after cardiac surgery); Adults: 1.69 ± 0.18 h (after cardiac surgery)
Clearance (decreased in renal impairment): excreted in urine as unchanged drug (83 %) and glucuronide metabolite (12 %). Age-dependent clearance: Infants: 3.8 ± 1 ml/kg/min (after cardiac surgery); Children: 5.9 ± 2 ml/kg/min (after cardiac surgery); Adults: 2 ± 0.7 ml/kg/min (after cardiac surgery)

Drug interactions:

Milrinone interacts with furosemide producing a precipitate.

Adverse effects:

Cardiovascular: ventricular and supraventricular arrhythmias [124], hypotension, angina, chest pain; must be used with caution in patients with background of atrial fibrillation or flutter, ventricular arrhythmia and right or left outflow tract obstruction

Respiratory: bronchospasm

Central nervous system: headache

Endocrine & metabolic: hypokalemia

Hematological: thrombocytopenia (0.4 %)

Hepatic: increased liver enzymes

Neuromuscular & skeletal: tremor

Renal: careful administration and dosage adjustment in patients with renal dysfunction

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of milrinone may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability).

Compatible diluents:

Milrinone is compatible with normal saline, half-saline and dextrose solutions, with a maximum recommended concentration of 200 μg/ml. It should be administered with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solution (lactate): 1 mg/ml (5, 10 and 20 ml vials); also in as a pre-mixed solution in dextrose, 200 μg/ml (100 and 200 ml).

Generic/Brand® Names:

-/Primacor®, Corotrop®, Corotrope®

5.4   Vasodilators: Calcium Channel Blockers

5.4.1   Nifedipine

Indication

Nifedipine is used in adults for the treatment of angina, hypertrophic cardiomyopthy, and hypertension (extended release forms of the drug) [125–127]. In pediatric patients there is scarce literature available, and it is predominantly used to treat systemic hypertension and hypertophic cardiomyopathy [128]

Mechanism of Action

Nifedipine prevents calcium ions from entering both vascular smooth muscle cells and myocardial cells via specific slow calcium channels. It thus decreases the intracellular concentration of calcium such that less is available to bind to contractile proteins in these cells. This results in vasodilation, including the coronary arteries, and a negative inotropic effect. The negative inotropic effect of nifedipine is less clinically significant than its vasodilatory effect.

Dosing

Neonates (**premature and full term**) **and Infants**: Specific dosing information has not been obtained for neonates and infants.

Children:

Oral or sublingual (S.L.):

Hypertensive emergencies: 0.25–0.5 mg/kg/dose P.O./S.L. every 4–6 h as needed. Maximum single dose is 10 mg/dose and daily dose is 1–2 mg/kg/day.

Hypertophic cardiomyopathy: 0.6–0.9 mg/kg/24 h in 3–4 divided doses.

Hypertension (*chronic treatment*): Extended release forms: Initial: 0.25–0.5 mg/kg/day in 1–2 doses/day. Titrate to desire effect. Maximum dose is 3 mg/kg/day up to 180 mg/day.

Adults:

Oral or S.L:

Capsules: Initial: 10 mg 3 times/day. Maintenance: 10–30 mg 3–4 times/day.

Extended release tablet: Initial: 30–60 mg once daily. Usual dosage for hypertension is 30–60 mg once daily. Maximum dose is 120 mg/day

Note: Doses are typically titrated to achieve the desired effect (e.g., reduce hypertension) over 1–2 weeks.

Pharmacokinetics

Onset of action:

S.L. or "bite and swallow": within 1–5 min

Oral:

Immediate release: within 20–30 min

Extended release: 2–2.5 h

Absorption:

Bioavailability:

Capsules: 45–75 %

Extended release: 65–85 %

Half-life:

Normal adults: 2–5 h
Adults with cirrhosis: 7 h

Duration:

Immediate release: 4–8 h
Extended release: 24 h

Protein binding: 92–98 %

Metabolism: In the liver to inactive metabolites

Elimination: In urine with>90 % excreted as inactive metabolites

Monitoring parameters: Blood pressure, CBC, and liver enzymes

Contraindications: Hypersensitivity to nifedipine (any component) and recent myocardial infarction

Adverse Effects

Cardiovascular: Hypotension, tachycardia, flushing, palpitations, syncope, and peripheral edema

Respiratory: Shortness of breath

Central nervous system: Headache, dizziness

Gastrointestinal: Nausea, diarrhea, constipation, and gingival hyperplasia

Hepatic: Elevated liver enzymes, cholestasis, jaundice, and allergic hepatitis (rare)

Neuromuscular and skeletal: Joint stiffness, arthritis with an elevated antinuclear antibody

Hematologic: Thrombocytopenia, leukopenia and anemia

Ophthalmologic: Blurred vision, transient blindness

Cutaneous/peripheral: Dermatitis, urticaria, purpura, and photosensitivity (rare)

Other: Fever, chills, and diaphoresis

Precautions

Initiation of anti-hypertensive therapy with nifedipine should be performed cautiously and with close blood pressure monitoring, since significant hypotension can occur. Upward titrations of dosing should be monitored similarly. Patients receiving concomitant treatment with β-blockers are at increased risk of hypotension. Angina and acute myocardial infarction in adults has been reported with initiation of nifedipine therapy. Patients with either congestive heart failure (CHF) or aortic stenosis are also at increased risk.

Drug Interactions

Concomitant use of β-blockers may increase cardiovascular adverse events. Hypotension may be accentuated with anesthetic doses of fentanyl. Nifedipine may increase the serum concentrations of phenytoin, cyclosporine, and possibly digoxin. It may decrease serum quinidine concentration. Cimetidine and saquinavir

may increase serum nifedipine concentration. Combined administration with cyclosporine in transplant patients appears to increase significantly the incidence of gingival hyperplasia. Delaviridine may decrease nifedipine metabolism and thus increase serum level. Administration of calcium typically reduces the effects of a calcium channel blocking agent.

Compatible Diluents/Administration

Administer tablets with food. Avoid co-administration with grapefruit juice, as this may increase oral bioavailability. Sustained release tablets should be swallowed whole. Nifedipine from liquid-filled capsules can be removed and administered either S.L. or swallowed (only a small amount of a S.L. dose is absorbed in the mouth).

Standard Concentrations

Capsule, liquid-filled: 10 mg, 20 mg
Procardia®: 10 mg
Tablet, extended release: 30 mg, 60 mg 90 mg

Generic/Brand® Names:

Yes/Adalat®CC, Afeditab™, Nifediac™CC, Nifedical™XL, Procardia®, Procardia XL®

5.4.2   Amlodipine

Indication

Amlodipine is a calcium channel antagonist used in adults for the treatment of angina pectoris and hypertension. In pediatric patients, amlodipine and other calcium channel antagonists are, along with the angiotensin-converting enzyme inhibitors, the most commonly prescribed anti-hypertensive medications due to their low adverse effect profiles [129–131].

Mechanism of Action

Amlodipine prevents calcium ions from entering both vascular smooth muscle cells and myocardial cells via specific slow calcium channels during depolarization. It decreases the intracellular concentration of calcium such that less is available to contractile proteins in these cells, resulting in vasodilatation. Relaxation of coronary vascular smooth muscle specifically treats anginal pain by increasing myocardial oxygen delivery.

Dosing

Neonates and Infants:

Specific dosing information has not been obtained for neonates and infants.

Oral: Hypertension: For children ages 6–17 years, the manufacturer's recommended dose is 2.5–5 mg P.O./N.G. once daily. Initial doses reported in the literature have varied from 0.05 to 0.13 mg/kg/day. Doses are typically titrated by 25–50 % every 5–7 days. Required doses reported in the literature have varied from 0.12 to 0.5 mg/kg/day, and younger patients tend to need higher doses for effect. Insufficient data exist on doses >5 mg/day in pediatrics.

Adults:

Oral:

Hypertension: Initial: 2.5–5 mg P.O./N.G. once daily, with a 2.5 mg/day dose recommended for smaller, less stable patients. Titrate dose to a maximum of 10 mg/day once daily over 7–24 days. Usual dose is 5 mg/day once daily.

Angina: 5–10 mg/dose P.O./N.G. once daily. Lower doses are appropriate for patients with hepatic impairment; no adjustment for renal impairment required.

Pharmacokinetics

Onset of action: 30–50 min
Absorption: Well absorbed orally

Distribution: Mean volume of distribution: Children >6 years: similar to adults on a per kg basis. Adults: 21 L/kg

Maximum effect: Peak serum concentration at 6–12 h

Half-life: Terminal half-life 30–50 h

Duration: ≥ 24 h with routine dosing

Protein binding: 93 %

Metabolism: In the liver with 90 % metabolized to inactive metabolites

Clearance: In children >6 years of age, weight-adjusted clearance is similar to adults

Elimination: 10 % of unchanged drug and 60 % of metabolites are excreted in the urine. Not removed by dialysis.

Monitoring parameters: Blood pressure and liver enzymes

Contraindications: Hypersensitivity to amlodipine or any of its components

Adverse Effects [129, 130]

Cardiovascular: Common: Flushing, palpitations, and peripheral edema. Rare: Hypotension, dysrhythmia, chest pain, syncope, peripheral ischemia, vasculitis, and myocardial infarction.

Respiratory: Dyspnea, pulmonary edema, and epistaxis

Central nervous system: Common: Headache, dizziness, somnolence, and fatigue. Rare: Insomnia, vertigo, depression, and anxiety

Gastrointestinal: Nausea, abdominal pain, dyspepsia, anorexia, constipation, diarrhea, dysphagia, pancreatitis, vomiting, xerostomia, and gingival hyperplasia

Hepatic: Jaundice, elevated liver enzymes

Genitourinary: Sexual dysfunction

Neuromuscular and skeletal: Muscle cramps, asthenia, arthralgia, myalgia, paresthesia, peripheral neuropathy, hypoesthesia, and tremor

Endocrine/metabolic: Weight gain or loss, gynecomastia, and hyperglycemia

Hematologic: Thrombocytopenia, leucopenia, and purpura

Ophthalmologic: Diplopia, abnormal vision, eye pain, and conjunctivitis

Cutaneous/peripheral: Rash, pruritis, erythema multiforma, and angioedema [132, 133]

Other: Tinnitus, diaphoresis, and increased thirst

Precautions

In adult patients with severe coronary artery disease, both initiation of amlodipine therapy and increased dosing have been associated with increased severity and frequency of angina as well as acute myocardial infarction. Acute hypotension is more common in patients with congestive heart failure and left ventricular outflow tract obstruction (i.e., aortic stenosis). Increased caution should be used in patients with impaired hepatic function due to amlodipine's hepatic metabolism. It is recommended not to discontinue amlodipine abruptly in patients with angina or significant coronary artery disease.

Drug Interactions

Concomitant administration of rifampicin may decrease serum amlodipine concentration. Azole antifungal agents (i.e., ketoconazole) may inhibit metabolism in the liver and increase serum amlodipine concentration. Amlodipine may increase serum cyclosporine level (uncertain). As for all calcium channel blocking agents, administration of calcium may mitigate the drug's effect.

Compatible Diluents/Administration

Amlodipine tablets may be administered without regard to food, as food does not affect its bioavailability. Nevertheless, concomitant ingestion of grapefruit juice has been reported as increasing amlodipine peak serum concentrations.

Standard Concentrations

Tablet: 2.5 mg, 5 mg, 10 mg

Liquid: Prepared extemporaneously by pharmacy; usual concentration 1 mg/ml.

Generic/Brand® Names:

Yes/Norvasc

5.4.3   *Nicardipine*

Indication

Nicardipine is used in adults for the treatment of angina pectoris and hypertension. In pediatric patients, it is used predominantly to treat hypertension. Both oral and intravenous preparations of the drug are available. The intravenous preparation is typically used in monitored in-patient settings (e.g., an intensive care unit) when oral dosing is either not possible or tighter blood pressure control is desired (e.g., early after cardiovascular surgery) [134].

Mechanism of Action

Nicardipine prevents calcium ions from entering both vascular smooth muscle cells and myocardial cells via specific slow calcium channels. It thus decreases the intracellular concentration of calcium such that less is available to contractile proteins in these cells, resulting in vasodilation. Relaxation of coronary vascular smooth muscle specifically treats anginal pain by increasing myocardial oxygen delivery.

Dosing

Neonates (premature and full term):

Oral: No information available.

I.V. continuous infusion: Dosing data from two studies (n = 28 patients) suggested an initial dose of 0.5 μg/kg/min I.V [135, 136]. Doses were titrated by blood pressure over the first day to a mean maximal dose of 0.74 ± 0.41 μg/kg/min (range 0.5–2 μg/kg/min).

Infants/Children: Data for infants and children are also limited, and dosing is not well established.

Oral: Case reports only. Doses of 20–30 mg/dose P.O. every 8 h in two 14-year old children have been reported.

I.V. continuous infusion: Initial: 0.5–1 μg/kg/min I.V., then titrate dose to achieve the desired blood pressure. Dosing changes can be made every 15–30 min. Maximum dose 4–5 μg/kg/min.

Adults:

Oral: Immediate release: Initial: 20 mg P.O. 3 times/day. Titrate to response allowing ≥ 3 days between dose increases. Usual dose 20–40 mg 3 times/day.

Sustained release: Initial: 30 mg P.O. twice daily. Usual dosage range 30–60 mg twice daily.

I.V. continuous infusion: Hypertension (patients not receiving oral Nicardipine): Initial: 5 mg/h I.V. Titrate dose by increasing infusion by 2.5 mg/h every 5–15 min until target achieved or maximum dose of 15 mg/h reached. Once target blood pressure is achieved, decrease infusion rate to 3 mg/h or lowest rate to achieve desired blood pressure.

Pharmacokinetics

Onset of action:
Oral: 0.5–2 h
I.V.: Within minutes

Absorption:
Oral dose: 100 %, but large first-pass effect
Bioavailability of oral dose 35 %

Distribution: Volume of distribution in adults: 8.3 L/kg

Maximum effect:
Immediate release capsules: 1–2 h
Sustained release capsules: Sustained 2–7 h after dose
I.V. continuous infusion: 50 % of maximum effect within 45 min, and final effect by 50 h

Half-life: Dose-dependent (non-linear) pharmacokinetics, so apparent half-life depends upon serum concentration

Oral dose: 2–4 h over first 8 h; terminal half-life 8.6 h

I.V. infusion: Serum concentration decreases exponentially in 3 phases - α (2.7 min), ß (44.8 min), and terminal (14.4 h)

Duration:

Immediate release capsules: <8 h
Sustained release capsules: 12 h
I.V. single dose: 3 h
I.V. continuous infusion: 50 % decrease in 30 min with gradual loss of antihypertensive effect over 50 h

Protein binding: 95 %

Metabolism: Saturable first-pass effect with dose-dependent pharmacokinetics. Extensive hepatic metabolism by cytochrome P450 isoenzyme CYP3A4.

Clearance: Decreased in patients with hepatic dysfunction, and may be decreased with renal dysfunction

Elimination: 60 % of an oral dose is excreted in the urine, with <1 % as unchanged drug. 35 % excreted in the feces. Not removed by dialysis.

Monitoring parameters: Blood pressure, heart rate, liver function, and renal function. Monitor blood pressure carefully, especially with I.V. infusion and dosing changes.

Contraindications: Hypersensitivity to nicardipine or any component, and significant aortic stenosis.

Adverse Effects

Cardiovascular: Vasodilation/flushing, tachycardia, palpitations, hypotension (6 % with I.V. form), orthostasis, syncope, peripheral and facial edema, increased angina, ECG changes, and myocardial infarction

Respiratory: Dyspnea

Central nervous system: Headache, dizziness, somnolence, paresthesias, anxiety, insomnia, and intracranial hemorrhage (0.7 % with I.V. form)

Gastrointestinal: Nausea, vomiting, dyspepsia, xerostomia, diarrhea, constipation, and abdominal pain

Genitourinary: Polyuria, nocturia, and hematuria (0.7 % with I.V. form).

Neuromuscular and skeletal: Asthenia, myalgia, malaise, tremor, and hypoesthesia

Endocrine/metabolic: Hypokalemia (0.7 % with I.V. form)

Ophthalmologic: Blurred vision

Cutaneous/peripheral: Rash

Other: Diaphoresis, injection site reaction or pain (I.V. form)

Precautions

In adult patients with severe coronary artery disease, both initiation of nicardipine therapy and increased dosing have been associated with increased severity and frequency of angina. Abrupt withdrawal may cause rebound angina in patients with coronary artery disease. Negative inotropic effects may occur in those patients with CHF and left ventricular dysfunction, resulting in low cardiac output. Symptomatic hypotension may occur, especially with the I.V. form. Because vessel irritation is common, peripheral infusion sites for the intravenous form should be changed every 12 h on therapy.

Drug Interactions

Nicardipine affects several cytochrome P450 isoenzymes and thus has numerous drug interactions. Serum concentrations of the following drugs may be increased by nicardipine: cyclosporine, metoprolol, vecuronium (I.V. nicardipine), and digoxin. Either serum concentrations or the effects of multiple other drugs that are substrates for various cytochrome P450 enzymes may be affected including, CYP2C8/9 substrates (e.g., amiodarone, warfarin), CYP2C19 substrates (e.g., phenytoin, propanol), CYP2D6 substrates (e.g., selected ß-blockers, lidocaine, risperidone) and CYP3A4 substrates (e.g., benzodiazepines, other calcium channel blockers, and tacrolimus). Drugs that are strong inhibitors of cytochrome P450 isoenzyme CYP3A4, such as azole antifungals, clarithromycin, propofol, and protease inhibitors, may all increase serum concentrations or effects of nicardipine, whereas drugs that induce isoenzyme CYP3A4, such as carbamazepine, phenytoin, phenobarbitol, and rifampin, may decrease the concentration of effects of nicardipine. Lastly, nicardipine may decrease serum the concentration or effects of common narcotic agents (e.g., codeine, hydrocodone, and oxycodone) that are prodrug substitutes for isoenzyme CYP2D6.

Compatible Diluents/Administration

For oral forms of nicardipine, administration of the drug with high fat meals may decrease peak concentrations. Concurrent use of grapefruit juice may increase serum concentration. The I.V. form should be protected from light. It can be diluted in either dextrose- (e.g., D5W) or saline-based I.V. fluid, but not lactated Ringer's solution. Nicardipine is not compatible with 5 % sodium bicarbonate, furosemide, heparin or thiopental.

Standard Concentrations

Capsule, as hydrochloride: 20 mg, 30 mg
Capsule, sustained release, as hydrochloride: 30 mg, 45 mg, 60 mg
Injection solution: 2.5 mg/mL (10 mL). The manufacturer recommends a concentration of 0.1 mg/mL for infusion.

Generic/Brand® Names:

Yes/Cardene® I.V., Cardene®SR, Cardene®

5.5   Nitrates

5.5.1   Nitroglycerin

Indication

Nitroglycerin is used in adult patients for both the acute treatment and prophylaxis of angina pectoris [137] and the acute treatment of congestive heart failure (e.g., associated with acute myocardial infarction). Other indications include hypertensive emergencies, pulmonary hypertension, and to improve coronary blood following cardiovascular surgery or transcatheter coronary

revascularization [138, 139]. In pediatric patients, it is used primarily for treatment of hypertensive emergencies and following cardiovascular surgery (especially with cardiopulmonary bypass) to improve coronary blood flow and myocardial perfusion.

Mechanism of Action

Nitroglycerin is a nitric oxide (NO) donor that causes relaxation of vascular smooth muscle and thus vasodilation by increasing the intracellular concentration of cyclic guanosine monophosphate (cGMP). Increased cGMP leads to an increased intracellular calcium concentration, which causes smooth muscle cells to relax.

Nitroglycerin appears to dilate veins more than arteries, although the coronary arteries respond well, resulting in improved myocardial oxygen delivery. Systemic venous dilation results in lower atrial filling pressures (preload) and ventricular end diastolic pressures; this effect reduces myocardial oxygen demand. Systemic arterial dilation also reduces myocardial oxygen demand by reducing afterload [140].

Dosing

Children:
I.V. continuous infusion: Initial: 0.25–0.5 mcg/kg/min I.V. Dose is titrated to achieve desired effect by 0.5–1 μg/kg/min increments every 3–5 min. Usual maximum dose is 5 μg/kg/min, but doses to 20 μg/kg/min have been described.

Adults:
Oral: 2.5–9 mg every 8–12 h

Sublingual: 0.2–0.6 mg every 5 min for maximum of 3 doses in 15 min

Lingual: 1–2 sprays into mouth or under tongue every 3–5 min for maximum of 3 sprays in 15 min. Can be used prior to activities that cause angina.

Ointment: 1–2″ every 8 h

Patch: Initial: 0.2–0.4 mg/h and titrate 0.4–0.8 mg/h. To minimize tolerance, have patch in place for only 12–14 h/day.

I.V. continuous infusion: Initial: 5 µg/min I.V.; increase by 5 µg/min every 3–5 min to 20 µg/min, then increase as needed by 10 µg/min every 3–5 min up to maximum dose of 200 µg/min.

Note:

Diminished efficacy of nitroglycerin, termed tolerance, typically occurs in 24–48 h of ongoing use [138]. Both the hemodynamic and anti-anginal effects of the drug are reduced. To minimize tolerance, a daily drug-free interval of 10–12 h/day is recommended along with the lowest effective dose possible. Tolerance may also be reversed with the administration of N-acetylcysteine.

Pharmacokinetics

(Table 5.3)
Distribution: Volume of distribution in adults: 3 L/kg
Half-life: 1–4 min
Protein binding: 60 %

TABLE 5.3 Pharmacodynamics of various forms of nitroglycerin

Dosage Form	Onset (min)	Duration
I.V.	1–2	3–5 min
Sublingual	1–3	30–60 min
Translingual spray	2	30–60 min
Buccal, extended release	2–3	3–5 h
Oral, sustained release	40	4–8 h
Topical ointment	20–60	2–12 h
Transdermal	40–60	12–24 h

Metabolism: Extensive first-pass; metabolized by red blood cells, blood vessel walls, and the liver

Clearance: Approximately 1 L/min/kg

Elimination: Inactive metabolites are excreted in the urine

Monitoring parameters: Blood pressure, heart rate (with I.V. infusion)

Contraindications:

Hypersensitivity to nitroglycerin and organic nitrates (rare) or any component (adhesive in transdermal patches included); glaucoma; severe anemia; increased intracranial pressure; concurrent use of sildenafil tadalafil, avanafil, or vardenafinil; I.V. form contraindicated in patients with hypotension, uncontrolled hypokalemia, pericardial tamponade, constrictive pericarditis, or obstructive hypertrophic cardiomyopathy.

Adverse Effects

Cardiovascular: Hypotension, reflex tachycardia, pallor, flushing, and cardiovascular collapse. Acute cessation of therapy may cause severe hypotension, bradycardia, and acute coronary insufficiency.

Central nervous system: Headache (most commonly reported side effect), dizziness, and restlessness

Gastrointestinal: Nausea, vomiting

Endocrine/metabolic: One I.V. formulation contains alcohol and may cause alcohol intoxication

Cutaneous/peripheral: Allergic contact dermatitis and exfoliative dermatitis (occur with patches and ointment)

Other: Perspiration

Precautions

An excessive vasodilatory effect of nitroglycerin may cause severe hypotension, so caution should be used in treating any patient who is either hypovolemic or hypotensive, including those with an acute myocardial infarction.

Drug Interactions

Nitroglycerin may antagonize the anticoagulant effect of heparin; thus, when nitroglycerin is discontinued, a reduction in heparin dose may be required. Alcohol and drugs that lower blood pressure, such as ß-blockers and calcium channel blockers, may potentiate nitroglycerin's hypotensive effect. Concomitant use of sildenafil or other phosphodiesterase-5 inhibitors may cause severe hypotension from excessive vasodilation.

Compatible Diluents/Administration

The I.V. form of nitroglycerin can be mixed in D5W. Because it attaches to plastics, nitroglycerin for I.V. infusion must be prepared in glass bottles and run through non-polyvinyl chloride tubing sets. I.V. nitroglycerin should not be mixed with other drugs. Multiple additional forms of nitroglycerin exist for oral (tablet, capsule, and aerosol) and topical (ointment, transdermal patch) administration.

Standard Concentrations

As above

Generic/Brand® Names:

Yes (including capsule, injection, patch, and tablet forms)/ Nitro-Bid®, Nitro-Dur®, Nitrogard®, Nitrol®, Nitrostat®, Nitro-Tab®

5.5.2   Isosorbide Dinitrate

Indication:

Isosorbide dinitrate is used in the prevention and treatment of angina pectoris. Additionally isosorbide dinitrate is often paired with the antihypertensive medication, hydralazine, and used for the treatment of chronic heart failure. In self-identified African Americans the addition of hydralazine and isosorbide

dinitrate therapy to standard therapy with an angiotensin converting enzyme inhibitor and/or a beta blocker was shown to be of significant benefit [141–144]. There is little data on the use of isosorbide dinitrate in the pediatric population [88].

Mechanism of Action: Acts as a nitric oxide donor that activates guanylate cyclase in vascular smooth muscle cells leading to vasodilation. [141, 145, 146]

Dosing

Adults:
Angina:

Oral:

Immediate release: initial: 5–20 mg 2–3 times/day; Maintenance: 10–40 mg 2–3 times/day or 5–80 mg 2–3 times/day [147, 148]

Sustained release: 40 – 160 mg/day has been used in clinical trials or 40 mg 1–2 times/day [147, 148]

Sublingual:

Prophylactic use: 2.5–5 mg administered 15 min prior to activities which may provoke an angina episode

Treatment of acute angina episode: use only if patient has failed sublingual nitroglycerin): 2.5–5 mg every 5–10 min for maximum of 3 doses in 15–30 min

Heart Failure:

Oral: Immediate release (Note: Use in combination with hydralazine):
Initial dose: 20 mg 3–4 times per day
Target dose: 160 mg/day in 4 divided doses

Pharmacokinetics

Onset of action: Sublingual tablet approximately 3 min; Oral tablet or capsule approximately 1 h [149].

Absorption: Sublingual administration produces maximal plasma concentrations of the drug by 6 min.

Distribution: 2– 4 L/kg.

Half-life: 45 min, the parent drug. The primary initial metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, have longer half-lives (2 h) and are presumed to contribute to the therapeutic efficacy of the drug

Metabolism: Hepatic metabolism with enzymatic denitration followed by glucuronide conjugation into two active metabolites, 2-mononitrate and 5-mononitrate. [1, 2, 6]

Elimination: Urine and feces

Monitoring parameters: Blood pressure, heart rate

Contraindications:

Hypersensitivity to isosorbide dinitrate or any component of the formulation; hypersensity to organic nitrates; concurrent use with phosphodiesterase-5 inhibitors (sildenafil, tadalafil, or vardenafil) [149].

Adverse Effects

Cardiovascular: Hypotension, bradycardia, rebound hypertension, syncope

Central nervous system: Increased intracranial pressure, headache, syncope [149]

Hematologic: Methemoglobinemia (Rare) [149]

Drug Interactions

Avoid concurrent use with PDE-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) Hypotensive agents may increase adverse effects. Isosorbide dinitrate decreases the metabolism of CYP3A4 substrates [150].

Tolerance:

Appropriate dosing intervals are needed to minimize tolerance development. Tolerance can only be overcome by short periods of nitrate absence from the body. Dose escalation does not overcome this effect. When used for heart failure in combination with hydralazine, tolerance is less of a concern.

Compatible Diluents/Administration

Capsules, tablets (both oral and sublingual) and extended release tablets are commercially available.

Generic/Brand® Names:

Yes/Isordil®

5.5.3 Sodium Nitroprusside

Indication

Nitroprusside (sodium nitroprusside) is a systemic vasodilator used to treat hypertensive crises and congestive heart failure. In pediatric and adult patients, nitroprusside has been used to decrease systemic vascular resistances (SVR) and generate controlled hypotension during surgery and reduce bleeding [151–153]. The rapid onset and short half-life of nitroprusside allow for ease of titration in an intensive care setting and it is commonly used to reduce SVR (afterload) in pediatric patients following cardiopulmonary bypass surgery. Nitroprusside in combination with esmolol has demonstrated efficacy in controlling hypertension post-coarctation repair in pediatric patients [154].

Mechanism of Action

Nitroprusside is a nitric oxide donor that induces vascular smooth muscle relaxation and vasodilation of veins and arteries including coronary arteries. It is more active on veins than arteries, but the selectivity for veins is less than that of nitroglycerin. Venous dilation allows for reduction in preload and the arterial dilation produces decreased afterload [151–153, 155].

Dosing

Neonates:

Limited data in neonates describes initial doses of 0.2 µg/kg/min as a continuous I.V. infusion and titrated to effect.

Infants and Children:

Initial: 0.5–1 μg/kg/min by continuous I.V. infusion. The dose is titrated in increments of 0.5 μg/kg/min to achieve the desired effect or until headache and/or nausea develop. The usual clinically effective dose is 3 μg/kg/min; maximum dose 8–10 μg/kg/min.

Adults:

Initial: 0.3–0.5 μg/kg/min by continuous I.V. infusion. The dose is titrated in increments of 0.5 μg/kg/min to achieve the desired effect or until headache and/or nausea develop. The usual clinically effective dose is 3 μg/kg/min; maximum dose 10 μg/kg/min.

Pharmacokinetics

Onset of action: 0.5–2 min (hypotensive effect)

Half-life: Parent drug 3–4 min; thiocyanate 3 days (prolonged with impaired renal function)

Duration: Effects cease within 10 min of discontinuation

Metabolism: Converted by erythrocytes and tissue sulfhydryl group interactions to cyanide, which is then converted to thiocyanate in the liver by the enzyme rhodanase

Elimination: Thiocyanate is excreted in the urine

Monitoring parameters: Blood pressure and heart rate (reflex tachycardia with hypotension) should be monitored continuously. Monitor closely for signs of cyanide and thiocyanate toxicity (see Poisoning Information), including acid–base status, blood cyanide, and thiocyanate levels (especially patients with renal or hepatic dysfunction).

Contraindications: Hypersensitivity to nitroprusside or any component; inadequate cerebral perfusion; unrepaired coarctation of the aorta; high output CHF; congenital optic atrophy.

Adverse Effects

Cardiovascular: Excessive hypotensive response, palpitations, reflex tachycardia, and substernal chest pain

Respiratory: Tachypnea or respiratory distress (from metabolic acidosis caused by cyanide toxicity), and hypoxemia

Central nervous system: Disorientation, restlessness, headache, dizziness, psychosis, and elevated intracranial pressure

Gastrointestinal: Nausea, vomiting

Neuromuscular and skeletal: Weakness, muscle spasm

Endocrine/metabolic: Thyroid suppression

Hematologic: Methemaglobinemia

Other: diaphoresis, tinnitus, cyanide and/or thiocyanate toxicity

Precautions

Use with caution in patients with either hepatic or renal dysfunction. Patients with renal dysfunction are at increased risk of thiocyanate toxicity, and patients with hepatic dysfunction are at increased risk of cyanide toxicity. See also Poisoning Information.

Drug Interactions

The addition of nitroprusside to treatment regimens that include other antihypertensive agents can lead to excessive hypotension.

Poisoning Information

Toxicity from nitroprusside can occur either by cyanide or thiocyanate toxicity. Signs and symptoms of excessive cyanide and thiocyanate levels include metabolic acidosis (with increased blood lactate), tachycardia, tachypnea, headache, psychosis, hyper-reflexia, confusion, weakness, tinnitus, miosis, seizures, and coma. Patients with hepatic dysfunction or anemia should have blood cyanide levels measured. Patients receiving nitroprusside doses of 4 μg/kg/min or greater, therapy lasting more than 3 days, or patients with renal dysfunction should have blood thiocyanate levels measured. A recent pediatric study showed that infusion rates greater than 1.8 μg/kg/min increased the risk of developing elevated cyanide levels [156, 157].

Reference ranges for cyanide and thiocyanate are as follows:

Thiocyanate	Cyanide
Therapeutic: *6–29 µg/mL*	*Normal*: *<0.2 µg/mL*
Toxic: *35–100 µg/mL*	*Normal* (*smoker*): *<0.4 µg/mL*
Fatal: *>200 µg/mL*	*Toxic*: *>2 µg/mL*
	Potentially lethal: *>3 µg/mL*

If *toxicity develops*, in addition to discontinuing nitroprusside administration, therapies include:

1. Support respiration and supply oxygen;
2. Antidotal therapy with sodium nitrite followed immediately by sodium thiosulfate [155, 158]

1. Sodium nitrite:
   Infants and Children: 6 mg/kg/dose (maximum: 300 mg) IV over 2–4 min
   Adults: 300 mg IV over 2–4 min
2. Sodium thiosulfate:
   Infants and Children: 150–200 mg/kg/dose (maximum 12.5 g) IV over 10 min
   Adults: 12.5 g IV infusion over 10 min
3. Dialysis (thiocyanate is removed by dialysis, but not cyanide)

Compatible Diluents/Administration

Nitroprusside should be prepared for intravenous administration by dilution in dextrose 5 %. Exposure to light causes nitroprusside to break down and form cyanide. It must be protected from light (e.g., by wrapping mixture in aluminum foil or opaque sleeve) at all times. Use only if mixed solution remains clear; slight discoloration (e.g., light brown, light orange) is common, but dark brown, orange, or any blue discoloration suggests break down to cyanide. Discard any solution suspected of degradation and prepare a fresh mixture. The solution

is stable at room temperature for up to 24 h if properly protected from light.

Standard Concentrations

Injection, as sodium: 25 mg/mL (2 mL)

Generic/Brand® Names:

Yes/Nipride®, Nitropress®

5.6   Other Systemic Vasodilators

5.6.1   Phenoxybenzamine

Indication

Phenoxybenzamine is a non-specific, long-acting, alpha-adrenergic antagonist used in the pediatric patients for the treatment of arterial hypertension, particularly when secondary to pheochromocytoma [159], and in the acute postoperative course of congenital or acquired cardiac anomalies. It is a potent systemic and mild pulmonary vasodilator. In some pediatric cardiac centers, it is considered to be an essential drug in the armamentarium for the treatment of low cardiac output state after weaning from cardiopulmonary bypass [160]. It may also be useful in treating radial artery grafts prior to surgical coronary revascularization procedures [161], and it may be used in combination with other vasodilators [162, 163]. Phenoxybenzamine can maintain organ perfusion on cardiopulmonary bypass and improve peripheral blood flow as demonstrated by smaller base deficits and temperature gradients intra-operatively and in the intensive care unit as compared to nitroprusside [164, 165]. It has efficacy in decreasing the incidence of sudden circulatory collapse after the first stage Norwood operation [166–168]. Lastly, it may also be beneficial in establishing more uniform re-warming following bypass and as a non-selective pulmonary vasodilator [163].

Mechanism of Action

Phenoxybenzamine forms a permanent and irreversible covalent bond with nitrogen atoms on the surface of alpha adrenoceptors, thereby blocking epinephrine and norepinephrine from binding with these receptors. This causes systemic vasodilatation, and to some extent, pulmonary vasodilation due to a reduction in vascular resistances. These activities are beneficial in controlling the effects of endogenously-released catecholamines in the peri-operative stress response.

It also acts upon alpha-1 and -2 receptors, reducing sympathetic activity, by affecting postsynaptic membrane adrenoceptors in the sympathetic nervous pathway. The resulting "chemical sympathectomy" induces further general vasodilation, miosis, an increase in gastrointestinal tract motility, secretions, and glycogen synthesis.

In addition to the alpha-blockade effect, phenoxybenzamine irreversibly inhibits responses to 5-hydroxytryptamine (serotonin), histamine and acetylcholine.

There is no known effect on the parasympathetic nervous system.

Phenoxybenzamine is a non-competitive (irreversible) antagonist, meaning that receptor blockade cannot be overcome by addition of agonist drugs.

Dosing

Phenoxybenzamine should be slowly titrated to the desired effect after a small initial dose and under close hemodynamic monitoring. It may be infused in D5W or in NaCl 0.9 %.

Neonates, infants and children:

Oral: 0.2–1 mg/kg P.O./N.G. every 12–24 h

I.V.: 1 mg/kg I.V. over 2 h, followed by 0.5 mg/kg/dose every 6–12 h administered over 2 h. It may be progressively increased to 2 mg/kg once or twice a day in patients <12 years or 1 mg/kg once or twice a day in patients >12 years.

Adults:

> Oral: 5–10 mg P.O./N.G twice a day; dose may be increased every other day to 20–80 mg two or three times a day.

Note: In patients with pheochromocytoma, if persistent or excessive tachycardia occurs, the use of a concomitant β-blocker may be necessary.

Pharmacokinetics

Onset of action: Rapid

Absorption: When administered orally, 20–30 % of the drug is absorbed in the active form [169]

Duration: 3 to 4 days

Metabolism: Hepatic

Half-life: The half-life or oral phenoxybenzamine is not well known; intravenously, the half-life is approximately 24 h, and effects may persist for 3–4 days. Effects of daily administration are cumulative for nearly a week. The duration of action is dependent not only on the presence of the drug, but also on the rate of synthesis of alpha receptors.

Elimination: Renal and biliary

Contraindications

> Phenoxybenzamine is contraindicated in patients with hypersensitivity to the drug or any of its components. The induction of alpha-adrenergic blockade leaves beta-adrenergic receptors unopposed. Compounds that stimulate both types of receptors may produce an exaggerated hypotensive response with reflex tachycardia.

Adverse Effects

Cardiovascular: Tachycardia, arrhythmias, hypotension (mostly in patients with intravascular volume depletion), and shock

Gastrointestinal: Vomiting

Metabolic: Water and sodium retention

Central nervous system: Dizziness, drowsiness, and postural hypotension
Neuromuscular and skeletal: Weakness
Opthalmologic: Miosis
Other: Nasal congestion, irritation, fatigue, and lethargy

Drug Interactions

Phenoxybenzamine interacts with compounds that stimulate both alpha- and beta-adrenergic receptors to produce severe hypotension and tachycardia. Phenoxybenzamine blocks the hyperthermia produced by norepinephrine and blocks the hypothermia produced by reserpine.

Poisoning Information

Overdosage of phenoxybenzamine produces symptoms of sympathetic nervous system blockade; symptoms and signs include hypotension, tachycardia, dizziness or fainting, vomiting, lethargy and shock. Treatment of overdosage consists of the following:

- Drug withdrawal
- Recumbent position with leg elevation

Intravenous volume

- Infusion of norepinephrine in cases of severe hypotension. Note: usual inotropic agents are not effective. **Epinephrine is contraindicated** since it stimulates both alpha- and beta-receptors, and because alpha-receptors are blocked, it may produce further hypotension via beta-receptor stimulation.

Antagonism with vasopressin has been described as effective, particularly for the treatment of phenoxybenzamine-induced side effects in patients following the Norwood procedure [168].

Generic/Brand® Names:

Yes/Dibenzyline®

5.6.2   Phentolamine

Indication

Phentolamine is a reversible, competitive, non-selective, alpha-adrenergic antagonist that has similar affinities for alpha-1 and alpha-2 receptors. Its effects on the cardiovascular system are very similar to those of phenoxybenzamine, and therefore, its primary action is systemic vasodilation. It may also have a positive inotropic and chronotropic effect on the heart.

The primary application for phentolamine is for the control of hypertensive emergencies, most notably due to pheochromocytoma [170]. It may also be used for the treatment of cocaine-induced hypertension [171], when one would generally avoid β-blockers and where calcium channel blockers are not effective. It has also been used to treat hypertensive crises secondary to monoamine oxidase inhibitor-sympathomimetic amine interactions and for withdrawal of clonidine, propranolol or other antihypertensives.

Mechanism of Action

Phentolamine is a long-acting, alpha-receptor blocking agent that can produce and maintain a "chemical sympathectomy" by oral administration. It increases blood flow to the skin, mucosa and abdominal viscera, and lowers both supine and erect blood pressures. It has no effect on the parasympathetic nervous system. Phentolamine works by blocking alpha receptors present in vascular smooth muscle, thereby inducing vasodilation. It also blocks receptors for 5-hydroxytryptamine (serotonin), and it causes release of histamine from mast cells. Phentolamine also blocks potassium channels [172], which can accentuate vasodilation.

In patients with congenital or acquired cardiac defects, phentolamine is used to induce peripheral vasodilation

and afterload reduction following cardiopulmonary bypass surgery. The use of phentolamine during bypass is associated with reduced systemic anaerobic metabolism and more uniform body perfusion [173].

Phentolamine can be used locally to prevent dermal necrosis after extravasation of an alpha-agonist or to relieve arterial spasms caused by intra-arterial catheters [174].

There have been anecdotal reports on its usefulness in improving mixing in newborns with transposition of the great arteries. Presumably, improved mixing of blood would be due to both a reduction in afterload and an alteration in the diastolic function of the right ventricle, allowing more left-to-right shunting across the atrial septal defect [175].

Phentolamine also has a diagnostic role in cases of pheochromocytoma and complex regional pain syndromes (e.g., reflex sympathetic dystrophy).

Interestingly, although widely used in the pediatric patients, literature describing its use is scant.

It is a competitive antagonist, meaning that blockade can be surmounted by increasing the concentration of agonist drugs.

Dosing

Phentolamine should be slowly titrated to the desired effect after a small initial dose and with rigorous hemodynamic monitoring. It may be infused in D5W or in NaCl 0.9 %.

Neonates, **infants and children**:

Treatment of hypertension or to achieve afterload reduction: 0.02–0.1 mg/kg (maximum 10 mg) I.V. to be administered over 10–30 min, followed by a continuous infusion at 5–50 μg/kg/h I.V.

Treatment of extravasation: Subcutaneous infiltration of the affected area with 0.1–0.2 mg/kg (maximum 10 mg) in up to 5 ml of sterile water for injection within 12 h of the event.

Diagnosis of pheochromocytoma: Single dose of 1 mg I.V.

Adults:

> Diagnosis of pheochromocytoma: Single dose of 5 mg I.V.
>
> Treatment of hypertension: 2.5–5 mg I.V. single doses as required to control blood pressure

Pharmacokinetics

Onset of action: Immediate
Duration: 30–45 min
Maximum effect: 2 min
Metabolism: Extensively metabolized in the liver
Half-life: 19 min (adults)
Elimination: 10 % excreted in the urine as unchanged drug
Contraindications

Phentolamine is contraindicated in patients with ischemic myocardial disease or cerebral ischemic disease and in cases of hypersensitivity to the drug or any of its components. Phentolamine should be used with additional care in patients with impairment of renal function, gastritis, peptic ulcer disease or a history of arrhythmia or angina.

Adverse Effects

Cardiovascular: Hypotension (mostly in patients with intravascular volume depletion), tachycardia, arrhythmias, shock, and ischemic cardiac events
Gastrointestinal: Vomiting, nausea, abdominal pain, diarrhea, and exacerbation of peptic ulcer
Neuromuscular and skeletal: Weakness
Central nervous system: Dizziness
Other: Flushing, nasal congestion

Drug Interactions

Vasoconstrictive and hypertensive effects of epinephrine and ephedrine are antagonized by phentolamine.

Poisoning information

Similar to phenoxybenzamine, overdosage is suspected in cases of excessive tachycardia, shock, vomiting and

dizziness (symptoms sympathetic nervous system block-
ade and of increased circulating epinephrine). Treatment
of overdosage consists of the following:

- Drug withdrawal
- Recumbent position with leg elevation
- Intravenous fluid administration
- Since this drug binds competitively as opposed to
  phenoxybenzamine, inotropic agents with alpha-
  agonist effects may be effective. Nevertheless, **epi-
  nephrine is contraindicated**, since it stimulates both
  alpha- and beta-receptors, and since alpha-receptors
  are blocked, it may produce further hypotension.

Generic/Brand® Names

Yes/Regitin®, Rogitin®

5.7   Dopaminergic Receptor Agonist

5.7.1   Fenoldapam

Indication:

The original indication of fenoldopam was in the treatment
of severe hypertension [176, 177] . Over the past decade,
fenoldopam's indication has evolved to use include use
in the attempt to prevent acute kidney injury [178, 179].
The efficacy of fenoldopam to augment renal blood flow,
increase diuresis in the attempt to prevent acute kidney
injury has been studied in smaller cohorts and those data
have been reviewed in meta-analyses. [178, 180–183] To
date, there are no large randomized controlled trials sup-
porting the use of fenoldopam to prevent renal injury.

Mechanism of Action:

Fenoldopam is a direct-acting vasodilator that binds to
postsynaptic dopaminergic type 1 (DA_1) receptors in
the renal, coronary, cerebral, and splanchnic vasculature
resulting in arterial dilation and lower mean arterial
pressure (MAP) and binds with moderate affinity to

alpha 2 receptors. In the renal vasculature fenoldopam causes renal vasodilation and inhibition of tubular sodium reabsorption, causing both an improvement in renal blood flow as well as diuresis [3]. It is six times as potent as dopamine in producing renal vasodilation.

Dosing

Infants/Children:
I.V. continuous infusion:
Doses used in the effort to increase renal blood flow:
0.05 μg/kg/min to 0.3 μg/kg/min I.V. have been the most commonly used dosing ranges [179, 184–186]. Up to 7 days is the longest documented infusion in current literature.
Hypertension (**severe**), **short-term treatment**:
Initial: 0.2 μg/kg/min I.V.; increase in increments of up to 0.3–0.5 μg/kg/min every 20–30 min; dosages greater than 0.8 μg/kg/min have resulted in tachycardia with no additional benefit; administer for up to 4 h.
Adults:
Increase renal blood flow:
0.03–0.1 μg/kg/min has been shown to increase renal blood flow without reducing systemic vascular resistance [7].
Hypertension (**severe**), **short-term treatment**:
Initial: 0.03–0.1 μg/kg/min I.V.; increase every 15 min by 0.05–0.1 μg/kg/min based on response; maximum rate 1.6 μg/kg/min; administer for up to 48 h [82].
Usual treatment length of 1–6 h with dose tapering of 12 % every 15–30 min.
No dosage adjustment required in renal or hepatic impairment.

Pharmacokinetics

Onset of action: 10 min with peak response in 30 min to 2 h
Absorption: Well absorbed orally with peak serum levels in approximately 1 h, but has a significant first-pass effect resulting in low plasma levels of drug
Distribution: Volume of distribution is about 0.6 L/kg
Half-life: Elimination half-life is approximately 10 min
Metabolism: Fenoldopam has an extensive first-pass effect. It is metabolized in the liver to multiple metabolites which may have some activity.

Elimination: 80 % is excreted in the urine and 20 % is excreted in feces

Monitoring parameters: Blood pressure, heart rate, electrocardiogram, renal and liver function tests, serum potassium concentrations

Contraindications: Hypersensitivity to fenoldopam or sulfites

Adverse Effects

Cardiovascular: Tachycardia or bradycardia, angina, flattening of T-waves (asymptomatic) [3], atrial fibrillation, atrial flutter, edema, hypotension [187]

Central nervous system: Headache, dizziness [177]

Dermatologic: flushing

Gastrointestinal: Diarrhea, nausea, vomiting, and dry mouth

Ophthalmologic: Increased intraocular pressure, blurred vision

Hepatic: Increased portal pressure in patients with cirrhosis

Drug Interactions: β-blockers increase the risk of hypotension, and acetaminophen may increase fenoldopam levels by 30–70 %.

Compatible Diluents/Administration: I.V.: dilute in 0.9 % NaCl or 5 % Dextrose to a final concentration of 40 μg/mL. Administer by continuous I.V. infusion; do not use a bolus dose.

Generic/Brand® Names:

Yes/Corlopam®

5.8   Prostaglandins

5.8.1   *Prostaglandin E₁*

Indication:

Prostaglandin E_1 is used for the temporary maintenance of patency of the ductus arteriosus in neonates with ductal-dependant congenital heart disease until the

patient can undergo an interventional procedure. Congenital heart defects that create ductal-dependent circulations include pulmonary atresia, critical pulmonary stenosis, tricuspid atresia, tetralogy of Fallot and pulmonary atresia without major aorto-pulmonary collaterals, transposition of the great arteries, hypoplastic left heart syndrome, critical aortic stenosis, critical coarctation of the aorta, and interrupted aortic arch [188–194].

Patients with severe pulmonary hypertension that is refractory to pulmonary antihypertensive drugs may benefit from a prostaglandin E_1 infusion. This drug will maintain patency of the ductus arteriosus, which may decompress the pulmonary circulation while maintaining an adequate systemic cardiac output, albeit at expense of systemic oxygen desaturation.

Mechanism of Action:

Prostaglandin E_1 causes vasodilation by exerting direct effects on vascular and ductus arteriosus smooth muscle.

Dosing

Neonates and Infants:

I.V. continuous infusion: 0.05–0.1 μg/kg/min I.V. initial infusion rate that may be slowly increased; the lowest effective dose should be used. Maintenance dose range: 0.01–0.4 μg/kg/min. The usual infusion rate is 0.1 μg/kg/min, but it is often possible to reduce the dose to ½ or 1/10 of this dose and maintain ductal patency.

Pharmacokinetics

Onset of action: Rapid; dilation of ductus arteriosus typically occurs within 30 min of I.V. infusion [188].

Duration: Ductus arteriosus will begin to close within 1–2 h after infusion is discontinued.

Maximum effect: In acyanotic congenital heart disease, the maximal effect is seen in 1.5–3 h, with a range of 15 min to 11 h. In cyanotic congenital heart disease, the usual maximal effect is seen within 30 min.

Half-life: The half-life is 5–10 min, therefore, prostaglandin E_1 must be administered by continuous infusion.

Metabolism: 70–80 % of prostaglandin E_1 is metabolized by oxidation during one pass through the lungs. One active metabolite (13–14 dihydro-PGE_1) has been identified in neonates.

Elimination: 90 % of prostaglandin E_1 is excreted in the urine as metabolites within 24 h.

Monitoring parameters:

Minimal non-invasive monitoring should include arterial blood pressure, heart rate, respiratory rate, and temperature. Patients receiving an infusion for longer than 5 days should be monitored for the development of gastric outlet obstruction [189].

Contraindications:

Respiratory distress syndrome without ductal-dependant congenital heart disease may be a contraindication. Prostaglandin E_1 may cause hypotension and worsen ventilation/perfusion matching in the lungs. In addition, it may worsen hypoxemia due to increased right-to-left shunting across either a patent foramen ovale and/or the ductus arteriosus.

Adverse Effects

Cardiovascular: Flushing, bradycardia, systemic hypotension, tachycardia, and edema

Respiratory: Apnea may occur in about 10 % of neonates, with greater risk in those weighing less than 2 kg at birth; usually occurs during the first hour of the infusion.

Central nervous system: Seizures, headache, and fever

Gastrointestinal: Gastric outlet obstruction secondary to antral hyperplasia [190]

Neuromuscular and skeletal: Cortical hyperostosis has been seen with long-term infusions and is related to duration of therapy and cumulative dose [3]. Most cases have occurred after 4–6 weeks of therapy, however, there is one report of it developing after 11 days [191].

Endocrine/metabolic: Hypocalcemia, hypokalemia, hyperkalemia, and hypoglycemia

Hematologic: May cause inhibition of platelet aggregation

Drug Interactions: Use with anti-hypertensive agents may increase the risk of hypotension.

Compatible Diluents/Administration: Compatible with 5 % Dextrose, 10 % Dextrose and 0.9 % NaCl solutions. Infuse into a large vein or an umbilical arterial catheter placed at the ductal opening. Maximum concentration for I.V. infusion is 20 μg/ml.

Generic/Brand® Names:

Yes/Alprostadil®, Prostine®

5.9   Miscellaneous

5.9.1   Hydralazine

Indication:

Management of moderate to severe hypertension.

Mechanism of Action:

Hydralazine is a direct-acting vasodilator that exerts effect on arterioles with little effect on veins and decreases systemic resistance. The precise mechanism of action is unknown.

Dosing

Infants/Children:

Oral: Initial: 0.75 to 1 mg/kg/day P.O./N.G. in 2–4 divided doses, not to exceed 25 mg/dose. Increase over 3–4 weeks to a maximum of 5 mg/kg/day in infants and 7.5 mg/kg/day in children given in 2–4 divided doses. Maximum daily dose: 200 mg/day.

I.M., I.V.: Initial: 0.1–0.2 mg/kg/dose I.V. (not to exceed 20 mg) every 4–6 h as needed; up to 1.7–3.5 mg/kg/day may be given in 4–6 divided doses.

Adults:

Oral: Initial: 10 mg four times a day P.O./N.G. Dose may be increased by 10–25 mg per dose every 2–5 days to a maximum of 300 mg per day. Usual dose range for hypertension: 25–100 mg per day in 2 divided doses.

I.M., I.V.: Hypertension: Initial 10–20 mg I.V. per dose every 4–6 h as needed. May increase to a maximum of 40 mg per dose.

Dosing in renal impairment: [195]

Cl_{cr} 10–50 mL/min/1.73 m^2: Administer every 8 h

Cl_{cr} <10 mL/min/1.73 m^2: Administer every 8–16 h in fast acetylators and every 12–24 h in slow acetylators.

Pharmacokinetics

Onset of action: Oral: 30 min; I.V.: 5–20 min

Distribution: Hydralazine crosses the placenta and is found in breast milk

Half-life: In adults with normal renal function, the range is 2–8 h; however, it may vary depending upon individual acetylation rates

Duration: Oral: 2–4 h; I.V.: 2–6 h

Protein binding: 85–95 % protein bound

Metabolism: Metabolized in the liver with an extensive first-pass effect with oral administration.

Elimination: 14 % is excreted unchanged in the urine

Precautions:

Hydralazine may cause a drug-induced, lupus-like syndrome, especially with large doses administered over a long time period. Discontinue therapy if patient develops this syndrome. Hydralazine is usually administered together with a diuretic and a β-blocker to counteract the side effects of sodium and water retention and reflex tachycardia [196–199].

Monitoring parameters:

Blood pressure should be closely monitored with I.V. administration, heart rate, and antinuclear antibody (ANA) titers (see Adverse Effects, Other).

Contraindications:

Hydralazine is contraindicated in patients with dissecting aortic aneurysms, mitral valve rheumatic heart disease, and significant coronary artery disease.

Adverse Effects

Cardiovascular: Tachycardia, palpitations, flushing, and edema

Central nervous system: Headache, and dizziness

Gastrointestinal: Nausea, vomiting, and diarrhea

Neuromuscular and skeletal: Arthralgias, weakness

Other: Drug-induced lupus-like syndrome [200]. Dose-related findings include: fever, arthralgia, lymphadenopathy, splenomegaly, positive ANA, maculopapular facial rash, positive direct Coombs' test, and pericarditis.

Drug Interactions:

The use of hydralazine concomitantly with monoamine oxidase inhibitors may cause a significant decrease in blood pressure. Hydrazine may cause an increase in the levels of metoprolol and propranolol (β-blockers that are not extensively metabolized in the liver are less affected). Indomethacin may decrease the hypotensive effect of hydralazine [201].

Compatible Diluents/Administration:

Usually administered by slow I.V. push over 3–5 min. Do not exceed an administration rate of 0.2 mg/kg/min. The maximum concentration for I.V. administration is 20 mg/ml.

Standard Concentrations:

20 mg/ml single dose 1 ml vials

Generic/Brand® Names:

Yes/Apresoline®

5.9.2 *Nesiritide (B-Type Natriuretic Peptide)*

Indication:

Used in the treatment of acute decompensated heart failure although a recent large clinical trial in adults comparing placebo versus nesiritide for the outcomes of relief of dyspnea or 30 day mortality associated with ADHF showed no difference in outcome between groups raises questions about its efficacy [202, 203].

In pediatric patients, safety and efficacy of nesiritide has only been studied in smaller case series where the drug has been shown to be safe and improve the consequences of heart failure including increased urine output and improve neurohumoral markers of heart failure [204–207].

Mechanism of Action:

Synthetic analogue of endogenous brain natriuretic peptide (BNP). It causes vasodilation secondary to smooth muscle cell relaxation by binding to guanylate cyclase receptor on vascular smooth muscle and endothelial cells resulting in increased intracellular cyclic GMP. Additionally, it promotes diuresis by natriuresis [208].

Dosing

Infants/Children:
Heart failure:
I.V. continuous infusion: 0.01–0.03 μg/kg/min [204, 209]

Adults:
Acute decompensated heart failure:
I.V.:
Initial: 2 μg/kg (bolus optional); followed by continuous infusion at 0.01 μg/kg/min.
Maximum dosing weight: According to the manufacturer (PRECEDENT trial_ capped dosing weight at 160 kg and the VMAC trial capped dosing weight at 175 kg) [210].

Dosing for renal impairment: No adjustment required but use cautiously in patients with renal impairement or patients who rely on the renin-angiotensin-aldosterone system for renal perfusion.

Dosing for hepatic impairment: No dosage adjustment recommended

Do not administer through a heparin-coated catheter

Pharmacokinetics

Onset of action: 15 min (60 % of 3-h effect achieved)

Distribution: Vss: 0.19 L/kg

Half-life: Initial distribution 2 min; terminal 18 min

Metabolism: Proteolytic cleavage by vascular endopeptidases and proteolysis following binding to the membrane bound natiuretic peptide and cellular internalization [210].

Elimination: Primarily eliminated by metabolism; also excreted in the urine

Monitoring parameters: Monitor blood pressure, hemodynamic response, renal function including BUN, creatinine and urine output [210].

Contraindications: Hypersensitivity to natriuretic peptide or any component of the formulation; cardiogenic shock (when used as primary therapy); hypotension (adult systolic blood pressure <90 mmHg) [210]

Adverse Effects

Anaphylactic/hypersensitivity reactions: Prepared through recombinant technology using E. coli; monitor for allergic or anaphylactic reactions [210].

Cardiovascular: Hypotension, angina, bradycardia, atrial fibrillation, AV node conduction abnormalities, ventricular tachycardia and premature ventricular contractions [210]

Central nervous system: Headache, dizziness, axiety, confusion, fever, tremor [210]

Dermatologic: Rash, Pruritis

Gastrointestinal: Nausea, abdominal pain, vomiting [210]
Respiratory: Apnea, increased cough [210]
Ophthalmologic: Amblyopia [210]
Hematologic: Anemia
Renal: May cause azotemia; use in caution in patients with renal impairment [210]

Drug Interactions: May enhance the adverse effects of other hypotensive agents

Compatible Diluents/Administration: Injection, powder for reconstitution (Rx Monographs). Protect from light. Following reconstitution, vials are viable for up to 24 h. Stable in D5W, D51/2NS, D51/4NS, NS [210]

Generic/Brand® **Names**:

Yes/Natrecor®

5.10   Vasoconstrictors

5.10.1   Vasopressin

Indication:

Vasopressin, also known as 8-arginine vasopressin and antidiuretic hormone, is a synthetic analogue of an endogenous posterior pituitary hormone. Although its original use was as a treatment for diabetes insipidus, it has an ever-expanding list of indications. Like terlipressin, vasopressin is now recommended for gastrointestinal hemorrhage due to its potent vasoconstrictive properties. It is also used in patients with septic shock refractory to alpha-adrenergic agonists. Several large trials have failed to demonstrate a mortality benefit to vasopressin over norepinephrine for adults with distributive shock, yet there are indications that sicker patients may benefit from earlier vasopressin administration. Vasopressin is now also used routinely following cardiopulmonary bypass for any adult patients

taking preoperative angiotensin-converting inhibitors (ACEi). There is a known suppression of vasopressin secretion with the administration of ACEi, although this has not been seen in children.

- There are now several studies demonstrating the efficacy of vasopressin in postoperative pediatric cardiac surgical patients [211–217]. It remains unclear why some patients respond well to vasopressin. Several groups have demonstrated low levels of vasopressin following pediatric cardiac bypass, yet no study has confirmed a correlation between low vasopressin levels and hemodynamic dysfunction. Nonetheless, vasopressin has been shown in retrospective studies to improve urine output and decrease inotrope requirements following complex congenital cardiac surgery [213].

Mechanisms of action [48, 212, 216, 218–223]

- All vasopressin receptors belong to the class of G-protein receptors. The binding of vasopressin to V1 receptors in the vascular smooth muscle activates phospholipase C as a second messenger and ultimately causes vasoconstriction through an increase in intracellular calcium. Paradoxically, the activation of V1 receptors on the endothelial cells leads to increased cyclic adenosine monophosphate (cAMP) and ultimately vasodilation via nitric oxide production.
- V2 and V3 receptors in the renal collecting duct are stimulated by vasopressin to reabsorb urea, sodium, and water. V2 receptor binding, via cAMP and protein kinase A, causes the synthesis of aquaporin, AQP2, which acts to reabsorb free water from the collecting duct. V2 receptor activation is also thought to increase coagulation by releasing Von Willebrand Factor. At higher concentrations, vasopressin stimulates cardiac oxytocin receptors, leading to the production of atrial natriuretic peptide. Finally, vasopressin also binds vascular P2 purinergic receptors, which results in the production of nitric oxide synthase and vasodilation,

Dosing:

Vasopressin is to be administered exclusively parenterally as a bolus or as a continuous infusion and has to be titrated within the therapeutic range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring. Furthermore, fluid intake and output, urine specific gravity and urine and serum osmolality should be carefully monitored.

Diabetes insipidus

Children: 2.5–10 units 2–4 times a day IM or SC; *continuous IV infusion*: 0.0005 to 0.01 units/kg/h

Adults: 5–10 Units 2–4 times a day IM or SC (maximum 60 units/day); *continuous IV infusion*: 0.0005 units/kg/h, double the dose as required to a maximum of 0.01 units/kg/h

Vasoplegic shock:

Children: 0.0002–0.007 units/kg/min or 0.04 units/kg/dose 4–6 times a day

Adults: 40 units, IV

Gastrointestinal bleeding:

Children: 0.002–0.005 units/kg/min IV continuous infusion, titrate as needed to a maximum dose of 0.01 units/kg/min. After 12 h of stability, withdraw over 24–48 h

Adults: 0.1–0.4 units/min IV continuous infusion; titrate as required to a maximum dose of 0.9 units/min. After 12 h of stability, withdraw over 24–48 h

Ventricular fibrillation or tachycardia unresponsive to initial defibrillation:

Adults: a single dose of 40 units IV

Pharmacokinetics:

Onset of action: 1 h
Duration: 2–8 h
Metabolism: most of the drug is rapidly metabolized in the liver and kidneys.
Protein-binding: 10–40 %
Half-life: 10–20 min.

Drug interactions:

Drugs that may increase vasopressin effect	Drugs that my decrease vasopressin effect
Chlorpropramide	Demeclocycline
Carbamazepine	Heparin
Hydrocortisone	Lithium
Clofibrate	Epinephrine
Tricyclic anti-depressant drugs	Alcohol

Adverse effects:

Cardiovascular: hypertension, bradycardia, arrhythmia, venous thrombosis, vasoconstriction, angina, heart block, cardiac arrest (all the above with high doses); pallor

Central nervous system: vertigo, headache, fever, seizures (careful use in case of background of comitial activity)

Cutaneous: tissue necrosis (extravasation), urticaria

Endocrine & Metabolic: water intoxication, hyponatremia

Gastrointestinal: abdominal cramps, nausea, vomiting, diarrhea

Neuromuscular & skeletal: tremor

Respiratory: wheezing, bronchospasm

Renal: careful use in patients with renal dysfunction, chronic nephritis

Hepatic: patients with chronic liver disease might require a dose adjustment (require lower doses)

Others: diaphoresis

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of vasopressin may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability). In case of extravasation, local administration of phentolamine or papaverine is indicated.

Compatible diluents:

Intravenous vasopressin may be diluted in normal saline or in dextrose solutions to a final concentration of 0.1–1 units/ml. IM and SC vasopressin is to be administered without further dilution. It should be administered into a central vein, except and transiently in urgent scenarios, with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solution (aqueous): 20 units/ml (0.5, 1 and 10 ml vials)

Generic/Brand® Names:

Pitressin®

5.10.2   Terlipressin

Indication [96, 224–232]

Terlipressin, or triglycyl-lysine-vasopressin, is a synthetic form of vasopressin that acts predominantly as a vasopressor but with less free water retention (and resultant hyponatremia) as seen with vasopressin. Its primary indication is in upper gastrointestinal bleeding, particularly cirrhotic esophageal variceal hemorrhage where it has proven survival benefit. There are also preliminary data for its use in cardiac arrest in combination with epinephrine [226]. One trial has confirmed that terlipressin effects more vasoconstriction than vasopressin in adult septic shock [228]. Finally, it has been recommended for use in hepatorenal syndrome Type I to preserve renal function while awaiting transplant [230]. Limited studies endorse the pediatric application of terlipressin for vasodilatory shock refractory to vasopressors and volume expansion. There is one case series supporting its use in pediatric post-operative cardiac surgery for refractory hypoperfusion. Presumably, terlipressin, much like vasopressin, is best suited to micro or

macrocirculatory dysfunction, i.e., vasoplegia. Caution should be exercised when implementing this therapy in patients with a failing myocardium as animal studies have demonstrated that bolus terlipressin may lead to such dramatic elevation in systemic vascular resistance that cardiac output falls, as does tissue oxygenation.

Mechanisms of action:

Terlipressin is a prodrug that is cleaved to form lysine vasopressin. It binds to endogenous vasopressin receptors, although it has increased affinity to the V1 receptor and binds very little to V2 receptors. V1 receptors are G-protein coupled and lead, via phospholipase C, to an influx of calcium. In the smooth muscle cells surrounding vasculature, this leads to vasoconstriction. In some vascular beds, however, the same V1 receptors on the endothelia cells can lead to the production of nitric oxide and actually promote vasodilation.

Dosing:

Given its long half-life, terlipressin is traditionally administered as a bolus dose, as is typical for gastrointestinal bleeding. There are some reports of its use as a continuous infusion as well.

Neonates:
Shock: 20 µg/kg every 4 h, 5 µg/kg/h continuous infusion has also been reported

Infants/Children:
Cardiac Arrest: 20 µg/kg boluses
Shock: 2–20 µg/kg boluses every 4–12 h (7 µg/kg every 6–12 h is common),
2–10 µg/kg/h as a continuous infusion
Hepatorenal Syndrome: 30 µg/kg/day as continuous infusion

Adults:
Catecholamine-resistant shock: 1 mg bolus every 4–12 h, alternatively µg/kg/h as a continuous infusion

Variceal hemorrhage: 2 mg every 4h for 48 h, then 1 mg every 4 h for the following 5 days

Hepatorenal Syndrome (Type I): 2–4 mg/day divided BID or QID.

Bronchial Administration for hemorrhage: 1 mg via bronchoscope during procedure

Pharmacokinetics

Onset of action: Peak level of triglycl-lysine-vasopressin is achieved within 10 min of administration. The peak level of the active lysine-vasopressin is seen in 60–120 min.

Duration: Intermediate, indicating a dosing schedule of 4–6 h. 5 µg/kg will produce a Lysine vasopressin plasma level of 220 ± 30 pg/mL 6 h after the dose. Correspondingly, 20 µg/kg yields a 6-h plasma level of 480 ± 180 pg/mL.

Metabolism:

Half-life: Terlipressin plasma half-life is 12 min during the initial 40 min distribution phase and then 80 min during the 80 min elimination phase. The release of lysine-vasopressin is maintained for at least 180 min.

Clearance: Terlipressin is cleaved by endopeptidases of the liver and kidney into lysine vasopressin. Metabolic clearance is about 9(ml/kg) x min and volume of distribution about 0.5 L/kg.

Drug interactions:

Terlipressin may enhance the effects of beta blockers, leading to significant bradycardia.

Adverse effects:

Cardiovascular: Reflex brachycardia, QTc prolongation, supraventricular and ventricular arrhythmias (including Torsade de pointes)

Respiratory: Bronchospasm, respiratory distress, respiratory failure, dyspnea

Central nervous systems: Headache, seizure, cerebrovascular accident

Endocrine & metabolic: Hyponatremia, hyperglycemia

Gastrointestinal: Intestinal ischemia, diarrhea, abdominal cramps, vomiting

Cutaneous & peripheral: cutaneous ischemia, more serious in obese patients

Poisoning information:

Overdose may result in paroxysmal hypertension with resultant decrease in cardiac output. Hypertension has been treated with clonidine anecdotally. Reflex bradycardia has been treated with atropine.

Compatible diluents:

Terlipressin is unstable in alkaline solutions and is distributed with a 5 mL diluents composed of sodium chloride, hydrochloric acid, and water. It is best administered through a central venous catheter given the risk of skin necrosis in the event of extravasation.

Standard concentrations:

Injection solution:

(acetate): 1 mg terlipressin acetate is equivalent to 0.85 mg terlipressin. 1 mL of reconstituted solution contains 0.2 mg of terlipressin acetate.

(diacetate): 1 mg Terlipressin diacetate is equivalent to 0.86 mg of terlipressin free base. 1 reconstituted vial consists of 1 mg of terlipressin diacetate in 5 mL of diluents.

Generic/Brand® Names:

Yes/Glypressine®, Variquel®

5.10.3   Phenylephrine

Indication:

Phenylephrine is an alpha-adrenergic agonist with a sym-pathominetic effect in various systems [101, 216, 219, 233–239] mainly circulatory, ophthalmic and nasal. In the cardiovascular patient, it is used as a pure vasoconstrictor drug to treat hypotension and vascular failure in distributive shock, and it is particularly useful for the treatment of tetralogy of Fallot's hypoxic spells unresponsive to sedation, volume load and beta-blocking or whenever it is required to increase peripheral resistances. There is evidence that use of phenylephrine after adult cardiac surgery increases oxygen extraction in the gut as compared to norepinephrine, and thus it should be used with caution. It may also be used as a vasoconstrictor in regional anesthesia, for symptomatic relief of nasal and nasopharyngeal mucosal congestion and as a mydriatic agent for ophhtalmic procedures. There are older studies recommending the use of phenylephrine for termination of supraventricular tachyarrhythmia; this is likely via a vagal mechanism and consequently phenylephrine should not be considered first-line therapy for such arrhythmias.

Mechanisms of action:

Phenylephrine is a potent alpha-agonist (alpha-adrenergic stimulator) with very little beta-adrenergic activity. Therefore, it produces a quite selective systemic arterial vasoconstriction, causes vasoconstriction of the nasal and conjunctival arterioles and stimulates the dilator muscle of the pupil producing mydriasis.

Dosing:

Phenylephrine is to be used as a bolus or as a continuous infusion and has to be titrated within the therapeutic

range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring. The following doses are exclusively described for cardiovascular purposes.

Severe hypotension, **Fallot's hypoxic spell and vasoplegic shock**: [101, 216, 219, 234–238]

Neonates, **Infants & Children**:

IM/SC: 0.1 mg/kg/dose (maximum 5 mg) every 1–2 h as required

IV bolus: 5–20 μg/kg/dose every 15–20 min as required

IV continuous infusion: 0.5–5 μg/kg/min titrated to effect

Adults:

IM/SC: 2–5 mg/dose (maximum 5 mg) every 1–2 h as required

IV bolus: 0.1–0.5 mg/dose every 10–15 min as required

IV continuous infusion: 40–180 μg/min titrated to effect

Paroxysmal supraventricular tachycardia: [235]

Children: 5–10 μg/kg IV, over 30 seconds

Adults: 0.25–0.5 mg IV, over 30 seconds

Pharmacokinetics:

Onset of action:
IM: 10–15 min
IV: immediate
SC: 10–15 min

Duration:

IM: 30 min–2 h
IV: 15–20 min
SC: 1 h
Metabolism: in the liver and the intestines by monoamine oxidase
Half-life: 2.5 h
Elimination: not elucidated

Drug interactions:

Drugs that may increase phenylephrine effect	Drugs that my decrease phenylephrine effect
Oxytocic drugs	Alpha-adrenergic blocking agents
Sympathomimetic agents ([a])	Beta-adrenergic blocking agents
Halogenated anesthetics ([a])	
MAO inhibitors	
Guanethidine	
Bretylium	

([a]) Tachycardia or arrhythmias may occur

Adverse effects:

Cardiovascular: hypertension, angina, severe reflex sinus bradycardia, arrhythmias, severe peripheral vasoconstriction. Phenylephrine is contraindicated in case of severe hypertension, pheocromocytoma, ventricular arrhythmias, myocardial disease

Respiratory: dryness, sneezing, rebound nasal congestion, dyspnea

Central Nervous System: restlessness, nervousness, headache, anxiety, dizziness

Cutaneous: dermal necrosis (extravasation), skin blanching, piloerection [10]

Neuromuscular & skeletal: tremor

Ocular: blurred vision, lacrimation, photophobia, stinging. Phenylephrine is contraindicated in case of narrow-angle glaucoma

Gastrointestinal: Phenylephrine is contraindicated in case of pancreatitis, hepatitis, mesenteric vascular disease

Renal: it may reduce renal flow and urine output

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of phenylephrine may be observed. In these circumstances it is recommended to transiently decrease

or even withdraw the drug, and treat symptomatically (significant individual variability). In case of extravasation, local administration of phentolamine or papaverine should be indicated.

Compatible diluents:

Phenylephrine is compatible with normal saline, dextrose solutions and Ringer's lactate. For IV boluses dilute 1 mg/ml (add 1 ml to 9 ml of diluting solution); recommended continuous infusion concentrations are 20–60 μg/ml. It should be administered into a central vein, except and transiently in urgent scenarios, with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solution (hydrochloride): 1 % solution, 10 mg/ml (1 ml vials)

Generic/Brand® Names:

Yes/Neosynephrine®

5.10.4   Metaraminol

Indication:

Metaraminol, also called hydroxynorephedrine or Metaradrine, is an alpha-adrenergic agonist with a weak beta-receptor stimulating action, used for the prevention or treatment of acute hypotensive situations [233], throughout cardiopulmonary bypass procedures [240], spinal anesthesia interventions or in vasoplegic shock states [234, 241–243] unresponsive to fluid volume replacement.

Mechanisms of action:

Metaraminol stimulates alpha-adrenergic receptors producing systemic arterial vasoconstriction. It also exerts a weak effect on beta 1-adrenergic receptors resulting

in increased contractility and heart rate. The increased vagal activity occurring as a reflex to increased blood pressure predominates over the chronotropic effect as bradycardia may occur. Metaraminol also releases norepinephrine from its storage sites.

Dosing:

Metaraminol is to be used as a bolus or as a continuous infusion and ought to be titrated within the therapeutic range and to the minimal efficient dose, until the desired response. It should be administered under comprehensive hemodynamic monitoring.

Treatment of severe hypotension or vasoplegic shock:

Neonates, **Infants & Children**: loading dose of 0.01 mg/kg or 0.3 mg/m^2 IV, followed by 0.4 mg/kg or 12 mg/m^2 infused at a rate titrated to desired results.

Adults: loading dose of 0.5–5 mg IV, followed by 15–100 mg infused at a rate titrated to desired results.

Prevention of hypotension:

Neonates: not recommended

Infants & Children: 0.1 mg/kg or 3 mg/m [2] IM or SC, repeated as required every 10 min.

Adults: 2–10 mg IM or SC, repeated as required every 10 min.

Pharmacokinetics

Onset of action:
IM: 10 min
IV: 1–2 min
SC: 5–20 min
Duration: 20–100 min
Half-life: 1–2 h
Metabolism: not elucidated
Elimination: not elucidated

Drug interactions:

Drugs that may increase metaraminol effect	Drugs that may decrease metaraminol effect
MAO inhibitors	Alpha-adrenergic blocking agents
Atropine	Digoxin ([a])
Tricyclic antidepressant drugs	
Ergot alkaloids	
Bretylium	
Inhaled anesthetic drugs (halothane, cyclopropane)	

([a]) Ectopic arrhythmias may occur

Adverse effects:

Cardiovascular: hypertension, tachycardia, bradycardia, palpitations, cardiac arrhythmias, cardiac arrest

Central Nervous System: headache, apprehension, dizziness, insomnia

Gastrointestinal: nausea, vomiting; careful use in patients with cirrhosis or mesenteric thrombotic disease

Metabolic: careful use in diabetes or thyroid disease

Cutaneous: dermal necrosis (extravasation), sloughing or abscess formation at the site of injection

Neuromuscular & skeletal: tremors

Other: diaphoresis, may activate a relapse in patients with a background of malaria and Mediterranean Family Fever [244] (used for provocation tests)

Poisoning information:

Adverse effects due to excessive doses or altered pharmacokinetics of metaraminol may be observed. In

these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability). Systemic vasodilators and anti-arrhythmic drugs might be required. In case of extravasation, local administration of phentolamine or papaverine should be indicated.

Compatible diluents:

Metaraminol is stable for 24 h when diluted in normal saline, dextrose solutions or Ringer's lactate. Maximal recommended concentration is 1 mg/ml for continuous infusion; it may be administered undiluted as a bolus. It must be administered into a central vein, except and transiently in urgent scenarios, with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solution (bitartrate): 10 mg/ml (10 ml vials)

Generic/Brand® Names:

-/Aramine®

5.11   Other Drugs with Cardiovascular Effect

5.11.1   Calcium Chloride

Indication:

Calcium chloride is a parenteral electrolyte supplement used for the treatment of symptomatic hypocalcemia, hypermagnesemia, hyperkalemia, tetany, and calcium-channel blocker toxicity. Hypocalcemia is a common electrolyte disturbance in critically ill children and has been shown to contribute to myocardial dysfunction and hypotension [245, 246]. For this reason, many centers use calcium supplementation in pediatric post-cardiac surgical patients to maintain serum calcium levels above 1.2 mmol/L, however

the safety and efficacy of this practice is not well established [247, 248]. According to guidelines published by the American Heart Association, the routine use of intravenous calcium during resuscitation is no longer recommended in pediatric patients due to increased risk of mortality and poor neurologic outcomes. Calcium is only recommended during resuscitation if cardiac arrest is associated with electrolyte disturbances or calcium-channel blocker toxicity [76, 249]. In cases of persistent bleeding and massive transfusion, calcium chloride administration may be necessary to maintain appropriate ionized calcium levels secondary to citrate in the blood products [250].

Mechanisms of action:

Calcium homeostasis is essential to maintain the functional integrity of the nervous, muscular, renal, and skeletal systems, as well as, cell membrane and capillary permeability. This cation is an important activator in many enzymatic reactions and is essential to a number of physiological processes including transmission of nerve impulses, myocardial contraction, smooth and skeletal muscle function, respiration, and coagulation. Calcium also plays a regulatory role in the release and storage of neurotransmitters and hormones, uptake and binding of amino acids, cyanocobalamin (vitamin B_{12}) absorption, and gastrin secretion [251–253].

Dosing:

Calcium chloride is administered as a bolus or continuous infusion, and titrated within the therapeutic range to the minimal efficient dose necessary to achieve the desired response. It should be administered under comprehensive hemodynamic monitoring. Furthermore, serum calcium, magnesium, potassium, and phosphorus concentrations should be carefully monitored.

Treatment of symptomatic hypocalcemia:

Neonates, **Infants & Children**: 10–20 mg/kg/dose (0.1–0.2 ml/kg of 10 % solution) slow IV (5–10 min), to be repeated if needed every 4–6 h

Adults: 500–1,000 mg (5–10 ml of 10 % solution) slow IV, to be repeated as needed every 6 h

Treatment of cardiac arrest associated with hypocalcemia, **hypermagnesemia**, **hyperkalemia**, **or calcium-channel blocker overdose**:

Neonates, **Infants & Children**: 20 mg/kg (0.2 ml/kg of 10 % solution) slow IV, to be repeated every 10 min as required

Adults: 500–1,000 mg slow IV (5–10 ml of 10 % solution), to be repeated every 10 min as required

Treatment of tetany:

Neonates, **Infants & Children**: 10 mg/kg (0.1 ml/kg of 10 % solution) slow IV (5–10 min), may repeat every 6–8 h or follow with a continuous infusion up to 200 mg/kg/day.

Adults: 1,000 mg slow IV (10 ml of 10 % solution) over 10–15 min, to be repeated as needed every 6 h

Treatment of symptomatic hyperkalemia:

Neonates, **Infants & Children**: 20 mg/kg (0.2 ml/kg of 10 % solution) slow IV (10–15 min) repeat as necessary

Adults: 500–1,000 mg (5–10 ml of 10 % solution) slow IV (10–15 min) repeat as necessary

Pharmacokinetics:

Onset of action: Immediate

Protein- binding: 45 % is bound to protein

Excretion: 80 % of calcium is excreted via feces and consists of non-absorbed calcium and calcium secreted via bile and pancreatic juice into the lumen of the gastrointestinal tract. The remaining 20 % of calcium is excreted by the kidneys

Clearance: Of the calcium filtered by the renal glomeruli, 20–25 % is reabsorbed in the ascending limb of the loop of Henle, 66 % in the proximal tubules, and the remaining 10 % in the distal tubules.

Drug Interactions:

(Table 5.4)

TABLE 5.4 Calcium chloride drug interactions

Calcium chloride may *antagonize* the effects of	Calcium chloride may *potentiate* the effects of	Miscellaneous interactions
Calcium channel blockers	Digoxin – increased risk of arrhythmias and cardiovascular collapse with rapid IV administration of calcium in digitalized patients [251, 253]	Thiazide diuretics Increased risk of hypercalcemia
Dobutamine		Ceftriaxone - Intravenous calcium supplements are contraindicated within 48 h of ceftriaxone in infants 28 days of age and younger due to an insoluble precipitate

Adverse effects:

   Cardiovascular: vasodilation, sinus bradycardia, syncope, hypotension, and cardiac arrhythmias (avoid rapid IV administration). *Contraindicated in ventricular fibrillation and use cautiously in digitalized patients*

   Central Nervous System: headache, dizziness, lethargy, coma

   Cutaneous: erythema, dermal necrosis (extravasation)

   Endocrine & metabolic: hypercalcemia, hypokalemia, hypomagnesemia, hypercalciuria, hypophosphatemia

   Neuromuscular & skeletal: weakness

   Gastrointestinal: dry mouth, constipation, nausea, vomiting, elevated serum amylase

Poisoning information:

   Adverse effects due to excessive doses or altered pharmacokinetics of calcium chloride may be observed. Clinical symptoms of intoxication may be: thirst, nausea, vomiting,

constipation, lethargy, abdominal pain, muscle weakness, mental disturbances and, in severe cases, cardiac arrhythmia and coma. In these circumstances, it is recommended to transiently decrease or discontinue the calcium and treat symptomatically. In severe cases, it is recommended to carefully monitor serum electrolytes and renal function, rehydrate the patient with 0.9 % sodium chloride infusion, and use loop diuretics to increase excretion [9]. In some cases, hemodialysis might be required to augment elimination [254]. In case of extravasation, local administration of hyaluronidase is indicated [253].

Compatible diluents:

Calcium chloride may be administered undiluted or diluted in dextrose or 0.9 % sodium chloride. In direct IV injection it is to be infused at a maximum rate of 50–100 mg/min. For a continuous IV infusion it is to be administered with a maximal concentration of 20 mg/ml. Calcium chloride is incompatible with bicarbonates, sulfates, and phosphates, as well as some antibiotics (tetracyclines). It must be *slowly* administered into a central vein, except transiently in urgent scenarios, with an infusion device allowing proper and reliable titration.

Standard concentrations:

Injection solutions: 10 % (100 mg/ml-equivalent to 27.2 mg of elemental calcium/ml or 1.4 mEq calcium/ml- 10 ml vials).

Generic/Brand® Names:

Yes/

5.11.2   Liothyronine

Indication:

Liothyronine, also called T_3 or L-Triiodothyronine, is the active form of thyroid hormone, produced from peripheral deiodination of thyroxine (T_4) which is secreted by the thyroid gland. Hypothyroidism, specifically low

serum levels of triiodothyronine, is a common occurrence following cardiac bypass in adults and, to a larger extent, in infants. Adult patients undergoing bypass who receive thyroid hormone supplementation have demonstrated a dose-dependent increase in cardiac output which has been associated with an improved clinical outcome. Several small studies in infants following bypass have similarly reported improvements in cardiac output by the administration of exogenous liothyronine; other limited studies have shown a more rapid achievement of negative fluid balance in neonates after aortic arch reconstruction [254–262]. The largest trial to date, the TRICC study, was a randomized, placebo-controlled trial of nearly 200 patients under 2 years of age. This study revealed a beneficial treatment effect in infants less than 5 months of age with shortened ventilator times and reduced inotropic requirements. However, infants older than 5 months had a small but significant worsening with triiodothyronine supplementation in terms of ventilator duration.

Mechanisms of action:

Triiodothyronine is a nuclear transcription factor, effecting the upregulation and downregulation of multiple genes. It is principally involved in regulation of basal metabolic rate, movement of sodium and water across cell membranes, calcium, phosphrous, protein, and lipid metabolism, as well as control of oxidative phosphorylation.

Dosing:

Liothyronine may be used in the context of perioperative course of pediatric cardiac surgery via parenteral administration as a bolus. It should be administered under comprehensive hemodynamic monitoring. Furthermore, clinical signs of hyperthyroidism and T_3 and TSH levels should be carefully monitored.

Neonates, **Infants & Children**: 0.1–0.4 µg/kg/dose (maximum of 20 µg,) IV every 8–12 h

Adults: 0.8 µg/kg, followed by 0.12 µg/kg/h for 6 h, IV

Pharmacokinetics:

> **Onset of action**: a few hours
> **Maximum effect**: 48–72 h
> **Half-life**: 16 h
> **Duration**: up to 72 h
> **Protein-binding**: almost nil, which makes it readily available to tissues
> **Metabolism**: in the liver to inactive compounds
> **Elimination**: 75–85 % in urine

Drug interactions:

> Liothyronine increases the effect of oral anti-coagulants and decreases the action of digoxin and theophylline. Cholestyramine and colestipol decrease Liothyronine's effects.

Adverse effects:

> **Cardiovascular**: palpitations, sinus tachycardia, cardiac arrhythmias, hypertension, angina, congestive heart failure, chest pain. *Cautious use in patients with ischemic disease*
> **Central Nervous System**: headache, fever, nervousness, agitation, insomnia
> **Gastrointestinal**: abdominal cramps, diarrhea, vomiting, increased appetite
> **Cutaneous**: alopecia, dermatitis herpetiformis
> **Cutaneous**: phlebitis at the site of infusion or injection
> **Neuromuscular & skeletal**: tremor
> **Metabolic**: use with precaution in patients with diabetes mellitus or insipidus, thyroid dysfunction, adrenal insufficiency
> **Other**: diaphoresis, heat intolerance, weight loss, fever

Poisoning information:

> Adverse effects due to excessive doses or altered pharmacokinetics of liothyronine may be observed. In these circumstances it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability).

Compatible diluents:

> For parenteral administration it is recommended to dilute a vial of liothyronine in 2 ml of normal saline, shake it until a clear solution is obtained and draw the required dose. IV liothyronine must be administered immediately after preparation in a central or peripheral line. It should not be mixed with any other solutions.

Standard concentrations:

> **Injection solutions** (sodium): 10 µg/ml (1 ml vials)

Generic/Brand® Names:

> Yes/Cytomel®, Triostat®

5.11.3   Levosimendan

Indication:

> Levosimendan is a new inodilator used in the treatment of decompensated cardiac failure and as an elective drug in patients with perioperative risk of ventricular failure, as well in the rescue therapy of patients with difficult weaning from cardiopulmonary bypass or from mechanical assistance. It has been shown to exert a potent positive inotropic and systemic vasodilator activity, therefore significantly increasing cardiac output, cardiac index and decreasing ventricular filling pressures. There are also reports documenting its favorable effect in reducing pulmonary vascular resistances and endothelin-1 levels and in improving right ventricular failure. Last but not least, levosimendan seems to induce a sustained lowering of atrial natriuretic peptide and it has not shown neither an arrhythmogenic effect nor a drug-induced increase in neurohormone levels [45, 102, 263–279]. Pediatric experience is limited to a few studies so far, but the overall reports are quite encouraging. It may be used with conventional inotropic support, has a simple dosing regime, does not alter diastolic function

(neutral or positive lusitropic effect) and demonstrates minimal hemodynamic side-effects [102, 264, 267, 273, 275–278].

Mechanisms of action:

Levosimendan is a pyridazinone-dinitrate that belongs to a new class of drugs, the calcium sensitizers. In contrast with other inotropic agents, this medication increases the sensitivity of the heart to calcium, thus increasing cardiac contractility without a rise in intracellular calcium. It acts by binding to myocardial troponin C by a calcium-dependent manner causing a configuration change in tropomyosin that exposes actin and myosin elements allowing a more efficient contraction. It offers the advantage of increasing systolic force without compromising coronary perfusion. Moreover, levosimendan opens adenosine triphosphate (ATP)-sensitive vascular potassium channels in vascular smooth muscles causing vascular relaxation (vasodilatory effect), coronary artery dilatation and myocyte mitochondrial activation. Moreover, by opening also the mitochondrial (ATP)-sensitive potassium channels in cardiomyocytes, the drug exerts a cardioprotective effect.

Dosing:

Levosimendan is to be used as a bolus or as a continuous infusion. It should be administered under comprehensive hemodynamic monitoring.

Neonates, **Infants & Children**: loading dose of 12 μg/kg over 1 h, followed by a continuous infusion of 0.1–0.2 μg/kg/min for 24 h. Levosimendan can also be administered over 48 h without a loading dose, especially in children on other vasodilator drugs like milrinone. Milrinone should be stopped during levosimendan infusion, to avoid excessive vasodilatation and hypotension.

Adults: loading dose of 8–36 μg/kg over 1 h, followed by a continuous infusion of 0.2–0.3 μg/kg/min for 24 h.

Pharmacokinetics:

> **Onset of action**: very rapid (in a dose-proportional manner)
> **Half-life**: 1 h
> **Duration**: 2–4 h
> **Protein-binding**: 97–98 %
> **Metabolism**: reduced in the gut into an amine metabolite
> **Clearance**: 296–368 ml/min; 70 % of the unchanged drug is excreted by the urine (30 %) and feces (40 %)

Drug interactions:

> No significant pharmacokinetic interactions have been reported with inotropic drugs, angiotensin-converting enzyme inhibitors, beta-blockers, felodipine, digoxin, warfarin, isosorbide mononitrate or carvedilol.

Adverse effects:

> **Cardiovascular**: palpitations, flushing, symptomatic hypotension (very rare)
> **Central Nervous System**: headache, dizziness, vertigo
> **Gastrointestinal**: nausea
> **Cutaneous**: irritation at the injection site

Poisoning information:

> Significant adverse effects due to excessive doses or altered pharmacokinetics of levosimendan have not been described. In case of any adverse reactions it is recommended to transiently decrease or even withdraw the drug, and treat symptomatically (significant individual variability).

Compatible diluents:

> Levosimendan may be diluted in normal saline or in dextrose solutions and administered ideally in a reliable central line, except in an emergency situation. It should be administered under comprehensive hemodynamic monitoring.

Standard concentrations

Injection solution: 2.5 mg/ml (5 and 10 ml vials)

Generic/Brand® Names:

-/Symdax®

5.12   Future Developments

5.12.1   Istaroxime

Indication:

Investigational steroid derivative that is currently under investigation in the United States for treatment of acute heart failure syndrome.

Mechanism of action:

Increases contractility by inhibiting Na+/K+ adenosine triphosphatase activity but in addition facilitates sequestration of calcium within the sarcoplasmic reticulum [280–283]. The combined mechanism allows for accumulation of cytosolic calcium during systole and rapid sequestration of calcium during diastole and myocardial relaxation [281]. This allows improvement of both systolic and diastolic function and efficiency of cardiac contraction (lower oxygen consumption for any level of cardiac work) and minimizes the risk of arrhythmias and ischemia [280–283]. In the HORIZON-HF trial, a randomized controlled trial evaluated the short term effects of istaroxime versus placebo in patients hospitalized with heart failure, patients treated with istaroxime had lower pulmonary capillary wedge pressures, increased systolic blood pressure and evidence of improved diastolic function. [284, 285]

There are no current dosing recommendations and further study into adverse effects, drug-drug interactions need to be performed.

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Chapter 6
Diuretics

**David M. Kwiatkowski, Amy Donnellan,
and David S. Cooper**

Abstract Diuretic medications compose one of the most frequently used drug classes in the care of pediatric cardiology patients. They have a vast range of indications, including congestive heart failure, hypertension and postoperative fluid overload. The main function of this class of medicines is to reduce plasma volume by increasing urine output. Although all have a similar function, diuretics are then grouped by which region of the kidney they act upon. The most commonly used diuretic among pediatric patients is furosemide, which acts upon the loop of Henle. Although furosemide may be used as a single agent, it is commonly used in conjunction with other diuretics for synergy or to negate adverse effects. Most specific diuretic medications have indications for all age ranges and many have intravenous and enteral formulations available. An understanding of the mechanism and specific

D.M. Kwiatkowski, MD (✉) • A. Donnellan, CNP
Department of Pediatrics, The Heart Institute, Cincinnati
Children's Hospital Medical Center, 3333 Burnet Ave., MLC 2003,
Cincinnati, OH 45229, USA
e-mail: david.kwiatkowski@cchmc.org

D.S. Cooper, MD, MPH
Department of Pediatrics, Cardiac Intensive Care Unit,
The Heart Institute, Cincinnati Children's Hospital Medical Center,
University of Cincinnati College of Medicine, Cincinnati, OH, USA

indications of these medications is necessary for optimal care of infants and children with cardiac disease.

Diuretic medications compose one of the most frequently used drug classes in the care of pediatric cardiology patients. The main function of this group is to reduce plasma volume by increasing urine output. This reduced plasma volume can help with symptoms of heart failure, postoperative fluid overload, hypertension or renal dysfunction. The general mechanism of action is similar in most diuretics: inhibition of renal ion transporters decreasing the reabsorption of sodium ions (Na^+), causing higher osmolarity in the urine. This leads to increased passive flow of water molecules into the urine causing diuresis. Manipulation of renal tubule ion channels, while effective at eliminating plasma volume, occurs at the cost of electrolyte abnormalities.

The subclasses of diuretic medications are categorized by the component of the renal tubule which they act upon. The potency and side effect profile of each group is based upon the mechanism of that region of the nephron. The more powerful loop diuretics can increase sodium secretion by more than 20 % creating strong diuresis, while the secretion of potassium sparing diuretics may be as little as 1–2 %.

In order to understand how diuretics influence electrolytes and fluid balances, it is important to review the normal electrolyte regulation of the kidneys and the concept of the five zones of the nephron (Fig. 6.1).

Fluid enters the kidney through the glomerular capillaries and filters through Bowman's capsule. This filtrate does not include blood cells or protein, but has high concentrations of glucose, sodium bicarbonate, amino acids and electrolytes. This filtrate is modified as it passes through the nephron system and towards the ureter.
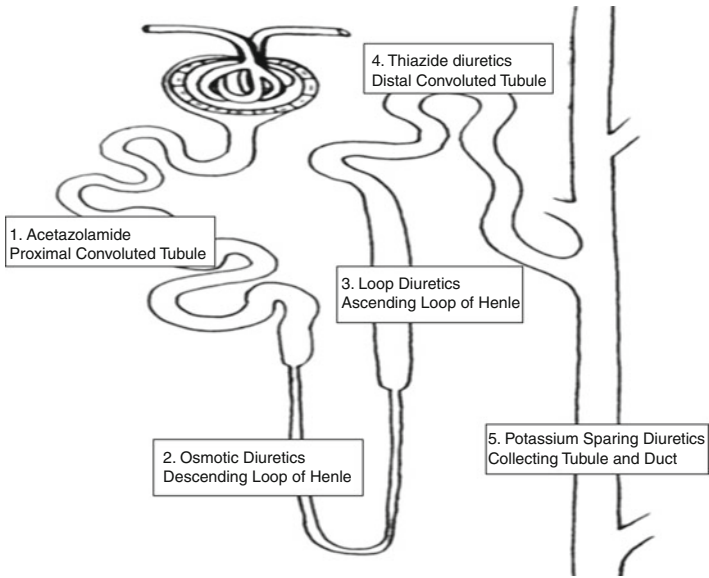
FIGURE 6.1 Schematic of nephron – the regions of the nephron are shown along with the main class of diuretic which acts upon each region

The proximal convoluted tubule is the first zone of the nephron and where the majority of reabsorption of filtered water, glucose, bicarbonate, amino acids and sodium occurs. Sodium is pumped out of filtrate by a Na^+/K^+ ATPase pump. The reabsorption of bicarbonate and organic solutes relies highly on carbonic anhydrase which is in the cell and luminal membrane. Water passively follows these solutes from the lumen into the interstitum.

The descending loop of Henle is the next zone and where urine osmolarity increases as water is reabsorbed into the renal medulla. This results in a net increase in tubular fluid salt concentration. This is the region where osmotic diuretics display their maximal effect. The next zone is the ascending loop of Henle where the tubular epithelium is impermeable to water but has active reabsorption of Na^+, K^+ and Cl^- mediated by a $Na^+/K^+/2Cl^-$ co-transporter. This area is where ¼ of all NaCl is resorbed and therefore loop diuretics, which affect this site, have major modifications on sodium balance.

The fourth zone is the distal convoluted tubule which is also impermeable to water. Here an additional 10 % of NaCl is reabsorbed via a Na^+/Cl^- transporter, along with calcium reabsorption. This zone is affected by thiazide diuretics. The final zone of the nephron is the collecting tubule in which Na^+, K^+ and water are reabsorbed with dependence on $Na^+/K^+/ATPase$ channels. This zone is where aldosterone has its effect, limiting Na^+ reabsorption and K^+ secretion. This is also the zone where vasopressin and antidiuretic hormone (ADH) have their effect. ADH receptors promote reabsorption of water from collecting tubules and ducts and decrease diuresis.

The main therapeutic uses of diuretics within pediatric cardiology are:

- heart failure
- postoperative oliguria
- hypertension
- pulmonary edema
- electrolyte correction(hyper/hypokalemia)
- renal dysfunction
- chronic lung disease.

Heart failure causes decreased effective blood flow to the kidney, making the kidney behave as if it were in a state of hypovolemia, and causes salt and water retention to increase blood volume. The mechanism by which diuretics help with heart failure is by the reduction of plasma volume, which decreases cardiac preload decreasing oxygen demand. Diuretics relieve pulmonary congestion and peripheral edema as well.

Patients who undergo heart surgery with cardiopulmonary bypass have increased body edema for multiple reasons. Bypass induces increased inflammatory states which cause capillary leak, and also may cause renal dysfunction and oliguria. Furthermore, postoperative low cardiac output causes edema by the above mechanism. Diuretics are an integral component of post-surgical treatment and typically are required in aggressive regimens.

The mechanism by which diuretics help with hypertension is the decrease in plasma volume which decreases afterload resulting in a lower blood pressure.

The management of postoperative oliguria and fluid overload after cardiopulmonary bypass is a popular topic. There is growing evidence that suggests the use of peritoneal dialysis early in the course of fluid overload due to postoperative acute kidney injury is a superior means of diuresis compared to medical management [1]. Studies have demonstrated worse clinical outcome with higher degrees of fluid overload [2] and suggest that peritoneal dialysis may be ultimately linked to improved outcomes.

The concept of synergy of medications is especially pertinent among diuretic management, both for potentiating effect and minimizing side effects. Many of the diuretics including loop diuretics and thiazides, have the side effect of potassium wasting. Therefore, a potassium-sparing diuretic is often used in conjunction with higher dosed diuretic regimens, most classically furosemide and spironolactone. Other synergistic combinations are used to potentiate effect. For example loop diuretics and thiazide diuretics are often given in concert, because despite the powerful effect of Na^+ secretion by loop diuretics, sodium is later reabsorbed in the distal convoluted tubule, increasingly as the medication is used for longer term treatments. If a thiazide diuretic is given prior to the loop diuretic, it prevents reabsorbed of sodium, thus maximizing the effect via a "sequential nephron blockade". Although never assessed in children, the addition of a thiazide diuretic in adult heart failure has been studied in more than 50 published reports and can double urine sodium secretion [3].

A consideration when using intravenous diuretics is the use of bolus medications versus continuous infusion. Although it is more common to give medications via bolus administration, there is data that suggests that continuous infusions may be safer. A prospective randomized study among infants after cardiac surgery found that continuous infusions was given at lower doses with similar urine output, and associated with less fluctuation in urinary output and need for fluid replacement [4, 5].

The five subclasses of medications will be discussed individually and key pharmaceutical agents within each subclass will be further described (Table 6.1).

TABLE 6.1 Mechanisms and representative agents of diuretic classes

Mechanism of action of diuretic classes		
Drug class	**Examples**	**Mechanism of action**
Loop diuretics	Furosemide	Inhibition of Na^+/K^+/$2Cl^-$ co-transporter in ascending loop of Henle
	Bumetanide	
	Torsemide	
	Ethacrynic acid	
Thiazide and thiazide-like diuretics	Chlorothiazide	Inhibition of Na^+/Cl^- co-transporter in distal convoluted tubule
	Hydrochlorothiazide	
	Metolazone	
Potassium sparing diuretics (aldosterone antagonists)	Amiloride (Spironolactone)	Inhibition of aldosterone-responsive Na^+ channel in distal nephron and collecting tubule (aldosterone antagonists reduce Na^+ channel and Na^+/K^+/ATPase)
Carbonic anhydrase inhibitors	Acetazolamide	Inhibition of proximal convoluted tubule sodium bicarbonate reabsorption
Osmotic diuretic	Mannitol	Increases the osmotic pressure of the glomerular filtrate, which inhibits the tubular reabsorption of water and electrolytes

6.1   Loop Diuretics

6.1.1   Indication

Loop diuretics are commonly used in the management of volume overload in congestive heart failure, postoperative cardiac surgery, acute and chronic renal insufficiency and

hepatic pediatric patients. They may be used alone or in combination with other medication classes to assist in the management of hypertensive patients.

6.1.2 Mechanism of Action

Loop diuretics inhibit the reabsorption of sodium and chloride from the ascending loop of Henle. They interfere with the $Na^+/K^+/2Cl^-$ cotransporter system and cease salt transport. This action causes an increase of excretion of water, sodium, chloride and potassium. The inhibition of the cotransporter system decreases absorption of calcium and magnesium in the ascending limb by eliminating the transepithelial potential difference. Bumetanide is a loop diuretic that is 40 times more potent than furosemide [6].

6.1.3 Monitoring Parameters

Serum sodium, potassium, chloride, and bicarbonate, renal function (BUN and Cr), blood pressure and hearing screening.

6.1.4 Contraindications

Anuria or increasing azotemia. The use of Ethacrynic acid should be avoided if hypotension, metabolic alkalosis with hypokalemia or hyponatremic dehydration is present.

Warning: loop diuretics are potent agents. Excess amounts may lead to profound diuresis with fluid and electrolyte loss. Close medical supervision and dose evaluation is required.

6.1.5 Poison Information

Symptoms of loop diuretic overdose may include acute and profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume and circulatory collapse

with a possibility of vascular thrombosis and embolism. Electrolye depletion may be manifested by weakness, muscle cramps, fatigue, dizziness, fainting, confusion, irregular pulse, dry mouth, dehydration, nausea, and vomiting. Decontamination using activated charcoal is recommended and other treatment is supportive and symptomatic. Replacement of fluid and electrolyte losses may be necessary.

6.2   Furosemide

6.2.1   Pharmacodynamics/Pharmacokinetics

The onset of action of loop diuretics is 30-60 minutes after oral administration. The peak effects occur within 1–2 h and the duration of action is 6–8 h. After an intravenous injection the diuresis begins in 5 min and typically lasts for 2 h. The hepatic metabolism of the drug is minimal and the half-life is approximately 30 min.

6.2.2   Dosing

Neonates, **Premature**:

> *Oral* (*poor bioavailability*): doses of 1–4 mg/kg/dose once or twice daily have been used
> *Intramuscular* (*I.M.*), *intravenous* (*I.V.*): 1–2 mg/kg/dose administered every 12–24 h
> Note: Significant absorption within ECMO circuit; avoid administration directly into circuit; high doses may be required for adequate diuretic effect [7].

Infants and Children:

> *Oral*: 1–6 mg/kg/day divided every 6–12 h
> *I.M.*, *I.V.*: 0.25–2 mg/kg/dose every 6–12 h
> *I.V. continuous infusion*: 0.05 mg/kg/h initially, titrate to clinical effect. (Usual dosage range – 0.1–0.4 mg/kg/h.)

Adults:

> *Oral*: initial, 20–80 mg/dose; increase in increments of 20–40 mg/dose at intervals of 6–8 h; usual maintenance dose interval is once or twice daily; may be titrated up to 600 mg/day for severe edematous states
>
> *I.M.*, *I.V.*: 20–40 mg/dose; repeat in 1–2 h as needed and increase by 20 mg/dose until the desired effect has been obtained; usual dosing interval, 6–12 h; for acute pulmonary edema, the usual dose is 40 mg I.V.; if not adequate, may increase dose to 80 mg
>
> *Continuous I.V. infusion*: initial I.V. bolus dose of 20–40 mg followed by continuous I.V. infusion doses of 0.1 mg/kg/h doubled every 2 h to a maximum of 0.4 mg/kg/h

6.2.3   Precautions/Adverse Effects

Adverse effects of furosemide use include serious depletion of total body Na^+ manifesting in hyponatremia or extracellular fluid volume depletion associated with hypotension, reduced glomerular filtration rate (GFR), or circulatory collapse. Can cause extracellular fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium and hypocalcemia. Also reported are dizziness, urticaria, hypokalemia, nausea, pancreatitis, headaches, photosensitivity, diarrhea, dehydration, and anemia. Ototoxicity from high doses of furosemide has been reported. Other effects may include hypochloremia, metabolic alkalosis, hypercalciuria, agranulocytosis, thrombocytopenia, nephrocalcinosis, prerenal azotemia, hyperuricemia, and interstitial nephritis. Oral solutions contain sorbitol, which may cause diarrhea. Pregnancy Class: C.

6.2.4   Drug-Drug Interaction

Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the effect of furosemide. There is increased ototoxicity with aminoglycosides and ethacrynic acid; and drugs affected by potassium depletion, such as digoxin. There is increased

anticoagulation by warfarin; decreased glucose tolerance may increase requirements of oral anti-diabetic agents; and there is decreased lithium excretion with furosemide administration.

6.2.5   Compatible Diluents/Administration

Injection can be administered undiluted or can be diluted in normal saline (NS) or 5 % dextrose in water (D5W) to a concentration of 1–2 mg/mL and will be stable for 24 h at room temperature. Administration is by direct I.V. injection at a maximum rate of 0.5 mg/kg/min.

6.3   Bumetanide

6.3.1   Pharmacodynamics/Pharmacokinetics

Bumetanide has an onset of action for oral or I.M. administration within 30–60 min after the initial dose and within a few minutes after the I.V. injection. The duration of action after a usual dose of the drug is 4–6 h. Bumetanide is almost completely absorbed from the gastrointestinal (GI) tract, with protein binding at 95 %. The drug undergoes partial hepatic metabolism, with the majority of the drug eliminated as the parent molecule or as a metabolite in the urine. The half-life of bumetanide is 1–1.5 h in adults and 2.5 h in infants younger than 6 months of age.

6.3.2   Dosing

Neonates:

   Oral, *I.M.*, *I.V.*: 0.01–0.05 mg/kg/dose every 24–48 h

Infants and Children:

   Oral, *I.M.*, *I.V.*: 0.01–0.1 mg/kg/dose every 6–24 h (maximum, 10 mg/day)

   Continuous I.V. infusion: the total daily I.V. intermittent dose can be administered as a continuous infusion over 24 h (5–50 µg/kg/h)

Adults:

> *Oral*: 0.5–2 mg/dose (maximum, 10 mg/day) once or twice
>   daily
> *I.M.*, *I.V*.: 0.5–1 mg/dose (maximum, 10 mg/day)
> *Continuous I.V. infusion*: 0.5–1 mg/h

6.3.3   Precautions/Adverse Effects

The injectable formulation of this drug contains benzyl alcohol and large amounts (>99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates. This syndrome consists of metabolic acidosis, respiratory distress, gasping respirations, central nervous system (CNS) dysfunction, hypotension, and cardiovascular collapse. In vitro animal studies have shown that benzoate, a metabolite of benzyl alcohol, displaces bilirubin from protein binding sites. Avoid or use injection cautiously in neonates. In vitro studies using pooled sera from critically ill neonates have also shown bumetanide to be a potent displacer of bilirubin. Avoid use in neonates at risk for kernicterus. There is an increased risk of ototoxicity with rapid I.V. administration, renal impairment, excessive doses, and concurrent use with other ototoxins. Use with caution in patients with previous hypersensitivity reactions to sulfonamides or thiazides. Adverse effects that may occur with bumetanide use include hypotension, chest pain, dizziness, headache, encephalopathy, vertigo, and potential rashes. Bumetanide can cause extracellular fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium and hypocalcemia. Other effects may include urticaria, hypokalemia, nausea, pancreatitis, photosensitivity, diarrhea, dehydration and decreased uric acid excretion. Hypochloremia, arthritic pain, metabolic alkalosis, hypercalciuria, agranulocytosis, thrombocytopenia, hyperuricemia, and cramps have also been reported. Pregnancy Class: C

6.3.4   Drug-Drug Interaction

Hypotension may occur when bumetanide is used with other antihypertensive medications and angiotensin-converting enzyme (ACE) inhibitors. NSAIDs decrease the effect of bumetanide. There is increased ototoxicity when bumetanide is used with aminoglycosides and ethacrynic acid; and drugs affected by potassium depletion, such as digoxin. With bumetanide administration, there is decreased glucose tolerance with anti-diabetic agents; and decreased lithium excretion. Increased potassium losses with torsemide increase the risk of digoxin toxicity.

6.3.5   Compatible Diluents/Administration

Administer undiluted by direct I.V. injection over 1–2 min; may be diluted in D5W or NS and infused over 5 min; dilute in D5W to 0.024 mg/mL for continuous infusion.

6.4   Torsemide

6.4.1   Pharmacodynamics/Pharmacokinetics

Rapidly absorbed; bioavailability, 80–90 %. Peak serum concentrations are reached in 1 h. Torsemide is metabolized by cytochrome P450. The halflife of torsemide is normally 2–4 h, but is increased to 7–8 h in cirrhosis. Of the total dose, 20 % is excreted unchanged in the urine.

6.4.2   Dosing

Neonates, **Infants**, **and Children**: no data is available

Adults:

Edema: *Oral*, *I.V.*: 10–20 mg once daily. Titrate up to maximum dose of 200 mg/day

Hypertension: *Oral*, *I.V*.: 5 mg once daily initially, then increase to 10 mg once daily, if needed, after 4–6 weeks

6.4.3   Precautions/Adverse Effects

Adverse effects that may occur with torsemide use include hypotension, chest pain, dizziness, headache, prerenal azotemia, and rashes. Torsemide can cause extracelluar fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium and hypocalcemia. Other effects may include hypokalemia, nausea, pancreatitis, photosensitivity, diarrhea, dehydration, and decreased uric acid excretion. Hypochloremia, arthritic pain, metabolic alkalosis, hypercalciuria, agranulocytosis, anemia, hyperuricemia, and cramps have also been reported. Pregnancy Class: B.

6.4.4   Drug-Drug Interaction

Use of torsemide with aminoglycosides or ethacrynic acid increases risk of ototoxicity. Torsemide use increases the anticoagulant effects of warfarin. NSAIDs decrease the diuretic effect of torsemide. Torsemide decreases lithium excretion; and decreased glucose tolerance with torsemide may increase requirements of oral anti-diabetic agents.

6.4.5   Compatible Diluents/Administration

Administer torsemide undiluted by direct I.V. injection over at least 2 min; torsemide may be diluted in D5W or NS to concentrations of 0.1, 0.2, 0.4, or 0.8 mg/mL for continuous infusion, and is stable for 24 h at room temperature.

6.5   Ethacrynic Acid

6.5.1   Pharmacodynamics/Pharmacokinetics

Ethacrynic acid has an onset of action within 30 min of administration of oral doses and within 5 min of I.V. injection. The duration of diuresis is approximately 6–8 h after oral and 2 h after I.V. administration. The drug is rapidly absorbed and hepatically metabolized to an active cysteine conjugate. The half-life ranges from 30–70 min, and the drug and metabolites are eliminated in the bile and urine.

6.5.2   Dosing

Children:

> *Oral*: 1 mg/kg/dose every 24–48 h; adjust dose as needed at 2–3-day intervals to a maximum of 3 mg/kg/day
> *I.V.*: 0.5–2 mg/kg/dose (maximum, 50 mg/dose) administered every 6–12 h

Adults:

> *Oral*: 25–400 mg/day in one to two divided doses
> *I.V.*: 0.5–1 mg/kg/dose (maximum, 100 mg/dose); repeat doses not routinely recommended but may be administered every 8–12 h
> **Note**: Avoid use in patients with a Cr clearance (ClCr) less than 10 mL/min

6.5.3   Precautions/Adverse Effects

Use with corticosteroids may increase risk of GI hemorrhage. Avoid use in patients with severe renal impairment (ClCr < 10 mL/min). Adverse effects of ethacrynic acid can cause extracelluar fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium

and hypocalcemia. Additional adverse effects can include hypotension, hyperglycemia, thrombocytopenia, neutropenia, agranulocytosis, abnormal liver function test results, GI irritation or bleeding, ototoxicity (higher risk than other loop diuretics), hyperuricemia, phlebitis, headache, rash, and hematuria. Pregnancy Class: B.

6.5.4   Drug-Drug Interaction

Ethacrynic acid administration causes increased potassium losses with amphotericin and steroids. Use of ethacrynic acid with aminoglycosides increases the risk of ototoxicity; increases the anticoagulant effects of warfarin; and decreases lithium excretion. Decreased glucose tolerance with ethacrynic acid may increase requirements of oral anti-diabetic agents.

6.5.5   Compatible Diluents/Administration

Ethacrynic acid is stable for 24 h at room temperature when mixed at 1 mg/mL in D5W or NS; inject slowly over 20–30 min. Ethacrynic acid is a tissue irritant and is not to be administered I.M. or subcutaneously.

6.6   Thiazide and Thiazide-Like Diuretics

6.6.1   Indication

Thiazide and Thiazide-Like diuretics are used for the treatment of mild to moderate hypertension. Additionally, they are used for the treatment of edema caused by CHF, pregnancy, bronchopulmonary dysplasia, nephrotic syndrome, or after cardiac surgery. Metolazone is also commonly used in conjunction with a loop diuretic in the management of edema secondary to CHF [8]. Thiazide is commonly used in conjunction with ACE-Inhibitors to control hypertension to offset potassium retention.

6.6.2   Mechanism of Action

The primary site of action of Thiazide diuretics (Chlorothiazide and Hydrochlorothiazide) is the distal convoluted tubule and the secondary site of action is the proximal tubule. In these regions, Thiazide and Thiazide-like diuretics block sodium reabsorption by inhibition of Na^+/Cl^- co-transporter causing increased excretion of sodium and water as well as potassium, bicarbonate, magnesium, phosphate, and calcium (transiently).

Similarly, Thiazide-like diuretics (Metolazone) primarily act upon the distal convoluted tubule and secondarily upon the proximal tubule. In these regions, metolazone inhibits sodium reabsorption, causing increased excretion of sodium and water as well as potassium and hydrogen ions.

6.6.3   Monitoring Parameters

Serum electrolytes, renal function (BUN and Cr), blood glucose, triglycerides, uric acid, blood pressure and fluid balance.

6.6.4   Contraindications

Anuria or an allergy to thiazide diuretics or sulfonamide. Hepatic coma.

6.6.5   Poison Information

Thiazide and Thiazide-like diuretic overdose is characterized by lethargy, dizziness, drowsiness, muscle weakness, arrhythmias, cramps, and fainting. On onset of these symptoms, drug administration should be stopped and symptomatic treatment should be initiated.

6.7   Chlorothiazide

6.7.1   Pharmacodynamics/Pharmacokinetics

Chlorothiazide has an onset of action of 2 h after oral administration and duration of action of 6–12 h. The duration of action is approximately 2 h after I.V. injection. Oral absorption of the drug is only 10–20 %, and protein binding ranges from 20 to 80 %. Chlorothiazide is not metabolized, and its half-life is 1–3 h. Almost the entire I.V. dose is eliminated unchanged in the urine within 3–6 h, and 35–60 % of the oral dose is excreted within 24 h.

6.7.2   Dosing

Note: I.V. dosage in infants and children has not been established. The following dosages in infants and children are based on anecdotal reports. Lower dosing regimens have been extrapolated from oral dosing recommendations, because 10–20 % of an oral dose is absorbed.

Neonates and Infants Younger than 6 Months:

> *Oral*: 20 mg/kg/day in two divided doses; maximum, 375 mg/day
> *I.V.*: 2–8 mg/kg/day in two divided doses; doses up to 20 mg/kg/day have been used

Infants older than 6 Months and Children:

> *Oral*: 20 mg/kg/day in two divided doses; maximum, 1 g/day
> *I.V.*: 5 mg/kg/dose administered every 6–24 h; doses up to 20 mg/kg/day

Adults:

> *Hypertension*:
> *Oral*: 125–500 mg once daily
> *Edema*:

Oral: 500 mg to 2 g/day divided in one to two doses
I.V.: 100–500 mg/day divided in one to two doses

6.7.3   Precautions/Adverse Effects

Warning: do not administer the injectable formulation I.M. or subcutaneously.

Use cautiously in patients with severe renal disease, reduced hepatic function, and in patients with high triglyceride or cholesterol levels. Side effects of chlorothiazide use include hypotension, rashes, hypokalemia, hypochloremic metabolic alkalosis, hyperglycemia, hyperlipidemia, hyperuricemia, prerenal azotemia, thrombocytopenia, cholestasis, photosensitivity, arrhythmias, nausea, vomiting, diarrhea, pancreatitis, and fevers. Rarely, blood dyscrasias may also occur. Pregnancy Class: C.

6.7.4   Drug-Drug Interactions

NSAIDs may decrease the antihypertensive effect of chlorothiazide. Steroids, loop diuretics, and amphotericin B will cause additive potassium losses. With chlorothiazide use, there is a decreased clearance of lithium; there is increased hyperglycemia with diazoxide; there are increased hypersensitivity reactions to allopurinol; and there is an increased risk of renal toxicity with cyclosporine.

6.7.5   Compatible Diluents/Administration

Do not administer chlorothiazide I.M. or subcutaneously; avoid extravasation; administer chlorothiazide by I.V. injection over 3–5 min or by I.V. infusion over 30 min at a maximum concentration of 25 mg/mL in D5W or NS; reconstituted injectable formulation is stable for 24 h at room temperature.

6.8 Hydrochlorothiazide

6.8.1 Pharmacodynamics/Pharmacokinetics

Hydrochlorothiazide has an onset of action within 2 h of oral administration, with duration of action of 6–12 h. The oral absorption in the GI tract is approximately 60–80 %. The half-life of hydrochlorothiazide is 5–15 h, and hydrochlorothiazide is eliminated almost completely via the kidneys as unchanged drug.

6.8.2 Dosing

Neonates and Infants Younger than 6 Months:

> *Oral*: 2–4 mg/kg/day in one to two doses; maximum daily dose, 37.5 mg

Infants Older than 6 Months and Children:

> *Oral*: 2 mg/kg/day in one to two doses; maximum daily dose, 200 mg

Adults:

> *Oral*: 12.5–100 mg/day in one to two doses; maximum, 200 mg/day
> **Note**: Daily dosages should be decreased if used with other antihypertensive agents.

6.8.3 Precautions/Adverse Effects

Use cautiously in patients with severe renal disease, reduced hepatic function, diabetes mellitus, systemic lupus erythematosus, and gout. Adverse side effects of hydrochlorothiazide may include drowsiness, paresthesia, hypokalemia, hyponatremia, hypochloremic metabolic alkalosis, hyperglycemia, nausea, vomiting, anorexia, pancreatitis, cholestasis,

hypotension, agranulocytosis, thrombocytopenia, leukopenia, prerenal azotemia, polyuria, and photosensitivity. Pregnancy Class: B.

6.8.4   Drug-Drug Interactions

There is a decreased antihypertensive effect with NSAIDS. With hydrochlorothiazide use, there are increased potassium losses with steroids and amphotericin B; and increased hypersensitivity reactions to allopurinol. With hydrochlorothiazide use, there is increased hyperglycemia with diazoxide; a decreased effectiveness of anti-diabetic agents; a decreased clearance of lithium; increased hypotension with ACE inhibitors; and increased renal toxicity with cyclosporine.

6.9   Metolazone

6.9.1   Pharmacodynamics/Pharmacokinetics

Metolazone has an onset of action of approximately 1 h and duration of action of 12–24 h. Oral absorption of the drug is dependent on the preparation used, and protein binding is 95 %. The half-life is 6–20 h and 70–95 % of the drug is eliminated unchanged in the urine.

6.9.2   Dosing

Metolazone is only available for oral/enteral administration.

Children:

   0.2–0.4 mg/kg/day divided every 12–24 h

Adults:

   Edema: 5–20 mg/dose every 24 h
   Hypertension: 2.5–5 mg/dose every 24 h

6.9.3   Precautions/Adverse Effects

Use cautiously in patients with severe renal disease, reduced hepatic function, diabetes mellitus, systemic lupus erythematosus, gout, and in patients with high triglyceride or cholesterol levels.

Common adverse reactions with metolazone use include palpitations, chest pain, hypotension, headaches, drowsiness, rash, and GI irritation. Hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hyperglycemia, thrombocytopenia, leukopenia, aplastic anemia, and hyperuricemia have also been reported. Patients may experience sensitivity to light, chills, and abdominal bloating. Pregnancy Class: B.

6.9.4   Drug-Drug Interactions

There is a decreased antihypertensive effect with NSAIDs. There are also increased potassium losses with steroids and amphotericin B; and increased hypersensitivity reactions to allopurinol. There is increased incidence of digoxin toxicity caused by hypokalemia and hypomagnesium.

6.10   Potassium-Sparing Diuretics

6.10.1   Indication

Potassium-Sparing diuretics are commonly used to prevent potassium loss caused by the usage of Loop and Thiazide-like diuretics for the management of edema. Spironolactone is more commonly used and has been shown to increase success in the treatment of patients with CHF in animal models [9]. It is used in the management of neonatal chronic lung disease. Potassium-Sparing Diuretics are also used to treat edema associated with hepatic cirrhosis and nephrotic syndrome as well as hypertension, hypokalemia, and primary aldosteronism.

6.10.2   Mechanism of Action

Potassium-sparing diuretics inhibit sodium reabsorption in the distal nephron and collecting tubule by either competing with, or inhibiting the aldosterone-responsive Na^+ channels in the distal nephron and collecting tubule. They increase the excretion of sodium, chloride, and water and inhibit the excretion of potassium and hydrogen. The effect of aldosterone on arteriolar smooth muscle may also be blocked.

6.10.3   Poisoning Information

Symptoms include nausea, vomiting, diarrhea, dehydration and electrolyte imbalances (hyperkalemia). Severe toxicity causes altered mental status, tachycardia, acute renal injury and arrhythmias secondary to hyperkalemia. Treatment of minor intoxication is oral rehydration and monitoring of hyperkalemia. Severe toxicity causing severe potassium abnormalities requires aggressive treatment with rehydration with IV fluids, calcium chloride, sodium bicarbonate, insulin, IV glucose and sodium polystyrene. Dialysis may be necessary.

6.10.4   Monitoring Parameters

Serum potassium, blood pressure, renal function (BUN and Cr), fluid balance

6.10.5   Contraindications

Anuria, hyperkalemia, diabetic nephropathy, renal failure

6.10.6   Drug-Drug Interactions

Potassium sparing diuretics increases serum potassium when used with potassium supplements, potassium-sparing

diuretics, ACE inhibitors, angiotensin receptor blockers, arginine, tacrolimus, sotolol, and cyclosporine. Amiloride decreases digoxin and lithium clearance. NSAIDs decrease the effects of amiloride. Spironolactone use may decrease clearance of digoxin; may cause a decreased response to norepinephrine; and may decrease the effects of oral anticoagulants.

6.11   Spironolactone

6.11.1   Mechanism of Action

Spironolactone is a potassium-sparing diuretic that competes with aldosterone for binding to receptor sites in the distal tubule of the kidneys. It increases the excretion of sodium, chloride, and water and prevents the excretion of potassium and hydrogen. The effect of aldosterone on arteriolar smooth muscle may also be blocked.

6.11.2   Pharmacokinetics

Spironolactone is well absorbed after oral administration, with bioavailability at approximately 90 %. The protein binding of the drug is greater than 90 % with hepatic metabolism to multiple metabolites, including the active agent, canrenone. The half-life of spironolactone is 1.4 h and the half-life of canrenone is 13–24 h. The duration of action is 2–3 days.

6.11.3   Dosing

Spironolactone is only available for oral/enteral administration.

Neonates:

   Diuretic: 1–3 mg/kg/day divided every 12–24 h

Children:

>   *Diuretic*, *hypertension*: 1.5–3.5 mg/kg/day or 60 mg/m^2/day in one to four divided doses daily

Adults:

>   *Edema*, *hypokalemia*: 25–200 mg/day in one to two divided doses
>   *Hypertension*: 25–50 mg/day in one to two doses daily

6.11.4   Precautions/Adverse Effects

Warning: severe hyperkalemia may result when used with ACE inhibitors, potassium supplements, and NSAIDs; monitor potassium levels and renal function closely.

Use with caution in patients with decreased renal function, hyponatremia, dehydration, or reduced hepatic function.

Adverse reactions associated with spironolactone include hyperkalemia, dehydration, hyponatremia, hyperchloremic metabolic alkalosis, headaches, fever, diarrhea, vomiting, nausea, lethargy, rash, anorexia, gynecomastia (in males), irregular menses, agranulocytosis, coughing, and decreased renal function. Pregnancy Class: C.

6.12   Amiloride

6.12.1   Mechanism of Action

Amiloride inhibits sodium-potassium ion exchange in the distal convoluted tubule, cortical collecting tubule and collecting tubule. Unlike spironolactone, this does not depend on aldosterone and has effect by inhibiting cellular sodium transport mechanisms and inhibits hydrogen ion secretion.

6.12.2   Pharmacokinetics

Amiloride has an onset of action of 2 h and peak at 3–4 h. Oral bioavailability is 15–25 %. The half-life in normal renal function is

6–9 h and up to 144 h in severe renal disease. Amiloride is eliminated in the urine and feces and not metabolized by the liver

6.12.3   Dosing

Amiloride is only available for oral/enteral administration.

Children 6–20 kg:

  0.625 mg/kg/day administered once daily (maximum dose, 10 mg/day)

Children Greater than 20 kg and Adults:

  5–10 mg/day (maximum dose, 20 mg/day)

In Patients with Renal Impairment: Reduce dose 50 % for ClCr 10–50 mL/min. Avoid use if ClCr is less than 10 mL/min

6.12.4   Precautions/Adverse Effects

Warning: Use with caution with potassium supplements or other potassium sparing diuretics; reduce dose in patients with renal insufficiency, hyponatremia, dehydration, electrolyte imbalance, diabetes, or decreased hepatic function. Adverse effects include hypotension, arrhythmias, hyperkalemia, hyponatremia, dehydration, hyperchloremic metabolic acidosis, nausea, vomiting, diarrhea, GI bleeding, liver function abnormalities, muscular weakness, paresthesias, neutropenia, aplastic anemia, headache, dizziness, confusion, insomnia, rash, and bladder spasms. Pregnancy Class: B.

6.13   Carbonic Anhydrase Inhibitors

6.13.1   Acetazolamide

The main indication of Acetazolamide within pediatric cardiology is to treat secondary metabolic alkylosis , however, it is also a weak diuretic. It is also is used to reduce intraocular pressure in glaucoma and in the treatment of neurologic illness including hydrocephalus, seizures, and altitude sickness [10].

6.13.2   Mechanism of Action

As a diuretic, acetazolamide initiates competitive, reversible inhibition of carbonic anhydrase, which results in increased renal secretion of sodium, potassium, sodium bicarbonate, and water. It is the secretion of bicarbonate which is clinically important in treating metabolic alkylosis. Acetazolamide also inhibits carbonic anhydrase in the CNS, thus, reducing discharges from CNS neurons.

6.13.3   Pharmacokinetics

Acetazolamide has an onset of action of 2 min after I.V. injection, 1–2 h after tablet ingestion, and 2 h after extended-release capsule administration. The duration of action of the drug is 4–5 h if administered I.V., 8–12 h after a tablet, and 18–24 h after an extended-release capsule. Absorption of acetazolamide is dose dependent, and acetazolamide distributes into erythrocytes and the kidneys. The half-life ranges from 2.4 to 5.8 h, with 70–100 % of the I.V. or tablet dose eliminated unchanged in the urine within 1 day.

6.13.4   Dosing

Children:

   Edema:
   Oral, *I.V*.: 5 mg/kg/dose or 150 mg/m^2/dose once every day
   Secondary metabolic alkalosis:
   Oral, *I.V*.: 3–5 mg/kg/dose every 6 h for four doses

Adults:

   Edema:
   Oral, *I.V*.: 250–375 mg once daily
   Urine alkalinization:
   Oral: 5 mg/kg/dose repeated two to three times over 24 h

In Patients with Renal Impairment:

ClCr 10–50 mL/min: administer every 12 h
ClCr less than 10 mL/min: avoid use

6.13.5   Monitoring Parameters

CBC, platelets, serum electrolytes. Liver enzymes and ASA/ acetaminophen levels in symptomatic patients.

6.13.6   Contraindications

Allergy to sulfonamides, hyperchloremic acidosis, severe renal disease, hepatic insufficiency, low serum sodium or potassium

6.13.7   Precautions/Adverse Effects

Warning: sulfonamides have caused fatalities caused by toxic epidermal necrolysis, Stevens-Johnson syndrome, hepatic necrosis, aplastic anemia, and other blood dyscrasias. Discontinue use at the first sign of rash or adverse reaction.

Use with caution in patients with chronic obstructive pulmonary disease, respiratory acidosis, gout, and diabetes mellitus; reduce dosage in patients with renal dysfunction.

The most common adverse effects include: paresthesias, renal calculi, metabolic acidosis, bone marrow depression, and rashes. Other more rare adverse effects include: taste disturbances, ataxia, gastritis, cholestatic hepatitis, and renal failure. Acetazolamide is basic and may be implicated in extravasation injury. Pregnancy Category: C.

6.13.8   Poisoning Information

Symptoms of acetazolamide overdose include confusion, drowsiness, nausea, vomiting, tachycardia, tachypnea and electrolyte abnormalities. Severe toxicity yields lethargy and severe metabolic acidosis.

6.13.9   Drug-Drug Interactions

Acetazolamide may decrease the rate of excretion of other drugs, such as sotalol, arsenic trioxide, droperidol, procainamide, flecainide, quinidine, cyclosporine, digoxin, high dose ASA, acetaminophen, amphetamines, and tricyclic antidepressants leading to toxicity. When available, levels should be followed. Acetazolamide may increase the risk of developing osteomalacia in patients receiving phenytoin or phenobarbital. Concomitant topiramate is not recommended due to the increase the risk of nephrolithiasis and paresthesia. Acetazolamide may increase or decrease lithium excretion.

6.13.10   Compatible Diluents/Administration

Reconstituted injectable formulation at 100 mg/mL concentration is stable for 1 week refrigerated. It may be diluted further in D5W or NS for I.V. infusion, with a stability of 5 days at room temperature and 44 days refrigerated.

6.14   Osmotic Diuretics

6.14.1   Mannitol

Mannitol is occasionally used to promote diuresis in the treatment of oliguria caused by acute renal failure. Mannitol is also used to reduce increased intracranial pressure associated with cerebral edema and to facilitate the urinary excretion of toxic substances.

6.14.2   Mechanism of Action

Mannitol is an osmotic diuretic that increases the osmotic pressure of the glomerular filtrate, which inhibits the tubular reabsorption of water and electrolytes, thus increasing urinary output.

6.14.3   Pharmacokinetics

The onset of action of mannitol begins within 1–3 h after injection and persists for 3–8 h. The drug remains confined to the extracellular space except in high concentrations or acidosis. The half-life of mannitol is 1.1–1.6 h and it is primarily eliminated in urine by glomerular filtration.

6.14.4   Dosing

Children:

    Test dose (*to assess adequate renal function*): 200 mg/kg (maximum 12.5 g) over 3–5 min to produce urine flow of at least 1 mL/kg/h for 1–3 h
    Initial: 0.5–1 g/kg over 20 min as a 20 % solution
        Maintenance: 0.25–0.5 g/kg administered every 4–6 h

Adults:

    Test dose: 12.5 g (200 mg/kg) over 3–5 min to produce urine flow of at least 30–50 mL of urine per hour over the next 2–3 h
    Initial: 0.5–1 g/kg (50–100 g)
    Maintenance: 0.25–0.5 g/kg administered every 4–6 h

6.14.5   Monitoring Parameters

Serum electrolytes, renal function (BUN and Cr), fluid balance, serum and urine osmolality (maintain serum osmolality 310–320 mOsm/kg for high intracranial pressure)

6.14.6   Contraindications

Severe pulmonary edema or congestion, severe renal disease, progressive oliguria after administration, dehydration, and active intracranial bleeding

6.14.7   Precautions/Adverse Effects

Mannitol should not be administered until adequate renal function and urine flow is established with test doses and cardiovascular status is evaluated. High doses may cause renal dysfunction—use caution in patients taking other nephrotoxic agents, with severe dehydration, with sepsis, or underlying renal disease. To minimize adverse renal effects, serum osmolality should be kept under 320 mOsm/L. Adverse reactions associated with mannitol include circulatory overload, CHF, headache, convulsions, fluid and electrolyte imbalance, dehydration, hypovolemia, plasma hyperosmolality, hyponatremia or hypernatremia, increased osmolar gap, blurred vision, and pulmonary edema. Pregnancy Category: C

6.14.8   Poisoning Information

Symptoms of mannitol overdose include acute renal failure, hypotension, pulmonary edema, cardiovascular collapse, polyuria, oliguria, seizures, hyponatremia, and hypokalemia. Replacement of fluid and electrolyte losses may be necessary. Hemodialysis will clear mannitol and reduce osmolality.

6.14.9   Drug-Drug Interactions

Mannitol use increases lithium toxicity. Its use may potentiate the effects of other medications that cause electrolyte abnormalities.

6.14.10   Compatible Diluents/Administrations

Do not administer mannitol with blood. Inspect mannitol for crystals before administration. Use a filter in administration set. Avoid extravasation.

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Chapter 7
β-Blockers

Traci Kazmerski, Carol G. Vetterly, and Ricardo Munoz

Abstract β-blockers are an essential component of pharmacologic therapy for children with congestive heart failure (CHF). Pediatric CHF is usually the result of primary systolic dysfunction that is most commonly caused by congenital structural defects. Patients born with single ventricle defects, especially those with a single right ventricle, appear to be particularly prone to ventricular dysfunction over time. This chapter details the proposed mechanism of action of

T. Kazmerski, MD (✉)
Division of Pulmonology, Department of Pediatrics,
Allergy and Immunology, Children's Hospital of Pittsburgh
of UPMC, 4401 Penn Ave., Pittsburgh, PA 15224, USA
e-mail: traci.kazmerski@chp.edu

C.G. Vetterly, PharmD, BCPS
Department of Pharmacy Services,
Children's Hospital of Pittsburgh of UPMC,
Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics,
University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA
e-mail: carol.vetterly@chp.edu

R. Munoz, MD, FAAP, FCCM, FACC
Cardiac Intensive Care Division, The Heart Institute, Children's
Hospital of Pittsburgh of UPMC, University of Pittsburgh,
Pittsburgh, PA, USA

β-blockers in CHF as well as common dosing initiation techniques. It also examines the indication, mechanism of action, dosing, pharmacokinetics, drug-drug interactions, and adverse effects of several commonly used β-blockers, including metoprolol, carvedilol, and propranolol.

Keywords β-blockers • Metoprolol • Carvedilol • Propranolol • Esmolol

7.1   Introduction

β-blockers are an essential component of pharmacologic therapy for adults with chronic congestive heart failure (CHF). They have been shown to decrease morbidity and mortality in several randomized controlled studies. Nonetheless, one has to take into consideration the differences that exist between pediatric and adult heart failure when considering β-blockers. Heart failure in adults is most often caused by left ventricular (LV) systolic dysfunction that occurs with damage from ischemia, hypertension, or older age. Pediatric heart failure is the result of primary systolic dysfunction most commonly caused by congenital structural defects. Patients born with single ventricle defects, especially those with a single right ventricle, appear to be particularly prone to ventricular dysfunction over time. Despite these differences in the etiology of heart failure, there is substantial evidence that infants and children have alterations in their neurohormonal axes that are similar to adults [1].

Although the exact mechanism by which β-blockers confer their benefit in heart failure is poorly understood, there are several proposed mechanisms:

(a) *Upregulation of β_1-adrenergic receptors and improved signaling*. In advanced heart failure, there is downregulation of β_1-adrenergic receptors, with resulting decreased contractility, ventricular dilatation, and apoptosis [2–5].
(b) *Protection from catecholamine myocyte toxicity*. The high level of circulating catecholamines found in severe heart failure is toxic to the myocardium [6].

(c) *Antiarrhythmic effects*. β-blockers suppress ventricular ectopic activity [7, 8].

(d) *Bradycardia*. Bradycardia may improve coronary blood flow and decrease myocardial oxygen demand [9].

(e) *Renin angiotensin inhibition*. When added to prior angiotensin converting enzyme (ACE) inhibitor therapy, β-blockade by metoprolol lessens circulating renin and angiotensin-II levels, thereby increasing inhibition of the renin-angiotensin system [9].

The initiation of β-blockade is a slow process that requires careful supervision and may temporarily worsen heart failure. The following principles apply to the use of all β-blocker agents:

1. Start with a lower dose and up-titrate slowly. If side effects occur, decrease the dose or advance more gradually.
2. Do not start β-blockers if the patient is hemodynamically unstable, and if possible, do not start β-blockers when the patient is in New York Heart Association (NYHA) class IV or severe class III heart failure.
3. Add β-blockers only to existing ACE inhibitors, diuretics and possibly digoxin.
4. Use only β-blockers that have been studied in heart failure, i.e. carvedilol, metoprolol and bisoprolol. Some of the original β-blockers, including propranolol and atenolol, have not been extensively researched in heart failure and their effects are less known [10].
5. One strategy used to appraise tolerance and benefits of β-blockers in a given patient employs IV continuous esmolol. It offers the advantage of being easy to titrate and has a very short half-life, which may be useful in case of poor tolerance.

7.2   Metroprolol

7.2.1   Indication

Metoprolol has been studied most extensively in adults with acute myocardial infarction for post-infarct protection and in stable symptomatic class II and class III heart failure [11].

In the pediatric population, three studies showed that metoprolol improved ventricular function and decreased the level of natriuretic peptide and norepinephrine [12–14].

7.2.2   Mechanism of Action

Metoprolol is a second-generation, cardioselective inhibitor of β_1-adrenergic receptors. It has no intrinsic sympathomimetic activity and weak membrane stabilizing activity [15]. Its β-selectivity is approximately 75-fold β_1/β_2. Higher doses (>100 mg/day in adults) exhibit more inhibitory effect on β_2 receptors. β_1-receptor blockade causes a fall in blood pressure by an undefined action. Possible mechanisms include blockage of reflex sympathetic stimulation in the heart with a resultant fall in cardiac output and/or a late decrease in peripheral vascular resistance.

7.2.3   Dosing (Heart Failure)

Neonates/Infants: No data available.

Children/Adolescents: There is limited pediatric dosing information available.

Initial oral dosing is 0.2–0.4 mg/kg/day divided twice daily to a target of 0.5–2.3 mg/kg/day divided twice daily over 8–12 weeks [12].

Adults: Oral: Initial oral dosing is 12.5–25 mg/day to a target of 200 mg/day (slow release metoprolol) over 8–12 weeks.

Dosage in Renal Failure: No dosage adjustment is required with metoprolol in patients with renal failure.

Dosage in Hepatic Insufficiency: Dosage adjustments may be required in patients with hepatic insufficiency since metoprolol is extensively metabolized in the liver. However, studies in patients with hepatic insufficiency are lacking.

7.2.4   Pharmacokinetics

Onset of Action: Immediate release metoprolol has an onset of action as an antihypertensive of 15 min and full β-blockade within 1 h.

Duration of Action: The β-blocking activity after a single immediate release oral dose is 3–6 h, with longer duration observed with higher doses.

Absorption: Almost completely absorbed when administered orally.

Bioavailability: Ranges between 50–70 % due to extensive first-pass metabolism.

Half-life: Varies with neonates exhibiting times of 5–10 h and adults 3–7 h. Continued administration, however, saturates the hepatic process that removes metoprolol from the circulation, and the effective half-life then becomes significantly longer.

Metabolism: Hepatic metabolism of metoprolol varies significantly in individual patients based upon the existence of the debrisoquine genetic polymorphism. Extensive hydroxylators may require several doses of the drug daily, whereas poor hydroxylators may do well with a single daily dose [16].

7.2.5   Monitoring Parameters

Monitor heart rate and blood pressure with oral administration. Monitor ECG and blood pressure with IV administration.

7.2.6   Precautions/Warnings

Metoprolol can exacerbate congestive heart failure. Use with care in patients with reactive airway disease. Use with caution in diabetes mellitus, hypoglycemia, renal failure. Use caution when discontinuing metoprolol to avoid withdrawal symptoms.

7.2.7   Drug-Drug Interactions

Interaction with amiodarone may cause a theoretical risk of hypotension, bradycardia, and cardiac arrest. Concomitant therapy with dihydropyridine calcium channel blockers (i.e., nifedipine, amlodipine, felodipine, nicardipine) may cause severe hypotension or impair cardiac performance. These effects are most prevalent in patients with impaired LV function, cardiac arrhythmias, or aortic stenosis. Cimetidine may cause bradycardia or hypotension. Therapy with ciprofloxacin may increase metoprolol concentrations and metoprolol dosage adjustment may be required. Abrupt withdrawal of clonidine while on a β-blocker may exaggerate the rebound hypertension due to unopposed alpha stimulation. Diclofenac and non-steroidal anti-inflammatory drugs (NSAIDs) may cause decreased antihypertensive effect. When β-blockers and digoxin are to be given concomitantly, both atrioventricular (AV) block and potential digoxin toxicity are possible. Diltiazem may cause hypotension, bradycardia, and AV conduction disturbances. Metoprolol toxicity (bradycardia, fatigue, bronchospasm) may be seen with diphenhydramine therapy through the inhibition of cytochrome P450 metabolism. Metoprolol toxicity through increased metoprolol bioavailability may be seen with hydralazine. Insulin may cause hypoglycemia, hyperglycemia, or hypertension. Paroxetine may cause increased risk of metoprolol adverse effects (shortness of breath, bradycardia, hypotension, acute heart failure) through inhibition of cytochrome P450. Phenobarbital causes decreased metoprolol effectiveness. An exaggerated hypotensive response to the first dose of the α-blocker phenoxybenzamine can occur. Propafenone may cause metoprolol toxicity through decreased metoprolol metabolism. Quinidine may cause bradycardia, fatigue, and shortness of breath through decreased metoprolol metabolism or clearance. Rifampin may cause decreased metoprolol effectiveness through increased metoprolol metabolism. Verapamil may cause hypotension and bradycardia.

7.2.8   Adverse Effects

Metoprolol is usually well tolerated with few unfavorable side effects. However, adverse reactions that have occurred include:

Central nervous system: drowsiness, insomnia, nightmares, confusion, depression

Cardiac: bradycardia, worsening of AV block, hypotension, chest pain, peripheral edema, CHF, reduced peripheral circulation, Raynaud's phenomenon

Pulmonary: bronchospasm

Gastrointestinal: nausea, abdominal pain, diarrhea or constipation

Dermatologic: rash, pruritus, and worsening of psoriasis.

7.2.9   Poisoning Information

Overdose may present as asystole, AV block, bradycardia, hypotension, cyanosis, CHF, hyperreflexia, insomnia, night terrors, confusion, respiratory arrest, seizures, wheezing, or metabolic acidosis. These following general measures can be employed if overdose or toxicity is suspected:

Elimination of the drug: Gastric lavage should be performed within 1 h of administration. Bradycardia/Hypotension: For bradycardia atropine should be administered. If there is no response, a continuous infusion of isoproterenol may be used. Temporary transvenous pacing may be required. Alternatively, a high-dose dobutamine infusion may be used to overcome the β-blockade. For hypotension use intravenous (IV) fluid resuscitation and vasopressors (i.e.., epinephrine, dopamine or dobutamine). Glucagon bolus of 50–150 mcg/kg IV over 1 min (usually about 10 mg in an adult) then a continuous IV infusion of 1–5 mg/h in D5W may be used as a first-line agent when an IV infusion is needed. Glucagon stimulates formation of cyclic adenine monophosphate (AMP) by bypassing the occupied

β-receptors. An infusion of a phosphodiesterase inhibitor such as milrinone or amrinone should also promote the accumulation of cyclic AMP.

Bronchospasm: A β_2-stimulating agent and/or a theophylline derivative should be administered.

7.3   Carvedilol

7.3.1   Indication

Carvedilol is a nonselective β-blocker that also has both α-mediated vasodilatory and antioxidant effects. It has been studied as an additional agent to standard therapy (digoxin, diuretics and ACE inhibitors) in adults with CHF and in post-infarct LV dysfunction [17]. It has been shown to decrease the risk of death and hospitalization, improve NYHA functional class, and reduce clinical progression in patients with mild CHF [4]. In pediatric patients with cardiomyopathy, carvedilol has been shown to improve symptoms and ventricular function [7, 18].

7.3.2   Mechanism of Action

Carvedilol is a nonselective β-receptor and α_1-receptor antagonist with no intrinsic sympathomimetic activity. It is available as a racemic mixture; the S(−) enantiomer possesses the nonselective β-blocking activity, while the alpha-adrenergic blocking activity is present in both R(+) and S(−) enantiomers at equal potency. The blockade of both β and α_1-receptors in CHF leads to decreased systemic blood pressure, decreased pulmonary capillary wedge pressure, decreased pulmonary artery pressure, decreased heart rate, decreased systemic vascular resistance, increased stroke volume index, and increased left ventricular ejection fraction. In addition, carvedilol has been shown to inhibit the action of oxygen-free radicals and to demonstrate antiproliferative effects on smooth muscle cells [19].

7.3.3   Dosing (Heart Failure)

Neonates: No data available.

Infants/*Children*: Initial dose: 0.03–0.08 mg/kg/dose by mouth given twice daily with a maximum initial dose of 3.125 mg given twice daily.

Maintenance dose: Increase (usually double) every 2–3 weeks as tolerated. Average maintenance dose at approximately 12 weeks is 0.3–0.95 mg/kg/dose by mouth twice daily with a maximum of 25 mg given twice daily. *Note*: Due to increased elimination of carvedilol in pediatric patients, three times daily dosing and a higher target dose per kg may be needed in children < 3.5 years of age [20].

Adults: Initial: 3.125 mg by mouth twice daily for 2 weeks. Maintenance: Increase (usually double) every 2–3 weeks as tolerated to a maximum of 25 mg twice daily in patients less than 85 kg, and 50 mg twice daily in patients more than 85 kg. In severe heart failure: 25 mg twice daily.

Dosing Adjustment in Renal Impairment: None recommended. *Note*: Mean area under the curves (AUCs) are 40–50 % higher in patients with moderate-to-severe renal dysfunction, but the ranges of AUCs are similar to patients with normal renal function.

Dosing Adjustment in Hepatic Impairment: Carvedilol is extensively metabolized in the liver and dose reductions are suggested in patients with hepatic insufficiency. One study suggests that carvedilol therapy be initiated with approximately 20 % of the normal dose in patients with liver cirrhosis [21]. The manufacturer recommends that carvedilol should not be administered to patients with severe liver failure. *Note*: Patients with cirrhotic liver disease achieved carvedilol serum concentrations four to sevenfold higher than normal patients following a single dose.

7.3.4   Pharmacokinetics

Onset: onset of action of α-blockade within 30 min and β-blockade within 1 h. Absorption: rapid and extensive, but with a large first-pass effect.

Bioavailability: 25–35 %. The first pass effect is stereoselective with the R(+) enantiomer achieving plasma concentrations 2–3 times higher than the S(−) enantiomer. Bioavailability is greatly increased in patients with CHF and/or liver disease [22]. Metabolism: in the liver primarily via cytochrome P450 isoenzymes. It is metabolized predominantly by aromatic ring oxidation and glucuronidation, and oxidative metabolites undergo conjugation via glucuronidation and sulfation. Metabolism is subject to genetic polymorphism and CYP2D6 poor metabolizers have a two to threefold higher plasma concentration of the R(+) enantiomer and a 20–25 % increase in the S(−) enantiomer compared to extensive metabolizers.

Half-life: dependent upon age: infants and children 6 weeks to 3.5 years-2.2 h, children 5.5–19 years-3.6 h, adults in general-7–10 h [20].

Elimination: less than 2 % of carvedilol is excreted unchanged in urine, and the metabolites are excreted via the bile into the feces.

7.3.5   Monitoring Parameters

Monitor heart rate and blood pressure; weight, renal function, liver function, serum glucose, cholesterol and triglycerides.

7.3.6   Contraindications

Cardiogenic shock, bradycardia or heart block, uncompensated congestive heart failure, asthma, and chronic obstructive lung disease, decompensated cardiac failure requiring ionotropic therapy, severe hepatic impairment.

7.3.7   Precautions/Warnings

Use with care in patients with reactive airway disease. Use with caution in diabetes mellitus, hypoglycemia, renal failure. Use caution when discontinuing to avoid withdrawal symptoms.

7.3.8   Drug-Drug Interactions

Interaction with amiodarone may cause a theoretical risk of hypotension, bradycardia, and cardiac arrest. Concomitant therapy with dihydropyridine calcium channel blockers (e.g., nifedipine, amlodipine, felodipine, nicardipine) may cause severe hypotension or impair cardiac performance. These effects are most prevalent in patients with impaired LV function, cardiac arrhythmias, or aortic stenosis. Cimetidine may cause increased adverse effects of carvedilol (dizziness, insomnia, gastrointestinal symptoms, postural hypotension). Abrupt withdrawal of clonidine while on a β-blocker may exaggerate the rebound hypertension due to unopposed α stimulation. Diclofenac and NSAIDs may cause decreased antihypertensive effect. When β-blockers and digoxin are to be given concomitantly, both AV block and potential digoxin toxicity are possible. Diltiazem may cause hypotension, bradycardia, and AV conduction disturbances. Carvedilol toxicity (bradycardia, fatigue, bronchospasm) may be seen with diphenhydramine therapy through the inhibition of metoprolol cytochrome P450. Insulin may cause hypoglycemia, hyperglycemia, or hypertension. An exaggerated hypotensive response to the first dose of the α-blocker phenoxybenzamine may occur. Verapamil may cause hypotension and bradycardia.

7.3.9   Adverse Effects

Cardiac: AV block, bradycardia, palpitations, syncope, peripheral edema, rebound or withdrawal hypertension following abrupt discontinuation of β-blocker therapy, postural hypotension

Central Nervous System: dizziness
 Endocrine/Metabolic hyperglycemia, hypertriglyceridemia and weight gain, mild hyperkalemia

Hematologic: decreases in hemoglobin and platelet counts

Hepatic: reversible liver dysfunction

Musculoskeletal: myalgia, joint and back pain, fatigue

Central Nervous System: headache, insomnia, somnolence
Genitourinary: microalbuminuria (in hypertensive patients), erectile dysfunction
Pulmonary: bronchospasm, rhinitis, pharyngitis, and dyspnea.

Abrupt withdrawal of β-blockers from some patients with angina pectoris may markedly increase the severity and frequency of the angina and result in severe cardiovascular problems (myocardial infarction, arrhythmias, and sudden death). β-blocker therapy should be gradually tapered rather than abruptly discontinued.

7.3.10   Poisoning Information

Overdose may present as asystole, AV block, bradycardia, hypotension, cyanosis, CHF, hyperreflexia, insomnia, night terrors, confusion, respiratory arrest, seizures, wheezing, or metabolic acidosis. These following general measures can be employed if overdose or toxicity is suspected:

Elimination of the drug: Gastric lavage should be performed within 1 h of administration. Bradycardia/Hypotension: For bradycardia atropine should be administered. If there is no response, a continuous infusion of isoproterenol may be used. Temporary transvenous pacing may be required. Alternatively, a high-dose dobutamine infusion may be used to overcome the β-blockade. For hypotension use intravenous (IV) fluid resuscitation and vasopressors (i.e.., epinephrine, dopamine or dobutamine). Glucagon bolus of 50–150 mcg/kg IV over 1 min (usually about 10 mg in an adult) then a continuous IV infusion of 1–5 mg/h in D5W may be used as a first-line agent when an IV infusion is needed. Glucagon stimulates formation of cyclic adenine monophosphate (AMP) by bypassing the occupied β-receptors. An infusion of a phosphodiesterase inhibitor such as milrinone or amrinone should also promote the accumulation of cyclic AMP.
Bronchospasm: A β_2-stimulating agent and/or a theophylline derivative should be administered.

7.4   Propranolol

7.4.1   *Indication*

Propranolol is a non-cardioselective β-blocking agent with equal effects on β_1 cardiac and β_2 receptors and a Class II antiarrhythmic agent In patients with CHF, propranolol has been shown to: reduce mortality, reduce LV mass, increase LV ejection fraction, and, in addition to digoxin/diuretic therapy, improve CHF symptoms in infants with congenital heart disease. In a prospective, open-label pediatric trial, infants with congenital heart disease and severe CHF due to left-to-right shunts demonstrated a significant improvement in Ross heart failure score, lowered renin and aldosterone levels, and lower mean heart rates [23]. Propranolol may be used to treat cyanotic spells in children with Tetralogy of Fallot [24].

7.4.2   *Mechanism of Action*

Propranolol's effects on both β-1 and β-2 receptors leads to decreased heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. β-1 blockade is responsible for the lowered heart rate and decreased myocardial contractility during periods of high sympathetic activity, such as during exercise. Cardiac output is also decreased. Additionally, blockade of β-receptors in cardiac conduction tissue results in the slowing of AV conduction and suppression of automaticity. β-2 blockade is responsible for many of the adverse effects of propranolol, including bronchospasm, hypoglycemia, and peripheral vasoconstriction.

7.4.3   *Dosing: Heart Failure*

Neonates: Limited data available. Initial: 0.5 mg/kg/dose by mouth twice daily.

Maintenance: Increase slowly every 2–4 weeks as tolerated to a maximum of 1 mg/kg/dose by mouth twice daily in 12–16 weeks.

Infants/Children: Initial: 0.5 mg/kg/dose by mouth twice daily.

Maintenance: Increase slowly every 2–4 weeks as tolerated to a maximum of 1.5 mg/kg/dose by mouth twice daily in 12–16 weeks.

Adults:

Angina Pectoris: initiate therapy with 20–40 mg twice daily, po; may increase to 160 mg a day

Arrhythmias: 10–30 mg three or four times daily, po

Life-threatening arrhythmias: 1–3 mg, slow IV, administered under careful monitoring

Post-myocardial Infarction: start with a 20 mg daily dose, po. If no adverse reaction is noted, increase the dose to 40 mg three times daily. The maximal dose may be increased to 80 mg three times daily (20 % of patients).

Hypertrophic Subaortic Stenosis: 20–40 mg, three or four times daily, po

7.4.4   Pharmacokinetics

Onset of action of 1–2 h after oral administration and 2 min after IV administration.

Duration: 6 h after oral dosing and 3–6 h after IV dosing.

Absorption: almost completely from the gastrointestinal tract. It has extensive first-pass Metabolism: extensive first-pass metabolism.

Bioavailablitiy: 30–40 %

Metabolism: in the liver to active and inactive compounds.

Half-life: for adults and children is approximately 4–6 h and is likely increased in neonates and infants.

Elimination: in the urine with 96–99 % as metabolites.

7.4.5   Monitoring Parameters

Monitor heart rate, blood pressure and ECG

7.4.6   Contraindications

Cardiogenic shock, bradycardia or heart block, uncompensated congestive heart failure, asthma, and chronic obstructive lung disease.

7.4.7   Precautions/Warnings

Propranolol can exacerbate congestive heart failure. Use with care in patients with reactive airway disease. Use with caution in diabetes mellitus, hypoglycemia, renal failure. Use caution when discontinuing propranolol to avoid withdrawal symptoms.

7.4.8   Drug-Drug Interactions

Phenobarbital, rifampicin and cimetidine increase propranolol clearance and decrease its activity. Propranolol's absorption is reduced by aluminum containing antacids. Phenothiazines may cause an additive hypotensive effect. Propranolol may increase the levels of direct acting alpha and beta agonists, alpha-1 blockers and alpha-2 agonists. Propranolol may also increase the effects of insulin, lidocaine, cardiac glycosides, and cholinergic agents. The levels of propranolol can be increased by amidarone, calcium channel blockers, dipyridamole, disopyramide, MAO inhibitoris, phosphodiesterase 5 inhibitors, prostacyclins, quinindine. Consult specific interaction reference for a comprehensive list.

7.4.9   Adverse Effects

Cardiovascular: hypotension, impaired myocardial contractility, congestive heart failure, bradycardia, AV block
Central Nervous System: lightheadedness, insomnia, vivid dreams, weakness, lethargy and depression
Endocrine/Metabolic: hypoglycemia, hyperglycemia, hyperkalemia
Gastrointestinal: nausea, vomiting, diarrhea
Hematologic: agranulocytosis
Pulmonary: bronchospasm.

7.4.10   Poisoning Information

Sympathomimetics can be used to treat bradycardia and hypotension. Symptoms include hypotension, bradycardia, bronchospasm, CHF and heart block. Overdose may present as asystole, AV block, bradycardia, hypotension, cyanosis, CHF, hyperreflexia, insomnia, night terrors, confusion, respiratory arrest, seizures, wheezing, or metabolic acidosis. These following general measures can be employed if overdose or toxicity is suspected:

Elimination of the drug: Gastric lavage should be performed within 1 h of administration. Bradycardia/Hypotension: For bradycardia atropine should be administered. If there is no response, a continuous infusion of isoproterenol may be used. Temporary transvenous pacing may be required. Alternatively, a high-dose dobutamine infusion may be used to overcome the β-blockade. For hypotension use intravenous (IV) fluid resuscitation and vasopressors (i.e.., epinephrine, dopamine or dobutamine). Glucagon bolus of 50–150 mcg/kg IV over 1 min (usually about 10 mg in an adult) then a continuous IV infusion of 1–5 mg/h in D5W may be used as a first-line agent when an IV infusion is needed. Glucagon stimulates formation of cyclic adenine monophosphate (AMP) by bypassing the occupied

β-receptors. An infusion of a phosphodiesterase inhibitor such as milrinone or amrinone should also promote the accumulation of cyclic AMP.

Bronchospasm: A β$_2$-stimulating agent and/or a theophylline derivative should be administered.

7.5   Esmolol

7.5.1   Indication

Esmolol is a β-blocker used as a Class II antiarrhythmic agent and antihypertensive drug. Esmolol is often used in the acute management of children with arrhythmias and/or hypertension; however, pharmacokinetic studies of the drug in children have been limited.

Please refer to Chap. 9.

Abbreviations

CHF   Congestive Heart Failure
LV   Left Ventricular
NSAIDs   Non-Steroidal Anti-Inflammatory Drugs
AV   Atrioventricular
NYHA   New York Heart Association

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Chapter 8
ACE Inhibitors and ARB's

Ryan Flanagan, Ricardo Munoz, and Carol G. Vetterly

Abstract Pharmacologic manipulation of afterload or systemic vascular resistance (SVR) has become increasingly important in the management of pediatric cardiac patients, just as it has for adult cardiac patients.

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R. Flanagan, MD (✉)
Division of Pediatric Cardiology, Department of Pediatrics,
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pediatrics, Womack Army Medical Center,
2817 Reilly Road, Fort Bragg, NC, USA

R. Munoz, MD, FAAP, FCCM, FACC
Cardiac Intensive Care Division, The Heart Institute, Children's
Hospital of Pittsburgh of UPMC, University of Pittsburgh,
Pittsburgh, PA, USA

C.G. Vetterly, PharmD, BCPS
Department of Pharmacy Services, Children's Hospital
of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics,
University of Pittsburgh School of Pharmacy,
Pittsburgh, PA, USA

8.1   Introduction

Pharmacologic manipulation of afterload or systemic vascular resistance (SVR) has become increasingly important in the management of pediatric cardiac patients, just as it has for adult cardiac patients. Specifically, the principal groups of pediatric patients with cardiovascular disease who may benefit from afterload reduction therapies include the following:

1. Patients with normal cardiac anatomy and myocardial function who have systemic hypertension;
2. Patients with normal cardiac anatomy but impaired myocardial function, either due to primary myocardial disease (e.g., familial cardiomyopathy), or acquired myocardial disease (e.g., dilated cardiomyopathy secondary to viral myocarditis);
3. Patients with congenital heart disease (CHD) who have undergone palliative (e.g., the modified Norwood procedure for hypoplastic left heart syndrome) or reparative surgery and developed myocardial dysfunction;
4. Patients with CHD immediately or early after cardiac surgery, especially cardiopulmonary bypass surgery.

The vasodilators are pharmacologic agents that produce relaxation of smooth muscle in the wall of blood vessels, leading to reduced vascular resistance and the potential for increased blood flow. Some vasodilators act on arterial vessels, others on venous vessels, and a third group on both arteries and veins. The vasodilators can be classified according to their predominant site of action or by their mechanism of action. In this chapter these agents will be classified by their mechanism of action, and Table 8.1 categorizes the agents described here by their actions.

TABLE 8.1 Vasodilators classified according to mechanism of action

Agent	Mechanism of action
Angiotensin-Converting Enzyme (ACE) Inhibitors	Inhibit angiotensin converting enzyme, which promotes the conversion of angiotensin I to the potent vasoconstrictor angiotensin II.
Captopril	
Enalapril	
Lisinopril	
Angiotensin II Receptor Blockers	Competitive binding to angiotensin II receptors
Losartan	

The types of vasodilators discussed included the following: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, nitrates and nitrate-like agents, α-adrenoceptor antagonists, dopaminergic receptor antagonists, prostaglandins, and the direct arteriolar vasodilator hydralazine.

8.2 Category: Angiotensin Convertin Enzyme Inhibitors

Individual agent: Captopril

8.2.1 Indication

Captopril is used in adults primarily to treat systemic hypertension, congestive heart failure (CHF), and left ventricular dysfunction in stable patients following a myocardial infarction [1]. In pediatric patients it is also used to treat systemic hypertension and CHF; additionally, it is used in CHD patients who have single ventricle anatomy, atrioventricular valve (AVV) regurgitation, and aortic valve regurgitation.

8.2.2   Mechanism of Action

Captopril is a competitive inhibitor of ACE; it therefore blocks the conversion of angiotensin I to angiotensin II. Angiotensin II is a strong vasoconstrictor, so reducing its blood level leads to less vasoconstriction. In addition plasma renin levels are increased and aldosterone secretion reduced.

8.2.3   Dosing

Neonates, Premature:

   Oral: Initial or "test" dose 0.01 mg/kg/dose P.O./N.G. Dose every 8–12 h and titrate dose for response.

Neonates:

   Oral: Initial or "test" dose 0.05–0.1 mg/kg/dose P.O./N.G. Dose every 8–24 h. Titrate dose to maximum of 0.5 mg/kg/dose and give every 6–24 h.

Infants/Children:

   Oral: Initial or "test" dose 0.15–0.5 mg/kg/dose P.O./N.G. Dose every 8–24 h. Titrate dose to maximum of 6 mg/kg/day in 1–4 divided doses. Usual dose is 2.5–6 mg/kg/day. For older children, initial dose is usually 6.25–12.5 mg/dose P.O./N.G. Dose every 12–24 h. Titrate dose to maximum of 6 mg/kg/day in 2–4 divided doses.

Adults:

   Oral: Initial dose 12.5–25 mg/dose P.O./N.G. Dose every 8–12 h. Titrate dose upward by 25 mg/dose at 1–2 week intervals to a maximum dose of 450 mg/day. Usual dose range is 25–100 mg/day in two divided doses.

   Note: Dosing for all age groups should be titrated to an individual patient's response, and the lowest dose that achieves this response should be chosen. Lower doses

are appropriate for patients who are also being treated with diuretics and are water- and sodium-depleted.

Dosing adjustment for renal impairment:

Creatinine clearance 10–50 mL/min/1.73 m^2: administer 75 % of dose

Creatinine clearance <10 mL/min/1.73 m^2: administer 50 % of dose

8.2.4   Pharmacokinetics

Onset of action: Decrease in blood pressure typically observed within 15–60 min

Absorption: 60–75 %

Distribution: 7 l/kg

Maximum effect: Hypotensive effect at 60–90 min; the full hypotensive effect may take weeks to occur.

Half-life: Infants with congestive heart failure: 3.3 h (1.2–12.4 h)

Children: 1.5 h (1–2.3 h)

Normal adults (dependent upon renal and cardiac function): 1.9 h

Adults with congestive heart failure: 2.1 h

Anuria: 20–40 h

Duration: Dose-related

Protein binding: 25–30 %

Metabolism: 50 % metabolized

Clearance: Time to peak serum concentration: 1–2 h

Elimination: 95 % excreted in urine in 24 h

8.2.5   Monitoring Parameters

Blood pressure, BUN, creatinine, urine dipstick for protein, WBC with differential, and serum potassium. Monitoring for blood pressure effect should focus on the period 1–3 h after dosing.

8.2.6   Contraindications

Hypersensitivity to captopril (any component) or other ACE inhibitors

8.2.7   Adverse Effects

Cardiovascular: Hypotension, tachycardia, chest pain and angina have been reported in adults

Respiratory: Cough, dyspnea. An isolated, dry cough has been reported in 17 % (7/42) of pediatric patients [2].

Central nervous system: Headache, dizziness, fatigue, and insomnia

Gastrointestinal: Loss of taste perception (related to zinc deficiency with long-term use)

Hepatic: Cholestatic jaundice, fulminant hepatic necrosis (rare, but potentially fatal)

Renal: Elevated BUN and serum creatinine, proteinuria, and oliguria

Endocrine/metabolic: Hyperkalemia

Hematologic: Neutropenia, agranulocytosis, and eosinophilia. The risk of neutropenia is increased by approximately 15-fold in patients with renal dysfunction.

Cutaneous/peripheral: Rash, angioedema

Other: Fever, anaphylactoid reaction

8.2.8   Precautions

Dosing should be adjusted downward in patients with renal impairment, collagen vascular disease, or obstruction to systemic arterial flow (e.g., aortic coarctation, renal artery stenosis). Monitor renal function closely in patients with known renal impairment, low cardiac output or volume depletion (e.g., co-administration of diuretic medications).

8.2.9   Drug-Drug Interactions

In patients who are also receiving potassium supplements or a potassium-sparing diuretic (e.g., spironolactone), an additive hyperkalemic effect may occur. In patients who are also receiving indomethacin or a NSAID, the anti-hypotensive effect of captopril may be diminished.

8.2.10   Compatible Diluents/Administration

Only available for oral/enteral administration. Administer either on an empty stomach 1 h before meals or 2 h after meals. Absorption may be reduced by presence of food in the gastrointestinal tract.

8.2.11   Standard Concentrations

Tablets: 12.5, 25, 50, and 100 mg
   Liquid: Prepared extemporaneously by pharmacy; usual concentration 1 mg/ml. Stability is limited in aqueous preparations.

8.2.12   Generic/Brand R Names

Yes/Capoten®

8.3   Individual Agent: Enalapril and Enalaprilat

8.3.1   Indication

Enalapril (oral/enteral administration) is used in adults primarily to treat systemic hypertension, CHF, asymptomatic left ventricular dysfunction, and proteinuria in steroid-resistant

nephrotic syndrome [1]. In pediatric patients, enalapril is also used to treat systemic hypertension and CHF; additionally, it is used in CHD patients who have single ventricle anatomy, AVV regurgitation, and aortic valve regurgitation [3]. Enalaprilat (I.V. administration) is used in hospital settings to treat systemic hypertension [4].

8.3.2   Mechanism of Action

Enalapril/Enalaprilat is a competitive inhibitor of ACE; it therefore blocks the conversion of angiotensin I to angiotensin II. Angiotensin II is a strong vasoconstrictor, so reducing its blood level leads to less vasoconstriction.

8.3.3   Dosing

Neonates:

Oral: Enalapril: Initial or "test" dose 0.1 mg/kg/dose P.O./N.G. Dose once every 24 h. Titrate dose and interval (up to every 12 h) every 3–5 days.

I.V.: Enalaprilat: Initial or "test" dose 5–10 mcg/kg/dose I.V. Dose every 8–24 h and titrate for response. Administer via an infusion over 5 min.

Infants/Children:

Oral: Enalapril: Initial or "test" dose 0.05–0.1 mg/kg/dose P.O./N.G. Dose once every 12–24 h. Titrate dose over 2 weeks to maximum of 0.5 mg/kg/day.

I.V.: Enalaprilat: Initial or "test" dose 5–10 mcg/kg/dose I.V. Dose every 8–24 h and titrate for response. Administer via an infusion over 5 min.

Adults:

Oral: Enalapril: Initial or "test" dose 2.5–5.0 mg/dose P.O./N.G. Dose every 12–24 h. Titrate dose upward by

2.5 mg/dose increments. Usual dose for hypertension is 10–40 mg/day given every 12–24 h. Usual dose for CHF is 5–20 mg/day in 2 divided doses. Maximum dose 40 mg/day.

I.V.: Enalaprilat: Initial or "test" dose 0.625 mg/dose I.V. Usual dosing 0.625–1.25 mg/dose I.V. given every 6 h. Maximum dose 5 mg/dose every 6 h (20 mg/day).

Note: Dosing for all age groups should be titrated to an individual patient's response, and the lowest dose that achieves this response chosen. Lower doses are appropriate for patients who are also being treated with diuretics and are water- and sodium-depleted, those with renal impairment and severe CHF, and patients with systemic arterial obstruction (e.g., coarctation of the aorta, renal artery stenosis). For additional dosing precautions in neonates, see Sect. 8.3.9.

Dosing adjustment for renal impairment:

Creatinine clearance 10–50 mL/min/1.73 m^2: administer 75–100 % of dose

Creatinine clearance <10 mL/min/1.73 m^2: administer 50 % of dose

No data exist for neonates and children ≤16 years with a glomerular filtration rate <30 mL/min/1.73 m^2, and use in these patients is not recommended.

8.3.4   Pharmacokinetics

Onset of action: Oral: within 1 h

I.V.: within 15 min

Absorption: Oral: 60 % in prodrug (enalapril) form
Distribution:
Maximum effect: Oral: 4–8 h

I.V.: 1–4 h

Half-life:

Enalapril:

Neonates 10–19 days of age with CHF (n = 3): 10.3 h (4.2–13.4 h)

Infants/Children (≤6.5 years) with CHF (n = 11): 2.7 h (1.3–6.3 h)

Adults: Healthy – 2 h; with CHF – 3.4–5.8 h

Enalaprilat:

Neonates 10–19 days of age with CHF (n = 3): 11.9 h (5.9–15.6 h)

Infants/Children (≤ 6.5 years) with CHF (n = 11): 11.1 h (5.1–20.8 h)

Infants 6 weeks – 8 months: 6–10 h

Adults: 35–38 h

Duration: Oral: 12–24 h

I.V.: 4–6 h (dose dependent)

Protein binding: 50–60 %

Metabolism: Enalapril is a prodrug (inactive) that is transformed in the liver to enalaprilat (active)

Clearance: Time to peak serum concentration: Enalapril – 0.5–1.5 h; Enalaprilat – 3–4.5 h

Elimination: 60–80 % in urine, with some in feces

8.3.5   Monitoring Parameters

Blood pressure, BUN, creatinine, WBC, serum potassium, serum glucose. Monitoring for blood pressure effect should focus on the period 1–3 h (enalapril) or 15–60 min (enalaprilat) after dosing.

8.3.6   Contraindications

Hypersensitivity to enalapril, enalaprilat, any component, or other ACE inhibitors. Also, patients with idiopathic or hereditary angioedema or a history of angioedema with

administration of ACE inhibitors should not receive these drugs.

8.3.7   Adverse Effects

Cardiovascular: Hypotension, tachycardia, and syncope
Respiratory: Cough, dyspnea, and eosinophilic pneumonitis. An isolated, dry cough has been reported in 17 % (7/42) pediatric patients receiving ACE inhibitors [2].
Central nervous system: Fatigue, vertigo, dizziness, headache, and insomnia
Gastrointestinal: Nausea, diarrhea, and loss of taste perception
Hepatic: Cholestatic jaundice, fulminant hepatic necrosis (rare, but potentially fatal)
Renal: Diminished renal function
Genitourinary: Impotence
Neuromuscular and skeletal: Muscle cramps
Endocrine/metabolic: Hypoglycemia, hyperkalemia
Hematologic: Agranulocytosis, neutropenia, and anemia
Cutaneous/peripheral: Rash, angioedema. The risk of angioedema is higher in the first 30 days of use and for enalapril and lisinopiril as compared to captopril.

8.3.8   Drug-Drug Interactions

In patients who are also receiving potassium supplements or a potassium-sparing diuretic (e.g., spironolactone), an additive hyperkalemic effect may occur. In patients who are also receiving indomethacin or a NSAID, the anti-hypertensive effect of enalapril may be diminished, and renal dysfunction may be exacerbated (usually reversible). Enalapril may increase serum lithium levels.

8.3.9   Poisoning Information

Enalaprilat contains benzyl alcohol (9 mg/mL) which may cause allergic reactions and a potentially fatal toxicity in

neonates called "gasping syndrome" at high doses (≥99 mg/kg/day). Gasping syndrome is manifested by metabolic acidosis, respiratory distress with gasping respirations, CNS dysfunction (seizures, hemorrhage), hypotension, and cardiovascular collapse. Therefore, enalaprilat should be used with caution and close monitoring in neonates.

8.3.10   Compatible Diluents/Administration

Enalapril is available for oral/enteral administration. It may be given without regard to the ingestion of food. Enalaprilat can be administered undiluted or diluted with normal saline; infuse over 5 min.

8.3.11   Standard Concentrations

Enalapril: Tablets (as maleate): 2.5, 5, 10, and 20 mg
    Enalprilat: Injection solution: 1.25 mg/ml in 1 ml or 2 ml vials

8.3.12   Generic/Brand R Names

Yes/Vasotec®

8.4   Lisinopril

8.4.1   Indication

Lisinopril is used in adults to treat systemic hypertension and as an adjunctive therapy in patients with CHF and left ventricular dysfunction following a myocardial infarction.6 In pediatric patients it is also used to treat systemic hypertension and CHF; additionally, it is used in CHD patients who have single ventricle anatomy, AVV regurgitation and aortic valve regurgitation.

8.4.2 Mechanism of Action

Lisinopril is a competitive inhibitor of ACE; it therefore blocks the conversion of angiotensin I to angiotensin II. Angiotensin II is a strong vasoconstrictor, so reducing its blood level leads to less vasoconstriction. In addition plasma renin levels are increased and aldosterone secretion reduced.

8.4.3 Dosing

Neonates (Premature and Full Term), Infants, and Children <6 Years:

No dosing information is available; because of this, the manufacturer recommends not using Lisinopril in patients <6 years of age.

Children >6 years:

Initial or "test" dose 0.07 mg/kg/dose P.O./N.G. Dose once per 24 h. Maximum initial dose 5 mg once daily. Increase dose at 1- to 2-week intervals for desired effect. No data available on doses >0.61 mg/kg or >40 mg.

Adults:

Oral: Initial or "test" dose 10 mg/dose P.O./N.G. given once daily. Increase dose by 5–10 mg/day at 1- to 2-week intervals for desired effect. Usual dose 20–40 mg/day given once daily. Maximum daily dose reported is 80 mg/day.

For adults with CHF: Initial or "test" dose 5 mg/dose P.O./N.G. given once daily. Increase dose by ≤ 10 mg/day at ≥ 2-week intervals based on clinical response. Usual dose is 5–10 mg/day given once daily. Maximum dose is 40 mg/day.

Note: Dosing for all age groups should be titrated to an individual patient's response, and the lowest dose that achieves this response chosen. Lower doses are appropriate for patients who are also being treated with

diuretics and are water- and sodium-depleted, those with renal impairment and severe CHF, and patients with systemic arterial obstruction (e.g., coarctation of the aorta, renal artery stenosis). For additional dosing precautions in neonates, see Sect. 8.3.9.

Dosing adjustment for renal impairment:

Creatinine clearance >30 mL/min/1.73 m^2: Usual dose 10 mg once daily
Creatinine clearance 10–30 mL/min/1.73 m^2: Initial dose 5 mg once daily
Creatinine clearance <10 mL/min/1.73 m$^{2.}$ Initial dose 2.5 mg once daily

In adults with renal impairment, dose titration should be performed cautiously. Also, lower doses (e.g., ½ those listed) should be used for patients with hyponatremia, hypovolemia, severe CHF, reduced renal function, or if receiving diuretics. Use is not recommended in children who have a creatinine clearance <30 mL/min/1.73 m^2 because no data or dosing recommendations exist for pediatric patients with a GFR of <30 mL/min/1.73 m^2.

8.4.4   Pharmacokinetics

Onset of action: 1 h (blood pressure lowered)
Absorption: Children (6–16 years): 28 %

Adults: 25 % (6–60 %)

Distribution:
Maximum effect: 6–8 h
Half-life: 11–13 h; increased with renal dysfunction
Duration: 24 h
Protein binding: 25 %
Metabolism:

Clearance: Time to peak serum concentration:

   Children (6–16 years): 6 h
   Adults: 7 h

Elimination: In urine [5] as unchanged drug. Can be removed by hemodialysis.

8.4.5   Monitoring Parameters

Blood pressure, BUN, serum creatinine, WBC, and serum potassium. Monitoring for blood pressure should be conducted with knowledge that the maximum effect is 6–8 h after dosing.

8.4.6   Contraindications

Hypersensitivity to lisinopril (any component) or other ACE inhibitors. Also contraindicated in patients with a history of idiopathic or hereditary angioedema or angioedema with prior ACE use.

8.4.7   Adverse Effects

Cardiovascular: Hypotension, chest discomfort, orthostatic hypotension, tachycardia and syncope
Respiratory: Cough, dyspnea, and eosinophilic pneumonitis
Central nervous system: Headache, dizziness, and fatigue
Gastrointestinal: Diarrhea, nausea, vomiting, loss of taste perception, and intestinal angioedema (rare)
Hepatic: Cholestatic jaundice, hepatitis, fulminant hepatic necrosis (rare, but potentially fatal)
Renal: Elevated BUN and serum creatinine
Endocrine/metabolic: Hyperkalemia

Hematologic: Neutropenia, agranulocytosis, and eosinophilia. The risk of neutropenia is increased in patients with renal dysfunction.

Cutaneous/peripheral: Rash, angioedema. The risk of angioedema is higher in the first 30 days of use and is greater for lisinopril and enalapril than captopril.

Other: Anaphylactoid reactions

8.4.8 Precautions

Note: Dosing for all age groups should be titrated to an individual patient's response, and the lowest dose that achieves this response chosen. Lower doses are appropriate for patients who are also being treated with diuretics and are water- and sodium-depleted, those with renal impairment and severe CHF, and patients with systemic arterial obstruction (e.g., coarctation of the aorta, renal artery stenosis).

Angioedema may occur in the head, neck, extremities, or intestines (rare). Airway obstruction can occur with swelling of the tongue, larynx, or glottis, especially in patients with a history of airway surgery. For patients at higher risk of airway obstruction, equipment to establish airway patency and medications to relieve airway swelling (e.g., epinephrine) should be available.

8.4.9 Drug-Drug Interactions

In patients who are also receiving potassium supplements or a potassium-sparing diuretic (e.g., spironolactone), an additive hyperkalemic effect may occur. In patients who are also receiving indomethacin or a NSAID, the anti-hypertensive effect of enalapril may be diminished, and renal dysfunction may be exacerbated (usually reversible). Enalapril may increase serum lithium levels.

8.4.10   Compatible Diluents/Administration

Only available for oral/enteral administration. Lisinopril may be administered without regard to ingestion of food.

8.4.11   Standard Concentrations

Tablets: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg

Liquid: Prepared extemporaneously by pharmacy; usual concentration 1 mg/ml or 2 mg/ml.

8.4.12   Generic/Brand R Names

Yes/Zestril®, Prinivil®

8.5   Category: Angiotensin II Receptor Antagonists: Losartan

8.5.1   Indication

Losartan is used in adults to treat systemic hypertension, diabetic nephropathy in patients with type 2 (non-insulin dependent) diabetes mellitus and hypertension, and to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy [6]. Losartan is commonly combined with a thiazide diuretic in adults to treat hypertension. For adult patients with CHF who develop persistent cough on an ACE inhibitor, losartan is often used to replace the ACE inhibitor. In pediatric patients, it is used predominantly to treat systemic hypertension, and it appears to have a protective effect on the kidneys in children with renal insufficiency and hypertension [7]. Recent data from animal studies and

limited human case series have suggested that angiotensin receptor blockers may attenuate the progression of aortic dilatation in patients with marfans syndrome, pediatric studies to evaluate this effect are currently oncgoing.

8.5.2   Mechanism of Action

Losartan (and its principal active metabolite E-3174) selectively blocks the binding of the potent vasoconstrictor angiotensin II to the AT_1 receptor. AT_1 receptors exist in many tissues, including vascular smooth muscle and the adrenal glands. By inhibiting angiotensin II binding to these receptors, losartan reduces vasoconstriction and aldosterone secretion, which lowers systemic blood pressure. Angiotensin II receptor antagonists may be more inhibitory than ACE inhibitors on the renin-angiotensin system, and in addition, they do not affect the vascular response to bradykinin (a potent vasodilator) or induce as much cough or angioedema as ACE inhibitors. Losartan is also a natriuretic and kaliuretic and increases urine output.

8.5.3   Dosing

Neonates, (Premature and Full Term) and Infants: No data available to guide dosing in neonates, infants, and children under 6 years of age.

Children:

Oral: Data from a single trial of pediatric patients (n = 177) aged 6–16 years forms the basis of pediatric dosing recommendations [8].

Children 6–16 years: 0.7 mg/kg P.O./N.G. once daily. Titrate dose based on response. Maximum dose 50 mg/day.

Adults:

> Oral: Usual starting dose is 50 mg P.O./N.G. once daily. Total daily doses range from 25 to 100 mg. May be given in 1 or 2 doses/day.

> Dosing adjustments:

1. Patients receiving diuretics or with low intravascular volume: Initial dose 25 mg once daily.
2. Renal impairment:
   Children: Use not recommended if creatinine clearance <30 mL/min/1.73 m^2
   Adults: No adjustment necessary
3. Hepatic impairment: Reduce initial dose in adults to 25 mg/day and give in two versus one dose/day. Extrapolated to pediatrics one half the typical starting dose is recommended.
4. No adjustment required for food.

8.5.4   Pharmacokinetics

Onset of action: 6 h
Absorption: Well absorbed; bioavailability 25–33 %
Distribution: Volume of distribution: Losartan – 34 l; E-3174 – 12 l
Maximum effect: Peak concentrations: Losartan – 1 h; E-3174 – 3–4 h
Half-life: Losartan – 1.5–2 h; E-3174 – 6–9 h
Protein binding: >98 %
Metabolism: Extensive first-pass effect. Metabolized in liver (14 %) via cytochrome P450 isoenzyme CYP2C9 and 3A4 to active metabolite E-3174
Clearance: Losartan: 600 mL/min; E-3174 50 mL/min
Elimination: Via the urine, 4 % as unchanged drug and 6 % as E-3174. Biliary secretion also occurs.

8.5.5   Monitoring Parameters

Blood pressure (while supine), serum electrolytes, BUN, serum creatinine, CBC, and urinalysis

8.5.6   Contraindications

Hypersensitivity to losartan or any component in its formulation or to other angiotensin II receptor antagonists; bilateral renal artery stenosis; pregnancy (particularly the 2nd and 3rd trimesters).

8.5.7   Adverse Effects

Cardiovascular: Chest pain, hypotension, orthostatic hypotension, first-dose hypotension, and tachycardia
Respiratory: Cough, bronchitis, upper respiratory infection, nasal congestion and sinusitis
Central nervous system: Fatigue, dizziness, hypoesthesia, and insomnia
Gastrointestinal: Diarrhea, gastritis, weight gain, dyspepsia, abdominal pain, and nausea
Genitourinary: Urinary tract infection (patients with diabetic nephropathy)
Neuromuscular and skeletal: Weakness, back pain, knee pain, leg pain, muscle cramps and myalgia. Rhabdomyolysis (rare)
Endocrine/metabolic: Hypoglycemia, hyperkalemia
Hematologic: Anemia, Thrombocytopenia
Cutaneous/peripheral: Cellulitis (patients with diabetic nephropathy)
Other: Fever, infections, and flu-like syndrome, angioedema

8.5.8   Precautions

Drugs that affect the angiotensin system in humans can cause injury or death to a fetus during the 2nd or 3rd trimester; therefore, losartan should be discontinued as soon as possible once

pregnancy is detected. Avoid use in nursing mothers since excretion in breast milk occurs. Because losartan can cause hypotension, especially with the initial dose, particular care should be used in patients who have low intravascular volume. Use with caution in patients who have baseline hepatic or renal dysfunction. Consider discontinuing potassium supplementation or potassium-sparing diuretics because of risk of hyperkalemia. Patients with unilateral renal artery stenosis or significant aortic or mitral stenosis are at risk for inadequate systemic blood flow.

8.5.9   Drug-Drug Interactions

Because losartan is metabolized in the liver by the cytochrome P450 system as a substrate of isoenzymes CYP3A4 and CYP2C9, it has multiple interactions with other drugs. The most significant interactions reported are as follows:

1. Losartan and E-3174 levels are decreased by concomitant administration of phenobarbital and rifampin;
2. Fluconazole decreases E3174 levels but increases Losartan levels;
3. Losartan may increase the levels or effects of CYP2C8 (e.g., amiodarone) and CYP2C9 (e.g., warfarin, phenytoin, and fluoxetine) substrates and lithium levels;
4. NSAIDs may reduce the effectiveness of Losartan.

8.5.10   Compatible Diluents/Administration

Losartan may be taken with or without food.

8.5.11   Standard Concentrations

Tablet, as potassium: 25 mg, 50 mg, and 100 mg

8.5.12   Generic/Brand R Names

No/Cozaar®

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Chapter 9
Antiarrhythmics

Jamie A. Decker and Timothy K. Knilans

Abstract Arrhythmias occur in children and adolescents with congenital heart disease as well as those with structurally normal hearts. Antiarrhythmic medications primarily affect the ion channels in cardiac myocytes that are responsible for generating currents that create the action potential. By altering the activity of these ion channels, the action potential is changed in an attempt to reduce the likelihood of sustained arrhythmias.

Arrhythmias occur in children and adolescents with congenital heart disease as well as those with structurally normal hearts. Antiarrhythmic medications primarily affect the ion

J.A. Decker, MD (✉)
Division of Pediatric Cardiology,
Johns Hopkins All Children's Heart Institute,
601 5th Street, South Saint Petersburg, FL, USA
e-mail: jamie.decker@allkids.org

T.K. Knilans, MD
Division of Pediatrics and Pediatric Cardiology, The Heart Institute,
Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
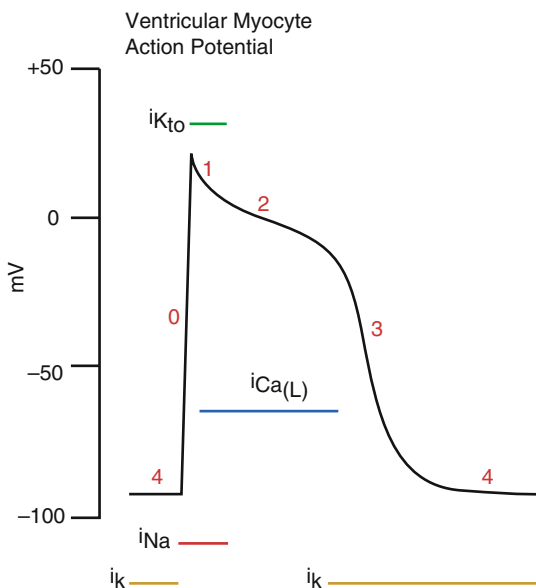
FIG. 9.1 Typical action potential of a ventricular myocyte

channels in cardiac myocytes that are responsible for generating currents that create the action potential. By altering the activity of these ion channels, the action potential is changed in an attempt to reduce the likelihood of sustained arrhythmias. To better understand how antiarrhythmic medications work, a quick review the cardiac myocyte is imperative.

Figure 9.1 shows the action potential of a ventricular myocyte. The action potential consists of four phases. Depolarization, known as phase 0, is caused by activation of fast inward sodium channels (I_{Na}). This results in an influx of sodium ions into the cell, resulting in a positive membrane potential. The change in membrane potential causes the sodium channels to be inactivated. Phase 1 is caused by opening of slow outward (I_{to1}) potassium channels. This is followed by a plateau phase (phase 2), which is primarily the result of a balance L-type calcium channels that result in inward movement of calcium and the delayed potassium channels (I_{ks}),

TABLE 9.1 Antiarrhythmic treatment of specific arrhythmias

Reentrant SVT (concealed AVRT, AVNRT)	Classes II, IV, Ia, Ic, III, digoxin
WPW	Classes II, Ia, Ic, III
Automatic atrial tachyardias (focal atrial tachycardia, chaotic atrial tachycardia)	Classes Ia, Ic, II, III, IV, digoxin (rate control)
Atrial flutter/fibrillation	Classes Ia, Ic, III,
Junctional ectopic tachycardia	Classes Ia (procainamide), III (amiodarone)
Ventricular tachycardia	Classes Ia, Ib, II, III, IV
Torsades de pointe/ventricular fib	Classes Ib, II, IV

AVNRT atrioventricular node reentrant tachycardia, *AVRT* atrioventricular reciprocating tachycardia, *SVT* supraventricular tachycardia, *WPW* Wolff-Parkinson-White syndrome

which continue the outflow of potassium channels. This is followed by a rapid repolarization phase (phase 3). This occurs with the closure of L-type calcium channels, while the I_{ks} channels remain open, creating a more negative membrane potential. This causes rapid delayed rectifier potassium channels to open (I_{kr}), resulting in an outflow of potassium ions. These remain open until the resting membrane potential is reached (phase 4).

The most common classification of antiarrhythmics, known as the Singh Vaughan-Williams classification, divides antiarrhythmics based on which ion channel is primarily affected. The Harrison modification subclassifies sodium channel blocking drugs. Although these classifications have limitations, as many of these medications affect multiple ion channels, it provides a good framework to understand antiarrhythmics and therefore is used in this chapter (Table 9.1). Antiarrhythmics are therefore divided into five classes:

Class I: Antiarrhythmics that affect sodium channels (slow depolarization)

Class II: Drugs that counteract the sympathetic nervous
system, predominantly beta-blockers
Class III: Drugs that affect potassium channels (prolong
repolarization)
Class IV: Drugs that affect calcium channels (Calcium
channel blockers)
Class V: Vagotonic drugs (Digoxin) and other miscella-
neous drugs

9.1   Class I Agents

The Harrison method divides Class I drugs into three catego-
ries based on the degree of sodium channel blockade and
effects on the duration of the action potential. Class Ia agents
block fast sodium channels intermediately and cause the
action potential to prolong. Class Ib agents block fast sodium
channels rapidly and shortens the action potential without
effecting depolarization (no change in QRS); and class Ic
block them slowly, resulting in slow depolarization (widening
of the QRS), and do not significantly alter the overall action
potential duration (see Fig. 9.2).

9.2   Class Ia Drugs

9.2.1   Procainamide

Indication: Procainamide can be effective in treating both
supraventricular and ventricular tachyarrhythmias.
Supraventricular arrhythmias include focal atrial tachycar-
dia, atrial fibrillation, reentrant supraventricular tachycar-
dia [1], as well as post-operative junctional ectopic
tachycardia (JET) [2].

Mechanism of Action: Procainamide blocks open sodium
channels and affects outward potassium channels. This
decreases the slope of phase 0 (prolongs depolarization),
which causes a widening of the QRS. It also prolongs
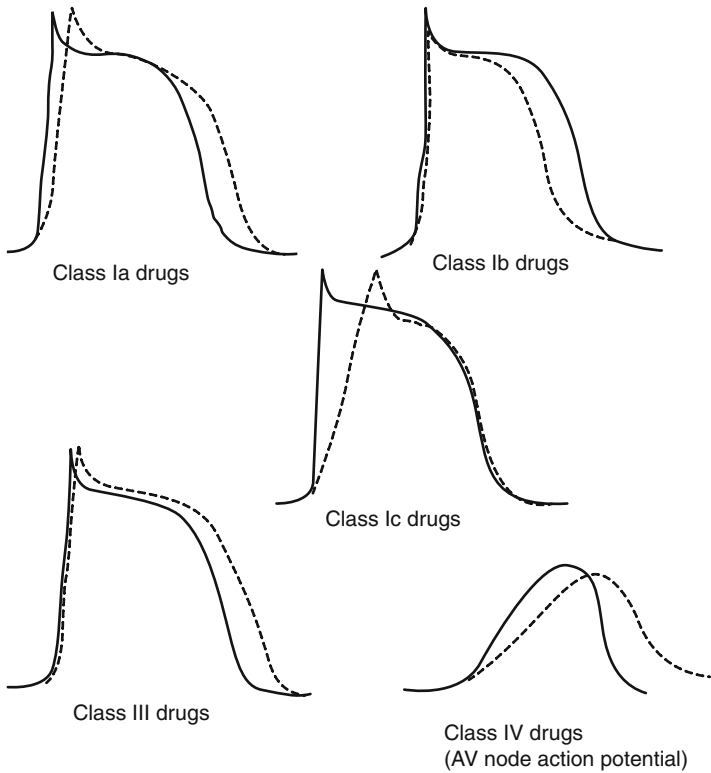
FIG. 9.2 Action potential effects by VW class antiarrhythmics

repolarization by its effect on potassium channels. It does prolong the refractory period of atrioventricular accessory pathways as well.

Dosing: Procainamide can be administered orally or intravenously.

Infants/Children:

Oral: 15–30 mg/kg/day, divided every 3–6 h (maximum, 4 g/day)

I.M.: 20–30 mg/kg/day, divided every 4–6 h (maximum, 4 g/day)

I.V.: loading dose of 3–6 mg/kg/dose over 5 min, not to exceed 100 mg/dose; may repeat every 5–10 min to a maximum load of 15 mg/kg; do not exceed 500 mg in 30 min

Maintenance: continuous I.V. infusion of 20–80 μg/kg/min (maximum dose, 2 g/day)

Adults:

Oral: Immediate release: 250–500 mg/dose every 3–6 h

Sustained release: 500 mg to 1 g every 6 h

Extended release: 1–2 g every 12 h

Usual dose: 50 mg/kg/day or 2–4 g/day

I.V.: Loading dose of 50–100 mg/dose repeated every 5–10 min until the patient is controlled, or load with 15–18 mg/kg (maximum load, 1–1.5 g)

Maintenance: continuous I.V. infusion, 3–4 mg/min; range, 1–6 mg/min

Dosing adjustment in renal dysfunction:

Clcr 10–50 mL/min: administer dose every 6–12 h

Clcr less than 10 mL/min: administer dose every 8–24 h

Pharmacokinetics: Procainamide is metabolized in the liver to an active metabolite, N-acetyl procainamide (NAPA) [3]. Its half-life is 1.7 h in children and 2.5–4.7 h in adults. The half life of NAPA is 6 h in children and 6–8 h in adults. Both are excreted in the urine primarily. It is moderately dialyzable by hemodialysis, but not by peritoneal dialysis. The therapeutic serum concentration of procainamide is 4–10 mg/L and 10–30 mg/L for NAPA. The time to peak effect is 60–90 min for the oral form, 15–60 min for the IM for and immediately for the intravenous form.

Monitoring Parameters: Electrocardiogram (ECG), hemodynamic monitoring, CBC, LFTs should be monitored. Serum levels of both procainamide and NAPA levels should be checked, especially in patients with renal insufficiency. Levels should be checked 1 h after a bolus and serially while on an intravenous infusion. If QRS duration increases >25 % baseline, consider decreasing dose. If QTc >500 ms, consider stopping medication. ANA titer should be monitored annually with chronic use.

Contraindications: Complete or second degree AV block without a pacemaker, history of torsades de pointes, cardiac glycoside intoxication, myasthenia gravis, and systemic lupus erythematosus.

Precautions/Warnings: Caution must be taken in patients with renal or hepatic dysfunction. Procainamide may exacerbate congestive heart failure (CHF). It can increase the ventricular response during atrial flutter and fibrillation and therefore appropriate rate response should be achieved prior to initiation. Hypokalemia may worsen toxicity. Long-term administration of procainamide results in the development of positive antinuclear antibodies in 50 % of patients, which may lead to a lupus erythematosus-like syndrome in 10–30 % of patients.

Drug Interactions: Ranitidine, amiodarone, ß-blockers, and trimethoprim may increase plasma levels. Procainamide may potentiate skeletal muscle relaxants.

Adverse Effects:

CV: hypotension, tachycardia, arrhythmias, AV block, QT prolongation, QRS widening

CNS: confusion, disorientation

GI: nausea, vomiting, GI complaints

Hematological: agranulocytosis, neutropenia

Hepatic: hepatomegaly, increased liver enzymes

Miscellaneous: drug fever, lupus-like syndrome (arthralgia, positive Coombs' test, thrombocytopenia, rash, myalgia, fever, pericarditis, and pleural effusion)

Poisoning Information Procainamide has a low toxic-to-therapeutic ratio and can easily produce fatal intoxication. Symptoms include sinus bradycardia and arrest; PR, QRS, and QT prolongation; torsades de pointes; depressed myocardial contractility; hypotension; pulmonary edema; seizures; coma; and respiratory arrest. Treatment of poisoning is symptomatic. Sodium bicarbonate may treat QRS prolongation and hypotension.

Compatible Diluents/Administration Do not administer procainamide faster than 20–30 mg/min. Severe

hypotension can occur with rapid I.V. push. Administer an I.V. loading dose over 25–30 min using a concentration of 20–30 mg/mL for the loading dose and 2–4 mg/mL for the maintenance infusion.

9.2.2   Disopyramide

Indication: Disopyramide is used in the conversion and management of atrial fibrillation, atrial flutter, and SVT.

Mechanism of Action: Disopyramide is a potent sodium and potassium channel blocker. It prolongs the action potential duration and slows conduction in normal atrial and ventricular myocytes. It slows the rate of phase 4 depolarization in cells with enhanced automaticity. It has little direct effect on the AV node, but enhances AV nodal conduction by an indirect vagolytic action.

Dosing: Disopyramide is only available in an enteral form
Infants/children:
Younger than 1 year: 10–30 mg/kg/day in four divided doses
1–4 years old: 10–20 mg/kg/day in four divided doses
4–12 years old: 10–15 mg/kg/day in four divided doses [4]
12–18 years: 6–15 mg/kg/day in four divided doses
Adults:
<50 kg, administer 100 mg every 6 h, or 200 mg every 12 h
>50 kg, administer 150 mg every 6 h, or 300 mg every 12 h
Adult dose adjustment in renal dysfunction:
Clcr 30–40 mL/min: 100 mg every 8 h
Clcr 15–30 mL/min: 100 mg every 12 h
Clcr less than 15 mL/min: every 24 h

Pharmacokinetics: Disopyramide is generally highly protein bound. The peak serum concentration is 0.5–3 h. Disopyramide has a half-life of 3–5 h in children.
Disopyramide is metabolized in the liver; its major metabolite has anticholinergic and antiarrhythmic effects. Disopyramide is eliminated in the urine.

Contraindications Cardiogenic shock, preexisting second- or third-degree heart block (without pacemaker), congenital long QT syndrome, and sick sinus syndrome.

Precautions/Warnings Use with caution in patients with pre-existing urinary retention, existing or family history of glaucoma, myasthenia gravis, CHF, sick sinus syndrome, Wolff-Parkinson-White (WPW) syndrome, and widening of QRS or lengthening of QT interval. Decrease dose in patients with renal or hepatic impairment. Disopyramide may increase the ventricular response rate in patients with atrial fibrillation or flutter; therefore, AV conduction should be controlled before initiating treatment.

Drug-Drug Interactions Hepatic microsomal enzyme-inducing agents (phenytoin, phenobarbital, and rifampin) may increase metabolism of disopyramide, and lower serum concentrations. Clarithromycin and erythromycin may increase disopyramide concentrations and should not be used with disopyramide. Other antiarrhythmics may increase adverse conduction effects. Adverse effects of disopyramide may be additive with amitriptyline, imipramine, haloperidol, thioridazine, dicapride, and other drugs that prolong the QT. Do not administer disopyramide 48 h before or 24 h after verapamil.

Adverse Effects
CV: CHF, edema, chest pain, syncope and hypotension, AV block, widened QRS and prolonged QT interval
CNS: fatigue, headache, malaise, nervousness, acute psychosis, depression, dizziness
Dermatological: rash
Endocrine and metabolic: hypoglycemia, weight gain, elevated cholesterol and triglyceride levels
GI: xerostomia, dry throat, constipation, nausea, vomiting, diarrhea, pain, gas, anorexia
Genitourinary (**GU**): urinary retention
Hepatic: elevated liver enzymes
Neuromuscular: weakness

Ocular: blurred vision
Respiratory: dyspnea

Poisoning Information Disopyramide has a low toxic-to-therapeutic ratio and may produce fatal intoxication. Symptoms of poisoning include sinus bradycardia, sinus arrest, and asystole; torsades de pointes; PR, QRS, and QT prolongation; depressed myocardial contractility; hypotension; pulmonary edema; dry mouth; dilated pupils; delirium; seizures; coma; and respiratory arrest. Treatment is symptomatic. Sodium bicarbonate may treat QRS prolongation or hypotension.

Administration Administer disopyramide on an empty stomach.

9.2.3   Quinidine

Indication Quinidine is used to maintain sinus rhythm after conversion from atrial fibrillation or flutter. It can be used to prevent recurrence of supraventricular tachycardia (SVT) and ventricular tachycardia (VT).

Mechanism of Action Quinidine is a sodium and potassium channel blocker. Sodium channel blockade predominantly occurs in the active state. Quinidine also exhibits low levels of α- and muscarinic-receptor blockade.

Dosing: Dosage is expressed in terms of the salt: 267 mg of quinidine gluconate equals 200 mg of quinidine sulfate.

Infants/children: test dose for idiosyncratic reaction, intolerance, syncope, and thrombocytopenia:
Oral, (*quinidine gluconate*): 2 mg/kg or 60 mg/m^2
Oral (*quinidine sulfate*): 30 mg/kg/day or 900 mg/m^2/day administered in five daily doses, or 6 mg/kg every 4–6 h; range, 15–60 mg/kg/day in four to five divided doses
Intravenous (*I.V.*) (*quinidine gluconate*): 2–10 mg/kg/dose every 3–6 h as needed (I.V. not recommended)
Adults: test dose for idiosyncratic reaction, intolerance, syncope, and thrombocytopenia:

Oral: 200 mg administered several hours before full dose

Oral (*quinidine sulfate*): 100–600 mg/dose every 4–6 h

Oral (*quinidine gluconate*): 324–972 mg every 8–12 h

I.M.: 400 mg/dose every 4–6 h

I.V.: 200–400 mg/dose diluted and administered at a rate of at most 10 mg/min

Dosing adjustment in renal impairment: creatinine clearance (Clcr) less than 10 mL/min, administer 75 % of normal dose

Pharmacokinetics: Quinidine is extensively protein bound, and is metabolized extensively in the liver. The half-life of quinidine in children is 2.5–6.7 h; the half-life in adults is 6–8 h. The route of elimination of quinidine is renal. Quinidine is slightly dialyzable by hemodialysis; and is not removed by peritoneal dialysis [5].

Monitoring Parameters: Complete blood cell count (CBC), with differential, liver and renal function tests, and serum quinidine concentrations should be routinely performed with long-term administration of quinidine.

Contraindications: Contraindications for quinidine are complete atrioventricular (AV) block, marked widening of QRS complex, cardiac glycoside- induced AV conduction disorders, and myasthenia gravis.

Precautions/*Warnings*: Hemolysis may occur in patients with glucose-6-phosphate dehydrogenase deficiency (G-6-PD).

Drug-Drug Interactions: Diltiazem, verapamil, and amiodarone may increase quinidine levels.

Phenobarbital, phenytoin, and rifampin may decrease quinidine levels. Quinidine may increase plasma concentration of digoxin; digoxin may need to be decreased by one-half when co-administering quinidine [6]. Quinidine may increase bradycardia when administered with β-blockers; quinidine enhances Coumadin anticoagulants. Quinidine potentiates non-depolarizing and depolarizing muscle relaxants. Quinidine interacts with ritonavir; therefore, concurrent use is not recommended.

Adverse Effects

CV: syncope, hypotension tachycardia, heart block, ventricular arrhythmias [7], vascular collapse, severe hypotension with rapid intravenous administration

Central nervous system (**CNS**): fever, headache

Dermatological: angioedema, rash

Gastrointestinal (**GI**): GI disturbances, nausea, vomiting, and cramps

Hematological: blood dyscrasias and thrombotic thrombocytopenic purpura

Hepatic: quinidine-induced hepatotoxicity, including granulomatous hepatitis, and jaundice

Respiratory: respiratory depression

Miscellaneous: Cinchonism (nausea, tinnitus, headache, impaired hearing or vision, vomiting, abdominal pain, vertigo, confusion, delirium, and syncope)

Poisoning Information: Quinidine has a low toxic-to-therapeutic ratio and may easily produce fatal intoxication. Symptoms include sinus bradycardia, arrest, or asystole; PR, QRS, or QT prolongation; torsades de pointes; depressed myocardial contractility; hypotension; pulmonary edema; dry mouth; dilated pupils; delirium; seizures; coma; and respiratory arrest. Treatment is primarily symptomatic. Sodium bicarbonate may treat QRS prolongation and hypotension.

Diagnostic or therapeutic endoscopy may be required in patients with massive overdose and prolonged elevated quinidine levels.

Compatible Diluents/Administration The maximum rate of I.V. infusion is 10 mg/min; with a maximum concentration of 16 mg/mL in dextrose; I.V. tubing should be minimized (quinidine is adsorbed to polyvinyl chloride tubing). For oral use, do not administer with grapefruit juice. Use of extended release products is not recommended in children. Bezoar formation is reported in pediatric patients.

9.3   Class Ib Agents

9.3.1   Lidocaine

Indication Lidocaine is used for treatment of ventricular ectopy, tachycardia, and fibrillation; local anesthetic.

Mechanism of Action Lidocaine treatment blocks the fast sodium channel and shows frequency dependence. It decreases the rate of phase 4 depolarization in ventricular myocardium. It has little or no effect on tissue above the His bundle.

Dosing
Infants/children:

I.V., *I.O.* (intra-osseous): loading dose of 1 mg/kg followed by continuous infusion of 20–50 μg/kg/min. May repeat bolus with 0.5–1 mg/kg. Patients with shock, hepatic disease, or CHF should receive one-half of the loading dose and lower infusion rates

Tracheal tube: 2- to 10-fold times the I.V. bolus dose

Adults:

I.V.: loading dose of 1–1.5 mg/kg. May repeat doses of 0.5–0.75 mg/kg every 5–10 min, to a total of 3 mg/kg. Continuous infusion, 1–4 mg/min. Decrease the initial bolus of 0.5–0.75 mg/kg in patients with CHF

Tracheal tube: 2–2.5 times the I.V. bolus dose

Pharmacokinetics: Metabolism of lidocaine diminished in heart failure. The onset of action is 45–90 s. The half-life is 2–3 h. Therapeutic levels of lidocaine are in the range of 2–5 μg/mL. Lidocaine is eliminated in the urine.

Monitoring Parameters: ECG should be continuously monitored. Measure serum concentrations of lidocaine. Monitor the I.V. site, because local thrombophlebitis has been seen with prolonged infusions.

Contraindications: Sinus, AV, or intraventricular block without pacemaker; WPW syndrome.

Precautions/Warnings: Use lidocaine with caution in patients with hepatic disease, heart failure, hypotension or shock; dose may need to be decreased.

Drug-Drug Interactions: β-blockers may increase lidocaine serum levels. Class I antiarrhythmics and amiodarone may increase adverse effects.

Adverse Effects

CV: bradycardia, hypotension, heart block, arrhythmias, cardiovascular collapse

CNS: lethargy, coma, agitation, slurred speech, seizures, anxiety, euphoria, hallucinations

GI: nausea, vomiting

Neuromuscular: paresthesias, muscle twitching

Ocular: blurred vision, diplopia,

Respiratory: respiratory depression or arrest

Miscellaneous: allergic reaction (rare)

Poisoning Information: Lidocaine has a narrow therapeutic index; severe toxicity is seen slightly above the therapeutic range, especially if lidocaine is administered with other antiarrhythmics [8]. Symptoms include sedation, confusion, coma, seizures, respiratory arrest, sinus arrest, AV block, asystole, hypotension, dizziness, paresthesias, tremor, ataxia, and GI disturbances. Treatment is supportive. Sodium bicarbonate may reverse QRS prolongation, bradyarrhythmias, and hypotension.

Compatible Diluents/Administration: Tracheal tube doses should be diluted to 1–2 mL with normal saline (NS). For I.V. push, dilute lidocaine to a maximum concentration of 20 mg/mL and administer over 5–10 min. The maximum I.V. push rate is 0.35–0.7 mg/kg/min.

9.3.2   Mexiletine

Indication: Mexiletine is indicated for management of ventricular arrhythmias [9].

Mechanism of Action: Mexiletine inhibits the fast sodium channel with greater effects at faster heart rates. Effects are exaggerated in diseased tissue, dependent on potassium concentration. Mexiletine suppresses early afterdepolarizations.

Dosing: Mexiletine is only available for enteral administration.

Infants/children:

Oral: 1.4–5 mg/kg/dose (mean, 3.3 mg/kg/dose) administered every 8 h. Increase dose according to effect

Adults:

Oral: initial, 200 mg every 8 h (may load with 400 mg, if necessary). Adjust dose every 2–3 days. Usual dose, 200–300 mg every 8 h; maximum dose, 1.2 g/day

Dosing adjustment in renal impairment: children and adults with Clcr less than 10 mL/min, administer 50–75 % of normal dose

Pharmacokinetics: Mexiletine is rapidly absorbed and undergoes hepatic metabolism. The half-life of Mexiletine is 10–14 h. Mexiletine is eliminated in the urine.

Monitoring Parameters: Liver enzymes, CBC, ECG, heart rate, and serum concentrations should be monitored.

Contraindications: Cardiogenic shock and second- or third-degree AV block without a pacemaker are contraindications.

Precautions/Warnings: Use mexiletine with caution in patients with seizure disorders, severe CHF, hypotension, or hepatic dysfunction. Blood dyscrasias have been reported.

Drug-Drug Interactions: Phenobarbital, phenytoin, rifampin, and other hepatic enzyme inducers may lower mexiletine plasma levels. Cimetidine may increase levels of mexiletine. Antacids, narcotics, or anticholinergics may decrease absorption of mexiletine. Metoclopramide may increase absorption of mexiletine. Mexiletine may increase concentrations of theophylline and caffeine.

Adverse Effects

CV: palpitations, bradycardia, chest pain, syncope, hypotension, atrial or ventricular arrhythmias

CNS: dizziness, confusion, ataxia
Dermatological: rash
GI: nausea, vomiting, diarrhea
Hematological: thrombocytopenia,   leucopenia,
  agranulocytosis
Hepatic: elevated liver enzymes, hepatitis
Neuromuscular: paresthesias, tremor
Ocular: diplopia
Otic: tinnitus
Respiratory: dyspnea

Poisoning Information: Mexiletine has a narrow therapeutic index; severe toxicity is seen slightly above the therapeutic range, especially with other antiarrhythmics. Symptoms include sedation, confusion, coma, seizures, respiratory arrest, sinus arrest, AV block, asystole, hypotension, dizziness, paresthesias, tremor, ataxia, and GI disturbances. Treatment is supportive. Sodium bicarbonate may reverse QRS prolongation, bradyarrhythmias, and hypotension.

9.3.3   Phenytoin

Indication: Phenytoin does not have current FDA labeled indications for treatment of arrhythmia, but has been used for ventricular arrhythmias, including those associated with digitalis intoxication and seizures [10].

Mechanism of Action: Phenytoin binds primarily to sodium channels in the inactivated state. High concentrations of phenytoin can have some calcium channel-blocking effects with decreases in sinus and AV nodal automaticity. Phenytoin depresses Phase 4 depolarization, which makes it useful for treating digoxin-induced arrhythmias. Phenytoin decreases sympathetic effects in the ventricle.

Dosing
Infants/children:
I.V.: loading dose, 1.25 mg/kg every 5 min, up to a total load of 15 mg/kg

Oral, *I.V*.: maintenance dose, 5–10 mg/kg/day in two to three divided doses

Adults:

I.V.: loading dose, 1.25 mg/kg every 5 min, may repeat up to a total loading dose of 15 mg/kg

Oral: loading dose, 250 mg four times per day for 1 day, 250 mg twice daily for 2 days, and then maintenance at 300–400 mg/day in divided doses one to four times per day

Pharmacokinetics: Peak serum levels occur 3–12 h after dose. Phenytoin is metabolized in the liver. The half-life is up to 24 h in infants. In patients older than 1 year, the half-life is 8 h. In adults, the half-life is 24 h. Phenytoin is eliminated in the urine.

Monitoring Parameters: Serum phenytoin concentration, CBC with differential, liver enzymes, and blood pressure with intravenous use should be monitored.

Contraindications: Heart block and sinus bradycardia are contraindications.

Drug-Drug Interactions: Phenytoin may decrease the effectiveness of ritonavir, valproic acid, ethosuximide, warfarin, oral contraceptives, corticosteroids, etoposide, doxorubicin, vincristine, methotrexate, cyclosporine, theophylline, chloramphenicol, rifampin, doxycycline, quinidine, mexiletine, disopyramide, dopamine, or nondepolarizing muscle relaxants. Serum phenytoin levels may be increased by cimetidine, chloramphenicol, felbamate, zidovudine, isoniazid, trimethoprim, or sulfonamide. Rifampin, zidovudine, cisplatin, vinblastine, bleomycin, antacids, and folic acid may decrease phenytoin levels.

Adverse Effects

CV: hypotension, bradycardia, arrhythmia, cardiovascular collapse

CNS: slurred speech, dizziness, drowsiness, lethargy, coma, ataxia, dyskinesias

Ocular: nystagmus, blurred vision, diplopia

Dermatological: hirsutism, coarsening of facial features, Steven-Johnson syndrome, rash

Endocrine and metabolic: folic acid depletion, hyperglycemia
GI: nausea, vomiting, gingival hyperplasia, gum tenderness
Hematological: blood dyscrasias, lymphoma
Hepatic: hepatitis
Local: thrombophlebitis
Neuromuscular: peripheral neuropathy
Miscellaneous: SLE-like syndrome

Poisoning Information: Symptoms of phenytoin poisoning include unsteady gait, slurred speech, confusion, nausea, hypothermia, fever, hypotension, respiratory depression, and coma. Treatment is supportive.

Compatible Diluents/Administration: Administer phenytoin by slow injection without dilution and flush with saline immediately, or dilute with NS for infusion to a concentration of less than 6 mg/mL. Do not exceed an I.V. infusion rate of 1–3 mg/kg/min and a maximum rate of 50 mg/min. Avoid extravasation.

9.4   Class Ic Agents

9.4.1   Flecainide

Indication: Flecainide is indicated for treatment of atrial, junctional, and ventricular arrhythmias [11, 12].

Mechanism of Action: Flecainide blocks slow sodium channels in the activated state, with some mild potassium channel-blocking properties. Flecainide has a long time constant and takes longer to dissociate from sodium channels. In specialized conduction tissue, refractory periods are shortened and automaticity is decreased. Ventricular action potential duration and refractory periods are prolonged to a minor degree.

Dosing
Children:
Oral: initial dose, 1–3 mg/kg/day or 50–100 mg/m^2/day, in three divided doses. Increase every few days to 3–6 mg/kg/day or 100–150 mg/m^2/day in three divided doses

Adults:

Oral: 50–100 mg every 12 h; increase by 100 mg/day every 4 days. Usual dose, at most 300 mg/day; maximum, 400 mg/day

Pharmacokinetics: Flecainide shows complete absorption. Flecainide is metabolized in the liver. The half-life in newborns is 29 h; infants, 11–12 h; children, 8 h; and adults, 12–27 h. Flecainide is eliminated in the urine. Flecainide is not dialyzable.

Monitoring Parameters: ECG, serum flecainide concentration, liver enzymes, and CBC should be monitored.

Contraindications: Contraindications for flecainide administration are preexisting second- or third-degree AV block, complete right bundle branch block (RBBB) with left hemiblock or trifascicular block, cardiogenic shock, and myocardial depression [13].

Precautions/*Warnings*: Use flecainide with caution in patients with CHF, conduction abnormalities, and myocardial, renal, or hepatic dysfunction. Inpatient monitoring for arrhythmia development is recommend for initiation [14].

Drug-Drug Interactions: Other antiarrhythmics may increase adverse cardiac effects. Flecainide may increase plasma digoxin levels. β-blockers, disopyramide, or verapamil may result in added negative inotropy. Antacids, carbonic anhydrase inhibitors, or sodium bicarbonate may decrease clearance of flecainide. Amiodarone may increase the serum concentration of flecainide. Use of flecainide with ritonavir is not recommended.

Adverse Effects:

CV: bradycardia, heart block, ventricular arrhythmias, CHF, palpitations, chest pain, edema, increased PR interval and widened QRS [15]

CNS: dizziness, fatigue, nervousness, headache

Dermatological: rash

GI: nausea

Hematological: blood dyscrasias

Hepatic: hepatic dysfunction

Neuromuscular: paresthesias, tremor
Ocular: blurred vision
Respiratory: dyspnea

Poisoning Information: Flecainide has a narrow therapeutic index and severe toxicity is seen slightly above the therapeutic range, especially if flecainide is combined with other antiarrhythmics. Signs include increases in PR, QRS, and QR intervals; AV block; bradycardia; hypotension; ventricular arrhythmias; and asystole. Symptoms include dizziness, blurred vision, headache, and GI upset. Treatment is supportive. Sodium bicarbonate may reverse QRS prolongation, bradycardia, and hypotension.

Compatible Diluents/Administration: Dairy products may interfere with the absorption of flecainide and should be given one hour before dairy products. Serum flecainide levels should be monitored when changing dairy intake.

9.4.2   Propafenone

Indication: Propafenone is indicated for treatment of atrial, junctional, and ventricular arrhythmias [16].

Mechanism of Action: Propafenone blocks sodium channels with a medium-range time constant for recovery. Propafenone has mild β-blocking properties. Propafenone has effects on the slow inward calcium current and delayed outward potassium current.

Dosing:
Infants/children:
Oral: 150–200 mg/m^2/day divided every 8 h. Upper dose range, 600 mg/m^2/day
Adults:
Oral: Immediate release: 150 mg every 8 h; increase every 3–4 days to 300 mg every 8 h
Extended release: 225 mg every 12 h; increase every 5 days to 325 mg every 12 h, to a maximum of 425 every 12 h

Pharmacokinetics: Propafenone is well absorbed. Propafenone is metabolized in the liver, with two genetically determined groups described (fast and slow metabolizers) [17]. Propafenone has a half-life of 2–8 h after a single dose and up to 10–32 h in chronic use.

Monitoring Parameters: ECG and blood pressure should be monitored.

Contraindications: Contraindications for propafenone use are sinoatrial (SA), AV, or intraventricular conduction disorders without a pacemaker; sinus bradycardia; cardiogenic shock; uncompensated heart failure; hypotension; bronchospasm; uncorrected electrolyte abnormalities; and concurrent use of ritonavir.

Precautions/Warnings: Monitor for proarrhythmia and increasing CHF with propafenone use. Administer propafenone cautiously in those with significant hepatic dysfunction.

Drug-Drug Interactions: Cimetidine, quinidine, ritonavir (contraindicated), fluoxetine, and miconazole may increase propafenone levels. Phenobarbital and rifampin may decrease propafenone levels. Propafenone may increase levels of digoxin, metoprolol, propranolol, theophylline, and warfarin. Use propafenone with caution with Class IA and III agents, erythromycin, antipsychotics, and tricyclic antidepressants.

Adverse Effects:
CV: proarrhythmia, CHF, AV block, syncope, chest pain, hypotension
CNS: dizziness, fatigue, headache, ataxia, insomnia, anxiety, drowsiness
Dermatological: rash
GI: nausea, vomiting, constipation, dyspepsia, diarrhea, anorexia, abdominal pain
Neuromuscular: tremor, weakness, arthralgia
Ocular: blurred vision
Respiratory: dyspnea

Poisoning Information: Propafenone has a narrow therapeutic index and severe toxicity is seen slightly above the therapeutic range, especially if propafenone is combined with other antiarrhythmics. Acute single ingestion of twice the daily dose of propafenone is life threatening. Signs include increased PR, QRS, and QR intervals; AV block; bradycardia; hypotension; ventricular arrhythmias; and asystole. Symptoms include dizziness, blurred vision, headache, and GI upset. Treatment is supportive. Sodium bicarbonate may reverse QRS prolongation, bradycardia, and hypotension.

9.5   Class II Antiarrhythmics: Beta-Blockers

9.5.1   Esmolol

Indication: Esmolol is used for treatment of SVT and atrial fibrillation/flutter (rate control), ventricular tachycardiaand hypertension in the postoperative setting [18, 19].

Mechanism of Action: Esmolol is an intravenous β-blocker with predominate β1-receptor selectivity. The predominant sites of action are the SA and AV nodes.

Dosing:
Infants/children:
I.V.: 100–500 μg/kg administered over 1 min, followed by continuous infusion starting at 50 μg/kg/min. Additional boluses can be administered, with an increase in the infusion rate up to 200 mg/kg/min
Adults:
I.V.: loading dose, 500 μg/kg over 1 min, followed by a 50 μg/kg/min infusion for 4 min. May re-bolus and increase continuous infusion to 100 μg/kg/min. Repeat until therapeutic dose or a maximum maintenance dose of 200 μg/kg/min is reached

Pharmacokinetics: Esmolol is metabolized in blood by esterases. The half-life of esmolol is 3–10 min.

Monitoring Parameters: Blood pressure, ECG, and heart rate should be monitored.

Contraindications: Contraindications of esmolol use are sinus bradycardia or heart block, uncompensated heart failure, and cardiogenic shock.

Precautions/Warnings: Use esmolol with care in patients with reactive airway disease. Use with caution in diabetes mellitus, hypoglycemia, and renal failure. Avoid extravasation. Caution should be exercised when discontinuing esmolol, to avoid withdrawal effects.

Drug-Drug Interactions: Morphine may increase esmolol concentrations. Theophylline or caffeine may decrease the effects of esmolol. Esmolol may increase digoxin or theophylline serum concentrations.

Adverse Effects:
CV: hypotension, bradycardia
CNS: dizziness, somnolence, confusion, lethargy, depression, headache
Endo: Hypoglycemia
GI: nausea, vomiting
Local: phlebitis
Respiratory: bronchoconstriction
Miscellaneous: sweating

Poisoning Information: Poisoning signs include hypotension, bradycardia, bronchospasm, CHF, and heart block. Fluid administration is a useful therapy for hypotension. Sympathomimetics can be used to treat bradycardia and hypotension.

Compatible Diluents/Administration: Esmolol must be diluted to a final concentration of 10 mg/mL. Concentrations greater than 10 mg/mL can cause thrombophlebitis.

9.5.2   Propranolol

Indication: Propranolol is used to treat atrial and ventricular tachyarrhythmias and systemic hypertension [20].

Mechanism of Action: Propranolol is a nonselective β-blocker with membrane effects on the sodium channel. Propranolol has no intrinsic sympathomimetic properties.

Dosing:
Infants/children:
I.V.: Neonates: 0.01 mg/kg slow I.V. push over 10 min; may repeat every 6–8 h as needed, increase slowly to maximum of 0.15 mg/kg/dose every 6–8 h

Infants/children: 0.01–0.1 mg/kg slow I.V. over 10 min, maximum dose of 1 mg in infants and 3 mg in children

Oral:
Neonates: 0.25 mg/kg/dose every 6–8 h; increase to maximum of 5 mg/kg/day

Children: 0.5–1 mg/kg/day in divided doses every 6–8 h; titrate over 3–5 days to usual dose of 2–4 mg/kg/day. Do not exceed 16 mg/kg/day or 60 mg/day

Adults:
I.V.: 1 mg/dose slow I.V. push; repeat every 5 min up to 5 mg total

Oral: 10–20 mg/dose every 6–8 h; increase gradually to a range of 40–320 mg/day

Pharmacokinetics: Propranolol has extensive hepatic metabolism and clearance. The half-life of propranolol in infants is 3–4 h; in children and adults, it is 6 h. Propranolol is excreted in the urine. Propranolol is not dialyzable.

Monitoring Parameters: Monitor ECG and blood pressure with I.V. propranolol administration; monitor heart rate and blood pressure with oral propranolol administration.

Contraindications: Propranolol is contraindicated with uncompensated CHF, cardiogenic shock, bradycardia or heart block, asthma, and chronic obstructive lung disease.

Precautions/***Warnings***: Use propranolol with care in patients with heart failure, because propranolol can exacerbate CHF. Use with care in patients with reactive airway disease. Use with caution in diabetes mellitus, hypoglycemia, and renal failure. Avoid extravasation. Caution should be

exercised when discontinuing propranolol to avoid potential withdrawal.

Drug-Drug Interactions: Phenobarbital and rifampin may increase propranolol clearance and decrease its activity. Cimetidine may reduce clearance and increase its effects. Aluminum-containing antacids may reduce absorption. Additive hypotensive activity can be seen with phenothiazines.

***Adverse Effects*:**
CV: hypotension, impaired myocardial contractility, CHF, bradycardia, AV block
CNS: lightheadedness, insomnia, vivid dreams, weakness, lethargy and depression
Endocrine and metabolic: hypoglycemia (especially infants and children), hyperglycemia
GI: nausea, vomiting, diarrhea
Hematological: agranulocytosis
Respiratory: Bronchospasm

Poisoning Information: Symptoms include hypotension, bradycardia, bronchospasm, CHF, and heart block. Sympathomimetics can be used to treat bradycardia and hypotension.

Compatible Diluents/Administration: Propranolol is incompatible with bicarbonate; protect from exposure to light.

9.5.3   Atenolol

Indication: Atenolol is used to treat atrial and ventricular tachyarrhythmias and systemic hypertension [21, 22].

Mechanism of Action: Atenolol is a selective β-blocker that primarily affects β1 receptors. Atenolol has no intrinsic sympathomimetic or membrane properties. Atenolol does not cross the blood brain barrier.

Dosing:
Infants/children:
Oral: initial, 0.8–1 mg/kg/day divided once or twice daily; maximum dose, 2 mg/kg/day. Do not exceed the adult maximum dose of 100 mg/day
Adults:
Oral: initial, 25–50 mg/dose administered once or twice daily; usual dose, 50–100 mg/dose administered once or twice daily. Maximum dose, 100 mg/day

Dosing adjustment in renal impairment: If Clcr 15–35 mL/min, use a maximum dose of 50 mg or 1 mg/kg/dose daily. If Clcr less than 15 mL/min, use a maximum dose of 50 mg or a 1 mg/kg/dose every other day.

Pharmacokinetics: Atenolol reaches a peak concentration 2–3 h after an oral dose; and has a half-life of up to 9–10 h. Atenolol has little hepatic transformation; no active metabolites; and is eliminated in urine and feces. Atenolol is moderately dialyzable [23].

Contraindications: Bradycardia, heart block, uncompensated CHF, cardiogenic shock, and pulmonary edema are contraindications.

Precautions/Warnings: Use atenolol with care in patients with renal impairment, reactive airway disease, diabetes mellitus, hypoglycemia, and CHF. Avoid extravasation. Caution should be exercised when discontinuing atenolol to avoid withdrawal.

Drug-Drug Interactions: Atenolol has additive effects with other antihypertensive agents. It may reverse the therapeutic effects of theophylline.

Adverse Effects:
CV: bradycardia, hypotension, second- or third-degree heart block
CNS: dizziness, fatigue, lethargy headache, nightmares
GI: constipation, nausea, diarrhea
Respiratory: bronchospasm

Poisoning Information: Symptoms include hypotension, bradycardia, cardiogenic shock, and asystole. CNS effects include coma, convulsions, and respiratory arrest. Treatment is symptomatic. Bradycardia may respond to atropine, isoproterenol, or glucagon.

9.5.4   Metoprolol

I*ndication*: Metoprolol is used to treat atrial and ventricular tachyarrhythmias and systemic hypertension. It reduces mortality in adults with CHF [24].

Mechanism of Action: Metoprolol is a selective β1 blocker. Metoprolol has no intrinsic sympathomimetic activity.

Dosing:
Infants/children:
Oral: Limited pediatric data is available for antiarrhythmic dosing in neonates and children
Adults:
I.V.: 1.25–5 mg every 6–12 h; titrate initial dose to response. Maximum dose, 15 mg every 3–6 h
Oral: initial dosing, 100 mg/day, in one to two doses a day. Increase at weekly intervals. Usual dosage, 100–450 mg/day

Pharmacokinetics: Metoprolol undergoes extensive first-pass hepatic transformation. Metoprolol has a half-life of 3–8 h; has no active metabolites; and is excreted in the urine.

Monitoring Parameters: Monitor ECG and blood pressure with I.V. use of metoprolol. Monitor heart rate and blood pressure with oral use.

Contraindications: Sinus bradycardia, second- or third-degree heart block (in patients without a pacemaker), cardiogenic shock, and uncompensated CHF are contraindications.

Precautions/***Warnings***: Use metoprolol with care in patients with heart failure, reactive airway disease, diabetes mellitus,

hypoglycemia, and renal failure. Avoid extravasation. Caution should be exercised when discontinuing metoprolol to avoid withdrawal.

Drug-Drug Interactions: Reserpine and monoamine oxidase (MAO) inhibitors may have additive effects of hypotension and bradycardia. Antihypertensive agents, diuretics, digoxin, amiodarone, calcium channel blockers, and general anesthetics may have additive effects. Verapamil may increase the oral bioavailability of metoprolol. Ciprofloxacin, hydralazine, oral contraceptives, and quinidine may increase metoprolol serum concentrations. Non-steroidal anti-inflammatory drugs (NSAIDs) may decrease antihypertensive effects. Barbiturate and rifampin may increase the metabolism of metoprolol. Metoprolol may increase lidocaine serum concentrations.

Adverse Effects:

CV: bradycardia, palpitations, CHF, hypotension, peripheral edema, heart block

CNS: dizziness, tiredness, depression, mental confusion, insomnia

Dermatological: rash, pruritus

GI: diarrhea, nausea, abdominal pain, constipation, vomiting

Hematological: agranulocytosis, thrombocytopenia

Hepatic: hepatitis, jaundice

Respiratory: bronchospasm, dyspnea

Poisoning Information: Symptoms include hypotension, bradycardia, cardiogenic shock, and asystole. CNS effects include coma, convulsions, and respiratory arrest. Treatment is symptomatic. Bradycardia may respond to atropine, isoproterenol, or glucagon.

9.5.5   Nadolol

Indication: Nadolol is used to treat atrial and ventricular tachyarrhythmias and hypertension [25].

Mechanism of Action: Nadolol is a nonselective β-blocker. Nadolol has no intrinsic sympathomimetic or membrane properties.

Dosing:

Infants/children:

Oral: limited information is available. Initial dose, 0.5–1 mg/kg, once daily. Gradually increase dose to a maximum dose of 2.5 mg/kg/day

Adults:

Oral: initial dose, 40 mg once daily. Increase gradually to usual dose of 40–80 mg/day, but may need up to 240–320 mg/day

Dose adjustment in renal impairment (**adults**): If Clcr 10–50 mL/min, administer 50 % of normal dose. If Clcr less than 10 mL/min, administer 25 % of normal dose

Pharmacokinetics: Nadolol is poorly absorbed, with peak plasma levels 3–4 h after administration. Nadolol has a half-life in infants of 3–4 h, in children, of 7–15 h, and, in adults, of 10–24 h. Nadolol has an increased half-life with decreased renal function. Nadolol is moderately dialyzable [26].

Monitoring Parameters: Monitor blood pressure and heart rate with nadolol use.

Contraindications: Uncompensated CHF, cardiogenic shock, asthma, and bradycardia or heart block are contraindications for nadolol administration.

Precautions/*Warnings*: Use nadolol with care in patients with heart failure, because nadolol can exacerbate CHF. Use with care in patients with reactive airway disease. Use with caution in diabetes mellitus, hypoglycemia, and renal failure. Caution should be exercised when discontinuing nadolol to avoid withdrawal.

Drug-Drug Interactions: Diuretic and phenothiazines may increase antihypertensive effects.

Nadolol may enhance the action of neuromuscular blocking agents. Abrupt withdrawal of clonidine may result in hypertensive crisis.

*Adverse Effects***:**

CV: bradycardia, orthostatic hypotension, CHF, edema

CNS: fatigue, dizziness, depression

Dermatological: rash
GI: abdominal discomfort, diarrhea, constipation
Endocrine and metabolic: impotence
Respiratory: bronchospasm

Poisoning Information: Symptoms include hypotension, bradycardia, AV block, cardiogenic shock, and asystole. CNS effects include convulsions, coma, and respiratory arrest. Treatment is symptomatic. Bradycardia and hypotension may respond to atropine, isoproterenol, or pacing.

9.6   Class III Antiarrhythmic Agents

9.6.1   Amiodarone

Indication: Amiodarone is used in a wide range of ventricular and atrial tachyarrhythmias that are unresponsive to conventional therapy with less-toxic agents [27–30]. Amiodarone is frequently used to treat postoperative junctional ectopic tachycardia.

Mechanism of Action: Amiodarone inhibits adrenergic stimulation; prolongs the action potential and refractory period of both atrial and ventricular myocardium; and decreases AV and sinus nodal function.

Dosing:
Infants/children:
I.V.: 5 mg/kg administered rapid bolus for pulseless VT/ventricular fibrillation (VF); or over 20–60 min for perfusing tachycardias. May repeat for a total load of 20 mg/kg in 5 mg/kg increments. Maintenance infusion, 5 μg/kg/min, this may be increased to as high as 15 μg/kg/min
Oral: for children younger than 1 year, use body surface area to calculate dose. Loading dose, 10–15 mg/kg/day, or 600–800 mg/1.73 m^2/day in two divided doses for 4–14 days. Dosage is then decreased to 5 mg/kg/day or 200–400 mg/1.73 m^2/day for several weeks. Keep decreasing the dose to the lowest effective dosage possible, usually 1–2.5 mg/kg/day

Adults:

I.V.: for pulseless VT/VF, use 300 mg diluted in 20–30 mL of 5 % dextrose in water (D5W) or NS administered rapid I.V. push. Supplemental bolus doses of 150 mg by rapid I.V. infusion for recurrent pulseless VT/VF may be used. Maximum total dose, 2.2 g/24 h

Perfusing tachycardias: loading dose, 1,000 mg over 24 h as follows: 150 mg administered over 10 min (15 mg/min), followed by 360 mg over 6 h (at a rate of 1 mg/min), and followed with a maintenance dose of 540 mg over 18 h (0.5 mg/min). After the first 24 h, the maintenance dose is continued at 0.5 mg/min. Additional supplemental boluses of 150 mg over 10–20 min may be administered for break-through arrhythmia. Maximum daily dose, 2 g

Oral: 800–1,600 mg/day in one to two doses for 1–3 weeks, then 600–800 mg/day in one to two doses for 1 month, gradually lower to 100–200 mg/day

Pharmacokinetics: Amiodarone is metabolized in the liver. The half-life in adults after an oral dose is 40 to 55 days, and after a single I.V. dose is 20–47 days. The half-life is shorter in children. Amiodarone is excreted in the feces and urine. Amiodarone is not dialyzable.

Monitoring Parameters: ECG, blood pressure, chest x-ray, pulmonary function tests, thyroid function tests, serum glucose, serum triglyceride, liver enzymes, and ophthalmo-logical exams should be monitored.

Contraindications: Severe sinus node dysfunction and sec-ond- or third-degree AV block (without a pacemaker) are contraindications.

Precautions/Warnings: In the United States, amiodarone may not be considered as a first-line antiarrhythmic in some institutions because of its high incidence of toxicity. However, in other countries, the experience with amioda-rone is more extensive and it may be considered as a first-line agent to treat various types of tachyarrhythmias. Approximately 75 % of patients may experience adverse effects with large doses. Pulmonary and hepatic toxicities

may be fatal. Amiodarone may cause hypothyroidism or hyperthyroidism. It may be proarrhythmic. Hypotension with rapid I.V. administration has occurred. Patients should be hospitalized for initiation of therapy and loading dose administration. Some I.V. Amiodarone preparations contain benzyl alcohol, which has been associated with the potentially fatal "gasping" syndrome in neonates (metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction, hypotension, and cardiovascular collapse).

Drug-Drug Interactions: Amiodarone increases plasma concentrations of digoxin, cyclosporine, flecainide, lidocaine, methotrexate, theophylline, procainamide, quinidine, warfarin, and phenytoin. Dosing reduction and monitoring of serum levels are recommended (50 % dosage reduction for digoxin, 30 % reduction for flecainide, and 30–50 % dosage reduction for warfarin). Combined use with β-blockers, digoxin, or calcium channel blockers may result in bradycardia, sinus arrest, and heart block. Amiodarone use with Class I antiarrhythmics may cause ventricular arrhythmias. Amiodarone use with general anesthetics may result in hypotension, bradycardia, and heart block. Combined amiodarone use with lovastatin or simvastatin may result in an increased risk of myopathy or rhabdomyolysis. Amiodarone may inhibit the metabolism of dextromethorphan. St. John's wort may decrease the concentration of amiodarone and is not recommended for concurrent use.

Adverse Effects:

CV: proarrhythmia: torsades de pointes, bradycardia, heart block, sinus arrest, hypotension, heart failure, and myocardial depression. Hypotension may be potentially fatal with I.V. use; in adults, I.V. daily doses greater than 2,100 mg have been associated with greater risk of hypotension

Respiratory: interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary fibrosis, and acute respiratory distress syndrome. Use of lower doses may be associated with lower incidence of pulmonary toxicity

CNS: lack of coordination, fatigue, malaise, dizziness, headache, insomnia, nightmares, ataxia, behavioral changes, fever

Dermatological: skin discoloration, photosensitivity, rash, pruritus

Endocrine and metabolic: hypothyroidism or hyperthyroidism, hyperglycemia, elevated triglycerides, syndrome of inappropriate antidiuretic hormone secretion

GI: nausea, vomiting, anorexia, constipation

Hepatic: elevated liver enzymes, bilirubin, serum ammonia, and severe hepatic toxicity. Hepatocellular necrosis, hepatic coma, acute renal failure, and death have been associated with I.V. loading doses of higher concentration and faster rates of infusion than recommended

Neuromuscular and skeletal: paresthesias, tremor, muscle weakness, rhabdomyolysis

GU: sterile epididymitis

Hematological: coagulation abnormalities, thrombocytopenia, neutropenia, pancytopenia, aplastic anemia, hemolytic anemia

Ocular: corneal microdeposits, halos or blurred vision, photophobia, optic neuropathy, optic neuritis

Poisoning Information: Symptoms include sinus bradycardia and/or heart block, hypotension, and QT prolongation. ECG monitoring is necessary for several days. Bradycardia may be atropine resistant.

Compatible Diluents/Administration:

The maximum concentration for peripheral intravenous administration is 2 mg/mL; for central administration it is 6 mg/mL. Amiodarone is stable in polypropylene syringes at concentrations of 1 mg/mL and 2.5 mg/mL for up to 26 h at room temperature without protection from light

Do not administer the oral dose with grapefruit juice

9.6.2 Dronedarone

Indication: Dronedarone is used in adults with a history of atrial flutter or atrial fibrillation that has resolved to prevent recurrences [31]. It should not be used in permanent atrial fibrillation due to increased risk of morbidity and mortality [32].

Mechanism of Action: Dronedarone prolongs repolarization in atrial myocytes. It also inhibits adrenergic stimulation
Dosing: Dronedarone is administered orally
Infants/children: Not recommended
Adults: *Oral*: 800 mg/day divided in two doses

Dosing adjustment in renal impairment: None

Pharmacokinetics: Dronedarone is metabolized by the liver. The half life is 13–19 h and reaches its peak 3–6 h after taken. Its excretion is mostly in feces.

Monitoring Parameters: ECG, blood pressure, heart rate, development of peripheral edema, electrolytes (magnesium and potassium in particular), and liver enzymes should be monitored periodically.

Contraindications: NYHA, class IV heart failure, history of congestive heart failure with recent decompensation (NYHA classes II or III) complete or second degree AV block without a pacemaker, bradycardia <50 beats per minute, QRS duration >500 ms, PR interval >280 ms, permanent atrial fibrillation, and liver failure are all contraindications.

Precautions/Warnings: There is a black box warning against the use of dronedarone in patient with chronic atrial fibrillation and decompensated heart failure. Two large randomized, double-blinded, placebo-controlled trials demonstrated increased mortality in these adult patients taking dronedarone [32, 33]. Care should be exercised in administering this medication to patients with adult congenital heart disease and atrial fibrillation, as there is no published data available.

Drug-Drug Interactions:
Use with caution in conjunction with digoxin and calcium-blocking agents, as it can cause significant bradycardia and AV block. Avoid concomitant use of other QT prolonging drugs.

Adverse Effects
Cardiovascular (**CV**): Congestive heart failure, QT prolongation, AV block, and bradycardia

Central nervous system (**CNS**):

Dermatological: Pruritus, rash, photosensitivity

Gastrointestinal (**GI**): Abdominal pain, nausea, vomiting, diarrhea, dyspepsia, elevated liver enzymes, and fulminant liver failure

Hepatic: Elevated liver enzymes and fulminant liver failure requiring liver transplant

Respiratory: Interstitial lung disease, pneumonitis, and pulmonary fibrosis have been described

Poisoning Information: Bradycardia, heart block, torsades de pointe from QTc prolongation can occur.

Compatible Diluents/Administration: Do not administer with grapefruit juice. Absorption is increased when taken with a high fat meal.

9.6.3   Sotalol

Indication: Sotalol is used to treat both ventricular and atrial tacharrhythmias [34].

Mechanism of Action: Sotalol is a nonselective β-blocking agent with Class III effects at higher serum levels (prolongation of repolarization); sotalol decreases heart rate and AV nodal conduction. Sotalol increases AV nodal refractoriness. It prolongs atrial and ventricular action potentials, and prolongs the effective refractory period of atrial and ventricular muscle. Sotalol has more Class III effect with higher doses.

Dosing: Should be initiated in the hospital setting due to its potential proarrhythmic effect.

Infants/children:

Oral: For those at least 2 years old, 90 mg/m^2/day in three divided doses; dose may be incrementally increased to 180 mg/m^2/day divided in three doses. Dose should be gradually increased. For those younger than 2 years, dose should be reduced by an age-related factor. Because younger patients require more time to achieve the steady

state, a greater time interval between dose adjustments is
necessary

Adults:

Oral: 80 mg twice a day; dose should be increased gradually
to 240–320 mg/day. Allow 3 days between dosing incre-
ments. Usual range, 160–320 mg/day

Dosing in renal impairment (**adults**): impaired renal function
can increase half-life

For treatment of ventricular tachyarrhythmias:

Clcr greater than 60 mL/min: administer every 12 h

Clcr 30–60 mL/min: administer every 24 h

Clcr 10–30 mL/min: administer every 36–48 h

Clcr less than 10 mL/min: individualize dose

For treatment of atrial arrhythmias:

Clcr greater than 60 mL/min: administer every 12 h

Clcr 40–60 mL/min: administer every 24 h

Clcr less than 40 mL/min: use is contraindicated (Fig. 9.3)
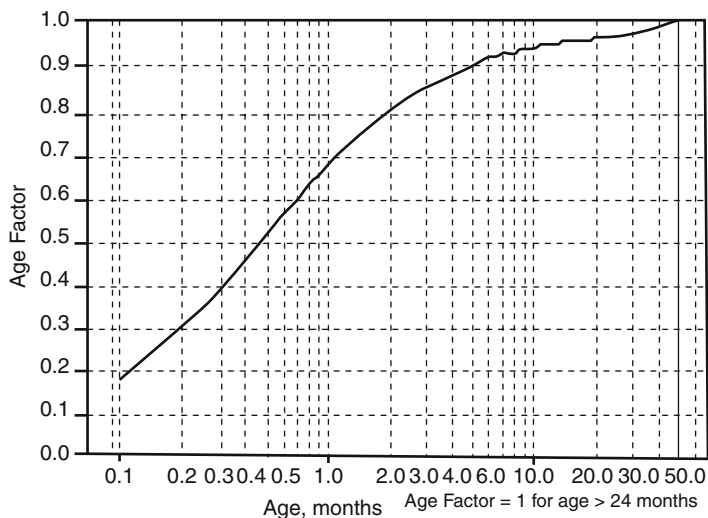
FIG. 9.3 Age factor versus age in months for sotalol dosing in chil-
dren younger than 2 years of age

Pharmacokinetics: Sotalol is not metabolized. The half-life in neonates is 8.4 h; in infants/children younger than 2 years old, it is 7.4 h; in children between 2 to 7 years old, it is 9.1 h; in children 7–12 years old, it is 9.2 h; and in adults, it is 12 h. The time to peak concentration in children is 2–3 h and, in adults, it is 2–4 h. Sotalol is excreted in the urine.

Monitoring Parameters: Serum magnesium, potassium, ECG, and renal function tests should be monitored.

Contraindications: Sinus bradycardia, second- or third-degree heart block (without a pacemaker), congenital or acquired long QT syndrome, uncontrolled CHF, asthma, baseline QTc greater than 450 milliseconds, or significantly reduced renal function.

Precautions/Warnings: Initiation of sotalol in a hospital setting with continuous monitoring is required. Dosing should be adjusted gradually, and QT interval monitored. Administer cautiously in heart failure. Use caution when administering with β-blockers or calcium channel blockers. Use sotalol with caution in patients with diabetes mellitus.

Drug-Drug Interactions: Do not use sotalol with drugs that prolong the QT interval (Class I and II antiarrhythmics, phenothiazine, tricyclic antidepressants), because these increase cardiovascular effects. Class I and II antiarrhythmics should be held for at least three half-lives before initiating sotalol use. Concomitant use of magnesium- and aluminum-containing antacids will decrease absorption of sotalol (administer antacids 2 h after sotalol).

Adverse Effects:
CV: proarrhythmia, bradycardia, chest pain, palpitations, CHF, QT prolongation, torsades de pointes, hypotension, syncope [35]
CNS: fatigue, dizziness lightheadedness, confusion, insomnia, depression, mood change, anxiety, headache
Dermatological: rash
GI: diarrhea, nausea, vomiting

Endocrine and metabolic: sexual dysfunction, hyperglycemia in diabetic patients
Hematological: bleeding
Neuromuscular: weakness, paresthesias
Ocular: visual problems
Respiratory: dyspnea, asthma
Miscellaneous: cool extremities, sweating

Poisoning Information: Symptoms of sotalol poisoning include cardiac arrhythmias, CNS toxicity, bronchospasm, hypoglycemia, and hyperkalemia. Most common cardiac symptoms include hypotension and bradycardia. CNS effects include convulsions, coma, and respiratory arrest. Treatment is symptomatic.

9.6.4   Dofetilide

Indication: Dofetilide is indicated for the treatment of atrial fibrillation/flutter [36] and ventricular tachycardia [37] in adults.
Mechanism of Action: As a class III agent, dofetalide prolongs repolarization by blocking the delayed rectifier potassium channels.

Dosing:
Infants/children: No safe dosing has been established in children
Adults:
Oral: Initial dosing is 500 mcg twice daily. Dose should be adjusted based on QTc interval and creatinine clearance. An ECG needs to be checked prior to the second dose. If the QTc increases by >15 %, then the dose should be decreased to 250 mcg twice daily. If the QTc becomes greater than 500 ms, the medication should be discontinued.
Dosing adjustment in renal impairment: For creatinine clearance between 40–60 ml/min, the dose should be 250 mcg twice daily and 125 mcg twice daily between 20–40 ml/min.

Pharmacokinetics: The oral bioavailability is 90 %. Maximum serum levels are seen in 2–3 h. The half life is 10 h. It is predominantly excreted in the urine (>80 %).

Monitoring Parameters: The risk of ventricular arrhythmias is dose dependent. Creatinine clearance should be calculated and renal function monitored. ECGs should be obtained every 12 h and the QTc calculated.

Contraindications: Do not administer dofetalide if the QTc >440 ms. It should not be administered concurrently with verapamil, trimethoprim, cimetidine, ketaconazole, or hydrochlorothiazide. Patients with Long QT Syndrome should not be given dofetalide.

Precautions/*Warnings*: Dofetalide should be initiated as an inpatient for at least 3 days to monitor for QT prolongation.

Drug-Drug Interactions: Avoid potassium sparring diuretics. Do not administer with class I or class III antiarrhythmics. Avoid drugs that activate the CYP3A4 system.

Adverse Effects
Cardiovascular (**CV**): Ventricular tachycardia/torsades de pointe, AV block, and bradycardia
Central nervous system (**CNS**): Headaches, dizziness
Dermatological: Rash
Gastrointestinal (**GI**): Nausea, vomiting, diarrhea, abdominal pain, bradycardia, MI,
Respiratory: Shortness of breath, respiratory tract infections

Poisoning Information: Treatment for overdose is supportive and the QT should be monitored in a hospital setting.

9.6.5   Ibutilide

Indication: Ibutilide is used in adult patients for termination of atrial fibrillation and flutter [38].

Mechanism of Action: The mechanism of action of ibutilide is prolongation of action potential by an unknown mechanism. Ibutilide causes prolonged refractoriness in both atrial and ventricular myocardium.

Dosing:

Infants/children: No dosing recommendations available

Adults: *I.V.*: for patients less than 60 kg, 0.01 mg/kg over 10 min. For those greater than 60 kg, 1 mg over 10 min. If no results at end of first infusion, may repeat dose.

Pharmacokinetics: Ibutilide has an extensive hepatic metabolism with a half-life of 6 h. Ibutilide is eliminated in the urine and feces.

Monitoring Parameters: Continuous ECG monitoring should occur for at least 4 h after infusion or until QTc has returned to baseline. Skilled personnel and proper equipment should be available during ibutilide administration and subsequent monitoring.

Contraindications: Ibutilide is contraindicated if the QTc is greater than 440 ms.

Precautions/Warnings: Potentially fatal arrhythmias can occur with ibutilide administration, usually torsades de pointes. No dosing adjustment is necessary in patients with renal or hepatic dysfunction. Correct hyperkalemia and hypomagnesemia before use. Monitor for heart block.

Drug-Drug Interactions: Ibutilide should not be administered with other Class III antiarrhythmics or Class IA antiarrhythmics secondary to a potential to prolong refractoriness.

Avoid other drugs that prolong the QTc (tricyclic antidepressants, phenothiazines, and erythromycin).

Adverse Effects:

CV: Torsade de pointes, non-sustained VT, hypotension, AV block, bradycardia, hypertension, and palpitations, CHF, syncope

CNS: headache

GI: nausea
RENAL: Renal failure

Poisoning Information: Symptoms of ibutilide poisoning include CNS depression, gasping breath, convulsions, and arrhythmias. Treatment is supportive.

Compatible Diluents/Administration: Ibutilide may be administered undiluted or diluted in 50 mL of diluent (0.9 % NS or D5W). Infuse over 10 min.

9.7   Class IV Antiarrhytmics: Calcium Channel Blockers

9.7.1   Verapamil

Indication: Verapamil is used to treat atrial and AV nodal dependent tachyarrhythmias (SVT, atrial fibrillation, and atrial flutter).

Mechanism of Action: Verapamil blocks calcium channels in vascular smooth muscle and myocardium during depolarization. Verapamil has the greatest influence on cells in the SA and AV nodes. Calcium channel blockade becomes more apparent at faster rates. Verapamil is effective in depressing enhanced automaticity.

Dosing:
Infants/children:
Verapamil is not recommended for those younger than 1 year of age. Administer verapamil with continuous ECG monitoring and I.V. calcium at bedside
I.V.: 0.1–0.2 mg/kg per dose. May repeat in 30 min if no response. For children older than 1 year, 0.1–0.3 mg/kg/dose, maximum dose of 5 mg. May repeat in 30 min, if necessary
Oral: 4–8 mg/kg/day divided every 8 h

Adults:
I.V.: 5–10 mg per dose. May repeat with 10 mg 15–30 min later, if necessary

Oral: 240–480 mg/24 h divided every 8 h. For sustained release, dose every 12 h, and, for extended release, dose every 24 h

Dosing adjustment in renal impairment: children and adults, Clcr less than 10 mL/min, administer 50–75 % of normal dose

Pharmacokinetics: Peak effect is seen in 1–2 h for the oral, immediate release form and within minutes of the intravenous form. The duration is 6–8 h for the oral form and 10–20 min of the I.V. form. It is metabolized in the liver. Its half-life is 4–7 h in infants/children and 4–12 h in adults. It is eliminated in the urine.

Monitoring Parameters: ECG and blood pressure should be monitored. Follow hepatic enzymes with long-term use.

Contraindications: Sinus bradycardia, heart block, VT, severe left ventricular dysfunction, hypotension, and WPW are contraindications.

Precautions/*Warnings*: Avoid I.V. use in neonates and young infants because of the risk of cardiovascular collapse [39]. Have I.V. calcium chloride 10 mg/kg available at the beside to treat hypotension. Use verapamil with caution in patients with severe left ventricle dysfunction, sick sinus syndrome, hepatic or renal impairment, and hypertrophic cardiomyopathy. Verapamil administration may worsen myasthenia gravis and may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy.

Drug-Drug Interactions: Verapamil has increased CV effects with β-blocking agents, digoxin, quinidine, and disopyramide. Verapamil may increase serum concentrations of digoxin, quinidine cyclosporine, and carbamazepine. Phenobarbital and rifampin may decrease verapamil serum concentrations. Erythromycin may increase verapamil serum concentration. Concomitant aspirin use may prolong bleeding times. Verapamil may prolong recovery from vecuronium.

Adverse Effects:

CV: severe hypotension resulting in asystole and cardiovascular collapse has been reported in infants with I.V. use. Verapamil may also cause bradycardia, heart block, and worsening of CHF

CNS: dizziness, fatigue, seizures, headache

GI: gingival hyperplasia, constipation, nausea

Hepatic: increase in hepatic enzymes

Respiratory: may precipitate insufficiency of respiratory muscle function in Duchenne's muscular dystrophy

Poisoning Information: Symptoms of verapamil poisoning include hypotension and bradycardia. Intraventricular conduction is usually not affected. Confusion, stupor, nausea, vomiting, metabolic acidosis, and hyperglycemia may also be observed. Impaired cardiac contractility should be treated with calcium. Glucagon and epinephrine may be used to treat hypotension.

Compatible Diluents/Administration: For I.V. push, dilute with D5W to a maximum concentration of 2.5 mg/mL and administer over 2–4 min, depending on blood pressure.

For I.V. continuous infusion, use a concentration of 0.4 mg/mL.

9.7.2   Diltiazem

Indication: Diltiazem is used to increase the degree of AV nodal block in atrial fibrillation and flutter and to terminate or prevent AV nodal dependent paroxysmal SVT [35].

Mechanism of Action: Diltiazem blocks inward calcium channels, with effects on the SA and AV nodes [40].

Dosing:

Infants/children: Diltiazem should be avoided in neonates.

I.V.: bolus, 0.15–0.45 mg/kg. Continuous infusion, 2 mg/kg/min (0.125 mg/kg/h)

Oral: 1.5–2 mg/kg/day divided into three to four doses; maximum, 3.5 mg/kg/day

Adults:

I.V.: initial bolus, 0.35 mg/kg over 2 min (average dose, 20 mg); repeat bolus after 15 min of 0.35 mg/kg (average dose, 25 mg). Continuous infusion, initiate infusion of 10 mg/h and increase by 5–15 mg/h. When increasing the infusion dose, administer for less than 24 h at a rate of less than 15 mg/h

Conversion from I.V. to oral dosing: start oral 3 h after bolus dose. The oral dose (mg/day) is equal to $[(\text{I.V. rate in mg/h} \times 3) + 3] \times 10$

Oral dose: Extended release: 180–240 mg every day, to 180–420 mg/day

Sustained release: 60–120 mg every 12 h, up to 240–360 mg/day

Pharmacokinetics: Diltiazem has an extensive first-pass effect. Diltiazem is metabolized in the liver. Diltiazem has a half-life of 3–4.5 h. It is not dialyzable.

Monitoring Parameters: Liver function tests, blood pressure, and ECG should be monitored.

Contraindications: Severe hypotension, second- or third-degree heart block or sinus node dysfunction, and acute myocardial infarction with pulmonary congestion are contraindications.

Precautions/Warnings: Use of diltiazem with β-blockers or digoxin can result in conduction abnormalities. Use diltiazem with caution in left ventricular dysfunction and with hepatic and renal dysfunction.

Drug-Drug Interactions: Cimetidine use may increase diltiazem serum concentrations.

The risk of bradycardia or heart block is increased with β-blocker or digoxin use. Diltiazem may decrease metabolism of cyclosporine, carbamazepine, digoxin, lovastatin, midazolam, and quinidine. Diltiazem use may increase the effect of digoxin and fentanyl. Rifampin may decrease

diltiazem serum concentration. Cardiac effects of anesthetics may be potentiated by diltiazem.

Adverse Effects:
CV: arrhythmia, bradycardia, hypotension, AV block, tachycardia, flushing, and peripheral edema
CNS: dizziness, headache
Dermatological: rash
GI: nausea, constipation, dyspepsia
Hepatic: elevations in liver function tests

Poisoning Information: Symptoms include hypotension (secondary to peripheral vasodilation, myocardial depression, and bradycardia) and bradycardia (secondary to sinus bradycardia, sinus arrest, or second- or third-degree heart block). Usually the QRS duration is normal. Non-cardiac symptoms include confusion, stupor, nausea, vomiting, metabolic acidosis, and hyperglycemia. Calcium may reverse depressed cardiac contractility. Glucagon and epinephrine may treat hypotension and heart rate.

Compatible Diluents/Administration: The final concentration for infusion of diltiazem should be 1 mg/mL.

9.8   Miscellaneous Drugs

9.8.1   Adenosine

Indication: Adenosine is indicated for termination of paroxysmal SVT (specifically AV nodal or AV reentrant tachycardia). Adenosine is useful for diagnosing atrial flutter [41].

Mechanism of Action: Adenosine is an endogenous purinergic agent. Adenosine blocks conduction through the AV node by increasing potassium channel conductance and depressing slow inward calcium current. Adenosine also causes peripheral vasodilation.

Dosing
Infants/children:
I.V.: 0.05–0.1 mg/kg per dose. If not effective, increase dose by 0.1 mg/kg increments to maximum dose of 0.4 mg/kg. Max dose is 12 mg. Adenosine must be administered by rapid IV push

Adults:
I.V.: initial dose of 6 mg. If not effective, may double to 12 mg. Adenosine must be administered by rapid IV push

Pharmacokinetics: Adenosine is metabolized by erythrocytes (cellular uptake) with a half-life of less than 10 s.

Monitoring Parameters: Continuous ECG, blood pressure, and respiratory rate should be monitored.

Contraindications: Second- or third-degree heart block or sinus node dysfunction, unless a pacemaker is in place.

Precautions/Warnings: Bronchospasm may occur with adenosine use in asthmatics. Use adenosine with caution in patients with underling SA or AV nodal dysfunction or obstructive lung disease. The initial dose of adenosine should be decreased in patients receiving dipyridamole. Adenosine should be used with caution in heart transplant patients and if utilized at all the initial dose should be halved [42].

Drug-Drug Interactions: Dipyridamole potentiates the effect of adenosine. Theophylline and caffeine antagonize the effect of adenosine. Carbamazepine increases heart block.

Adverse Effects:
CV: flushing, arrhythmias (including atrial fibrillation, bradycardia and heart block), hypotension
CNS: lightheadedness, headache, apprehension, blurred vision
GI: nausea
Respiratory: dyspnea, bronchospasm

Poisoning Information: Adverse events are self-limited because of the short half-life of adenosine, although bronchospasm will last longer than the half-life

Compatible Diluents/Administration: Adenosine should be administered by rapid I.V. push followed immediately by a NS bolus.

9.8.2   Atropine

Indications: Atropine is used to treat bradycardia or asystole [43].

Mechanism of Action: Atropine is an anticholinergic and antispasmodic. Atropine blocks acetylcholine receptors at parasympathetic sites in smooth muscle, secretory glands, and the CNS. It increases cardiac output and antagonizes histamine and serotonin.

Dosing:
Infants/children:
I.V., *I.O.*: 0.02 mg/kg per dose, with a minimum dose of 0.1 mg. Maximum single dose, 0.5 mg in children and 1 mg in adolescents. May repeat in 5 min. Total dose of 1 mg for children and 2 mg for adolescents

Tracheal tube: 0.02 mg/kg per dose, with a minimum dose of 0.1 mg. Maximum single dose of 0.5 mg in children and 1 mg in adolescents. May repeat in 5 min. Total dose of 1 mg for children and 2 mg for adolescents. Atropine must be diluted if administered via tracheal tube; mix with NS to a total volume of 3–5 mL

Adults:
I.V.: 1 mg per dose. May repeat in 3–5 min. Total dose, 0.04 mg/kg

Tracheal tube: 2–2.5 times the usual I.V. dose. Dilute in 10 mL of NS

Pharmacokinetics: Atropine has complete absorption with a wide distribution. Atropine is metabolized in the liver. Atropine has a half-life in children younger than 2 years of 7 h; in children older than 2 years, of 2.5 h; and in adults, of 3 h. Atropine is eliminated in the urine.

Monitoring Parameters: ECG, blood pressure, and mental status should be monitored.

Contraindications: Glaucoma, thyrotoxicosis, obstructive disease of the GI or GU tract, and asthma are contraindications.

Precautions/Warnings: Psychosis can occur with atropine use in sensitive individuals. Use atropine with caution in hyperthyroidism, CHF, tachyarrhythmias, and hypertension. Use with caution in children with spastic paralysis.

Drug-Drug Interactions: Atropine has additive effects when administered with other anticholinergic drugs. Atropine may interfere with β-blockers.

Adverse Effects:
CV: arrhythmias, tachycardia, flushing
CNS: fatigue, delirium, restlessness, tremor, headache, ataxia
Dermatological: dry, hot skin, dry mucous membranes
Ocular: blurred vision, photophobia, dry eyes
GI: impaired GI motility, abdominal distension
GU: urinary retention, impotence

Poisoning Information: Indications of atropine poisoning are dilated and unreactive pupils, blurred vision, dry, hot skin and dry mucous membranes, difficulty swallowing, decreased bowel sounds, urinary retention, tachycardia, hyperthermia, and hypertension. For atropine overdose with severe life-threatening symptoms, physostigmine (0.02 mg/kg; adult dose, 1–2 mg) subcutaneously or slow I.V. may reverse effects.

Compatible Diluents/Administration: Atropine is administered undiluted by I.V. push over 1–2 min.

9.8.3   Magnesium Sulfate

Indications: Magnesium sulfate is used to treat torsades de pointes in acquired or congenital long QT syndrome [44] and to treat and prevent ventricular tachyarrhythmias, particularly in the postoperative course of cardiac disease.

Mechanism of Action: Magnesium sulfate suppresses early after-depolarizations that can trigger torsades de pointes.

Dosing:
Infants/children:
I.V.: 25–50 mg/kg per dose, not to exceed 2 g/dose. Infusion rate, 0.5–1 mg/kg/h
Adults:
I.V.: 2 g bolus over 10–20 min. bolus may be administered within 5–15 min. Infusion rate, 0.5 g/h

Dosing in renal impairment: patients with severe renal failure should not receive magnesium

Pharmacokinetics: Magnesium sulfate has an immediate onset of action when administered I.V. The duration of action is 30 min.

Monitoring Parameters: Blood pressure and ECG should be monitored.

Contraindications: Heart block, serious renal impairment, and coma are contraindications.

Precautions/Warnings: Use magnesium sulfate with caution in patients with renal dysfunction and those receiving digoxin. Monitor serum magnesium levels. Use extreme caution in patients with myasthenia gravis.

Drug-Drug Interactions: Aminoglycosides can potentiate neuromuscular blockade. CNS depressants will increase central depressant effects. Use magnesium sulfate with caution with neuromuscular blocking agents.

Adverse Effects:
CV: hypotension and asystole with rapid administration, flushing, complete heart block
CNS: somnolence, CNS depression
GI: diarrhea
Neuromuscular: decreased neuromuscular transmission and deep tendon reflexes
Respiratory: respiratory depression

Poisoning Information: Symptoms of magnesium sulfate poisoning usually occur with serum magnesium levels greater than 4 mEq/L. See Adverse Effects. Levels greater than 12 mEq/L may be fatal. Intravenous calcium can reverse respiratory depression or heart block.

Compatible Diluents/Administration: Magnesium sulfate is incompatible when mixed with fat emulsions, calcium gluceptate, clindamycin, dobutamine, hydrocortisone, polymyxin B, procaine hydrochloride, nafcillin, tetracyclines, and thiopental.

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Chapter 10
Immunosuppressive Agents in Pediatric Heart Transplantation

Kelli L. Crowley and Steven Webber

Abstract All pediatric heart transplantation programs currently use a calcineurin inhibitor (CNI), either cyclosporine or tacrolimus, as a primary immunosuppressant. Although these drugs have much toxicity, there is insufficient data to show that CNI-free immunosuppression is safe or feasible from the time of transplantation. Most centers also use an additional adjunctive agent, either in the form of an antimetabolite (most commonly mycophenolate mofetil) or less commonly an mTOR (target of rapamycin) inhibitor. The addition of these agents may reduce early acute rejection events, allow for lower CNI target levels and may improve long-term graft and patient outcomes. The most controversial issue is whether corticosteroids should be routinely added to form "triple therapy". Many pediatric transplant centers have successfully used complete steroid avoidance or early

K.L. Crowley, PharmD (✉)
Department of Pharmacy Services, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics,
University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA
e-mail: kelli.crowley@chp.edu

S. Webber, MBChB, MRCP
Department of Pediatrics,
Vanderbilt University School of Medicine, Nashville, TN, USA
e-mail: steve.a.webber@vanderbilt.edu

steroid withdrawal. Finally, there is no agreement on whether intravenous antibody induction therapy should be routinely employed although use has increased significantly in recent years. If used, there is also no agreement as to whether it should be in the form of a polyclonal T cell-depleting antibody (e.g. thymoglobulin) or an interleukin-2 receptor (IL2R) antagonist (e.g. basiliximab).

10.1   Introduction

All pediatric heart transplantation programs currently use a calcineurin inhibitor (CNI), either cyclosporine or tacrolimus, as a primary immunosuppressant. Although these drugs have much toxicity, there is insufficient data to show that CNI-free immunosuppression is safe or feasible from the time of transplantation. Most centers also use an additional adjunctive agent, either in the form of an antimetabolite (most commonly mycophenolate mofetil) or less commonly an mTOR (target of rapamycin) inhibitor. The addition of these agents may reduce early acute rejection events, allow for lower CNI target levels and may improve long-term graft and patient outcomes. The most controversial issue is whether corticosteroids should be routinely added to form "triple therapy". Many pediatric transplant centers have successfully used complete steroid avoidance or early steroid withdrawal. Finally, there is no agreement on whether intravenous antibody induction therapy should be routinely employed although use has increased significantly in recent years [1]. If used, there is also no agreement as to whether it should be in the form of a polyclonal T cell-depleting antibody (e.g. thymoglobulin) or an interleukin-2 receptor (IL2R) antagonist (e.g. basiliximab). A summary of the options for induction and maintenance therapy is shown in Table 10.1. It should be noted that there have been no large-scale randomized controlled trials of any form of immunosuppressive therapy in pediatric thoracic transplantation.

TABLE 10.1 Potential combinations of immunosuppressive drugs used in pediatric thoracic transplantation.

Number of agents	Potential combinations	Comments
Monotherapy	Tacrolimus or cyclosporine	Monotherapy rarely used with cyclosporine. Monotherapy not used in lung transplantation.
Dual therapy	Tacrolimus or cyclosporine *with* Azathioprine or mycophenolate mofetil or sirolimus or corticosteroids	Little experience with the mTOR (target of rapamycin) inhibitors sirolimus and everolimus in children. Steroid avoidance increasingly common in pediatric heart transplantation.
Triple therapy	Tacrolimus or cyclosporine *with* Corticosteroids *with* Azathioprine or mycophenolate mofetil or sirolimus	In triple therapy regimens, mycophenolate mofetil is being used with increasing frequency in lieu of azathioprine.

Notes: All the above oral maintenance regimens may be used with or without induction therapy with T cell depleting monoclonal or polyclonal antibody preparations or with the newer interleukin-2 receptor antagonists

10.2   Corticosteroids (Methylprednisolone, Prednisone)

10.2.1   Indication

Broad immunosuppressive and anti-inflammatory effects. Many pediatric heart transplant centers are using steroid avoidance regimens or early steroid withdrawal to avoid the many side effects and complications associated with long-term

use in children. High-dose steroids remain the standard therapy for treatment of acute rejection episodes.

10.2.2   Mechanism of Action

Decrease inflammation through the suppression of the migration of polymorphonuclear leukocytes and the reversal of increased capillary permeability. Corticosteroids prevent immune activation by inhibiting antigen presentation, cytokine production and proliferation of lymphocytes [2]. High dose therapy can cause lympholysis.

10.2.3   Dosing

Acute rejection treatment: High-dose intravenous (I.V.) methylprednisolone is the standard for most episodes of acute rejection; typical dosing 10 mg/kg (maximum 1,000 mg/dose) once daily for three days. Some centers use moderate dose oral (P.O.) steroids for less severe episodes of acute rejection (e.g. 2 mg/kg/day for 5 days sometimes followed by a steroid taper).

Maintenance therapy: Those centers that use long-term maintenance therapy typically use prednisone in doses of 0.5–1 mg/kg/day (maximum 40 mg) P.O. in single daily dosing for the first two weeks post-transplantation with subsequent weaning to long-term maintenance doses of 0.05–0.15 mg/kg/day. Some centers continue low dose prednisone indefinitely, while others wean to discontinuation in the first few months if rejection history is benign. Increasing evidence suggests that complete steroid avoidance beyond the intraoperative period is possible in most children.

10.2.4   Pharmacokinetics

Peak and duration are dependent on the route of administration of the drug. Oral: peak effect occurs within 1-2 h and duration is 30–36 h; I.V: peak plasma time is 30 min with effect evident within 1 h and variable duration. Metabolized

in liver to inactive glucuronide and sulfate metabolites. Elimination is via the kidneys [3].

10.2.5   Precautions/Warning

Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use or with stress.

10.2.6   Monitoring Parameters

Blood pressure, weight, height, serum electrolytes, glucose and for signs of infection [3].

10.2.7   Drug-Drug Interactions

Fosphenytoin/phenytoin, phenobarbital, and rifampin increase clearance of corticosteroids.

Azole antifungal agents, calcium channel blockers, cyclosporine may decrease the metabolism of corticosteroids.

Corticosteroids may enhance the adverse/toxic effect of non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates specifically gastrointestinal ulceration and bleeding.

Corticosteroids may enhance the anticoagulant effect of warfarin.

Potassium-depleting diuretics (loop diuretics and thiazides) and amphotericin B enhance potassium depletion.

Circulating glucose levels may be increased by corticosteroids. Permanent diabetes mellitus may be precipitated when used in combination with cyclosporine or tacrolimus.

Tacrolimus levels may be increased by I.V. bolus doses of methylprednisolone.

10.2.8   Adverse Effects [4]

CV: Edema, hypertension
CNS: Seizures, psychoses and pseudotumor cerebri

Dermatologic: Acne, skin atrophy, impaired wound healing and hirsutism

Hematologic: Transient leukocytosis

Endocrine and Metabolic: Cushing's syndrome, pituitary-adrenal axis suppression, growth suppression, glucose intolerance, hypokalemia, alkalosis, weight gain, hyperlipidemia and sodium and water retention

Ocular: Cataracts, glaucoma

GI: Peptic ulcer, vomiting

Neuromuscular and Skeletal: Muscle weakness, osteoporosis and fractures

10.3   Calcineurin Inhibitors (Tacrolimus; Cyclosporine)

Tacrolimus is being used as the cornerstone of maintenance therapy in lieu of cyclosporine in more and more centers but these agents have not been compared in large randomized trials in children after transplantation of thoracic organs [1]. One small, single-center (26 children) randomized trial in pediatric heart transplantation has been done but was not powered to identify differences between immunosuppressive regimens [5]. Tacrolimus appears to be somewhat more potent in preventing acute rejection than cyclosporine. A three-arm randomized trial of tacrolimus versus cyclosporine (along with corticosteroids and either sirolimus or mycophenolate mofetil as adjunctive therapy) in adult heart transplantation showed lower acute rejection rates in patients treated with tacrolimus [6]. To date, there is no definitive evidence that either tacrolimus or cyclosporine is associated with less chronic rejection, less graft loss, or improved survival in pediatric thoracic transplantation. Renal toxicity appears comparable between tacrolimus and cyclosporine in pediatric heart transplantation [7]. Late renal dysfunction is common after pediatric heart transplantation, with the black race at an increased risk. Decreased renal function at 1 year post-transplant, but not at time of transplant, is a predictor of the onset of late renal dysfunction [8].

10.3.1 Tacrolimus

Indication
Used as primary immunosuppressant after all forms of solid
   organ transplantation in children.

Mechanism of Action
A macrolide antibiotic produced from *Streptomyces tsuku-
   baensis*. Tacrolimus inhibits T-cell activation by inhibiting
   calcineurin. Binds to an intracellular protein, FKBP-12, an
   immunophilin structurally related to cyclophilin, and a
   complex forms which inhibits phosphatase activity and
   prevents dephosphorylation and nuclear translocation of
   NFAT, inhibiting T-cell activation [3].

Dosing
Children: Initial: Oral: starting dose is typically 0.05–0.1 mg/
   kg/day in divided does every 12 h. I.V. continuous infusion:
   0.02–0.05 mg/kg/day may be used until oral intake toler-
   ated [9]. (However, now rarely used I.V. and may lead to
   decreased urine output following cardiopulmonary bypass.
   When renal function is impaired, induction therapy with T
   cell-depleting antibodies is generally used with delayed
   introduction of tacrolimus P.O.); the first dose of oral
   therapy should be given 8–12 h after discontinuing the I.V.
   infusion; reduce the dose by approximately two-thirds if
   concurrent voriconazole or posaconazole; reduce the dose
   by 40–60 % if fluconazole used concomitantly [3].
Adults: Initial: Oral: 0.075 mg/kg/day divided every 12 h. I.V.
   continuous infusion (rarely used): 0.01 mg/kg/day; the first
   dose of oral therapy should be given 8–12 h after discon-
   tinuing the I.V. infusion [10].

Pharmacokinetics
Oral bioavailability ranges from 5–67 % with an average of
   30 %. Administration with meals reduces absorption by an
   average of 33 %. Metabolized in the liver by the CYP450
   system (CYP3A) to multiple metabolites. Plasma protein
   binding ranges from 75–99 %. Average half-life of 8.7 h,
   ranging from 4–40 h. Pediatric patients clear the drug
   twice as rapidly as adults and require higher doses on a

mg/kg basis to achieve similar blood concentrations. Primarily eliminated in bile with <1 % excreted as unchanged drug in urine [3].

Monitoring Parameters

Trough blood tacrolimus concentrations; liver enzymes, blood urea nitrogen (BUN), serum creatinine (SCr), glucose, potassium, magnesium, phosphorus, complete blood count (CBC) with differential; blood pressure; neurologic status; electrocardiogram (EKG)

Reference Range: Trough (whole blood ELISA): 5–15 ng/mL. Typical levels 10–12 ng/ml in first few weeks post-transplant, 7–10 ng/ml for remainder of first year, and 5–7 ng/ml late after transplantation. Patient specific adjustments to be based on rejection history.

Drug-Drug Interactions [3, 10]

Tacrolimus is metabolized via the CYP3A and CYP2C9 isozyme pathways and has drug interactions with medications that are substrates, inducers or inhibitors of these pathways (see Table 10.2). Additional interactions are listed below.

Tacrolimus should not be used in combination with cyclosporine.

Serum concentrations of tacrolimus may be decreased by sirolimus.

QTc-prolonging effect of tacrolimus may be enhanced by ciprofloxacin.

Tacrolimus may increase the serum concentration of fosphenytoin/phenytoin (CYP2C9).

Potassium-sparing diuretics and angiotensin-converting enzyme (ACE) inhibitors may enhance the hyperkalemic effect of tacrolimus.

Adverse Effects

Common: Neurotoxicity (tremor, headache, paresthesias). nephrotoxicity and hyperglycemia (glucose intolerance especially when used with corticosteroids) [3]

GI: Diarrhea, vomiting and dyspepsia

CV: Hypertension, QT interval prolongation

TABLE 10.2 Cyclosporine and tacrolimus CYP3A4/2C9 isozyme drug-drug interactions

	CYP3A4 inducers	CYP2C9 inducers	CYP3A4 inhibitors/substrates	CYP2C9 inhibitors/substrates
Increased cyclosporine levels			CCBs	
			Azole antifungals	
			Proton pump inhibitors	
			Sulfonamide derivatives	
			Metoclopramide	
			Methylprednisolone/ prednisolone	
			NSAIDs	
Decreased cyclosporine levels	Carbamazepine	Barbiturates		Fosphenytoin/phenytoin
	Barbiturates	Rifampin		
	St. John's Wort			
	Rifampin			
	Fosphenytoin/ phenytoin			

TABLE 10.2 (continued)

	CYP3A4 inducers	CYP2C9 inducers	CYP3A4 inhibitors/substrates	CYP2C9 inhibitors/substrates
Increased tacrolimus levels			CCBs	Serotonin reuptake inhibitors/antagonists
			Azole antifungals	Metronidazole
			Proton pump inhibitors	Azole antifungals
			Macrolide antibiotics	
			Metoclopramide	
			Methylprednisolone/ prednisolone	
				Fosphenytoin/phenytoin
Decreased tacrolimus levels	Rifampin	Rifampin		
	Caspofungin			
	Carbamazepine			
	Barbiturates			
	Fosphenytoin/ phenytoin			
	St. John's Wort			

Abbreviation: *CCB* calcium channel blocker

Endocrine and Metabolic: Hyperkalemia, hypomagnesemia, glucose intolerance and diabetes mellitus

Dermatologic: Pruritus, rash and alopecia

Renal: Elevated SCr/BUN, acute and chronic nephrotoxicity

CNS: Headache, agitation, seizures, insomnia, hyperesthesia and dysarthria

Miscellaneous: Opportunistic infections, post-transplant lymphoproliferative disorders

*Poisoning Information*Symptoms of tacrolimus overdose are extensions of immunosuppressive activity and adverse effects. Symptomatic and supportive treatment is required. Parenteral benzodiazepines may be used if seizures occur. Not removed by hemodialysis. Addition of rifampin or rifamycin derivatives may be considered for the purpose of increasing metabolism and accelerating clearance of tacrolimus (through induction of CYP3A enzymes).

Compatible Diluent/Administration

Stable for 24 h when mixed in D_5W or NS in glass, polyolefin containers or plastic syringes; do not store in polyvinyl chloride (PVC) containers; polyvinyl-containing administration sets adsorb drug and may lead to a lower dose being delivered to the patient; do not refrigerate oral suspension [3].

10.3.2   Cyclosporine

Indication

Cyclosporine is used in conjunction with other immunosuppressive agents to prevent organ rejection after all forms of solid organ transplantation.

Mechanism of Action

Cyclosporine is a neutral cyclic polypeptide consisting of 11 amino acids. It is the major metabolic product of the fungus *Tolypocladium inflatum*.

Cyclosporine is a potent immunosuppressant which interferes with interleukin-2 gene transcription that is essential

for activation and proliferation of T lymphocytes. Cyclosporine crosses the T cell membrane and binds to cyclophilin. In the presence of intracellular calcium and calmodulin, the cyclosporine-cylophilin complex binds to an active site on calcineurin. This binding to calcineurin makes calcineurin unable to dephosphorylate nuclear factor of activated T cells (NFAT), thus inhibiting NFAT from moving into the nucleus and binding to cytokine promoters and ultimately impairing cytokine production (interleukin-2 and interferon-gamma) [2].

Dosing

Oral dosage is approximately three times the I.V. dosage.

- I.V.: Initial: 2–10 mg/kg/day as 24-h continuous infusion or in 2–3 divided doses; adjust based on serum levels; patients should be switched to oral cyclosporine as soon as possible; reduce the dose by at least 50 % if fluconazole or itraconazole is used concomitantly and reduce the dose by 75 % if concurrent voriconazole.
- Oral: Initial: 10–15 mg/kg/day usually divided into twice daily dosing; adjust based upon serum levels; maintenance dose may be tapered to 3–10 mg/kg/day divided into twice daily dosing in some patients. Neoral® and Sandimmune® are **not** bioequivalent and cannot be used interchangeably [3].

Pharmacokinetics

Incomplete and erratic oral absorption. Low absorption may be due to metabolism by CYP450 enzymes in the gastrointestinal tract. Bioavailability of Sandimmune® capsules and oral solution (non-modified formulation) are equivalent; 28 % in children, ranging from 17 to 42 %; bioavailability of oral solution is ~30 % of the I.V. solution. Bioavailability of Neoral® capsules and oral solution (modified formulation) are equivalent; 43 % in children, ranging from 30 to 68 %. Currently, almost all children receive modified formulations which have more predictable bioavailability. Extensively metabolized in the liver by CYP450 3A enzyme system to at least 25 metabolites; metabolized to a lesser extent by the gastrointestinal tract and kidneys. Clearance is affected by age. Pediatric patients

clear cyclosporine more rapidly than adults. Half-life is
7–19 h in children and 19 h (10–27 h) in adults. Metabolites
are excreted primarily through the bile into feces; approximately 6 % eliminated in the urine, with 0.1 % as unchanged
drug; remainder eliminated as metabolites [3].

Administration

Do not administer liquid from a plastic or Styrofoam cup.
May dilute

Neoral® oral solution with orange juice or apple juice. May
dilute Sandimmune® oral solution with milk, chocolate milk,
or orange juice. Avoid changing diluents frequently.

Mix thoroughly and drink at once. Use syringe provided to
measure dose. Mix in a glass container and rinse container
with more diluent to ensure total dose is taken. Do not
rinse or use cleansing agents on syringe before or after use
(may cause dose variation) [3].

I.V.: Administer over 2–6 h. However, many transplant centers administer as divided doses (2–3 doses/day) or as a
24-h continuous infusion. Patients should be under continuous observation for at least the first 30 min of the infusion and monitored frequently thereafter [3].

Monitoring Parameters: Blood drug concentration (trough),
renal and hepatic function, serum electrolytes, lipid profile,
and blood pressure.

Reference Range: Target serum trough concentrations:
Typically, 300 ng/mL in first few weeks, then 200 ng/mL
over subsequent months, and 100–150 ng/mL during longterm follow-up. Trough levels should be obtained 12 h
after oral dose (chronic usage), 12 h after intermittent I.V.
dose, or immediately prior to next dose [3].

When cyclosporine is administered through a single-lumen,
silicone central venous catheter and blood samples for
therapeutic drug monitoring are drawn through the same
catheter, cyclosporine concentrations may be artificially
elevated despite appropriate flushing. When central venous
administration is used, peripheral venipuncture, capillary
pin prick, or a double lumen catheter should be used to
draw blood samples for therapeutic drug monitoring.

Drug-Drug Interactions [3, 11]

- Cyclosporine is metabolized via the CYP3A isozyme pathways and has drug interactions with medications that are substrates, inducers or inhibitors of this pathway (see Table 10.2). Additional interactions are listed below.
- Cyclosporine should not be used in combination with tacrolimus.
- Cyclosporine may increase the levels/effects of calcium channel blockers (CCBs), cardiac glycosides, fentanyl, HMG-CoA reductase inhibitors, methylprednisolone/prednisolone and sirolimus through competition at the CYP3A4 pathway and of NSAIDs and loop diuretics through competition at the CYP2C9 pathway,
- Levels/effects of cyclosporine may be increased by ACE inhibitors, aminoglycosides, potassium-sparing diuretics and sirolimus.
- Cyclosporine may decrease the levels/effects of mycophenolate and vaccines.

Adverse Effects

- Principal adverse reactions to cyclosporine therapy are renal dysfunction, hypertension, hyperkalemia, tremor, hyperlipidemia, hirsutism and gingival hyperplasia. Nephrotoxicity occurs in the majority of patients treated long-term [11].
- CV: Hypertension, tachycardia and flushing
- CNS: Headaches, seizure and insomnia
- Endocrine and Metabolic: Hyperkalemia, hyperlipidemia, hypomagnesemia and hyperuricemia
- GI: Diarrhea
- Miscellaneous: Hepatotoxicity, hirsutism
- Neuromuscular and Skeletal: Tremor, paresthesias
- Renal: Elevated SCr/BUN, acute and chronic nephrotoxicity

Poisoning Information

- Acute poisoning with cyclosporine is characterized by symptoms such as nausea, headaches, acute sensitivity of the skin, flushing, gum pain and bleeding, and a sensation of increased stomach size. Hypertension, nephrotoxicity, and hepatotoxicity may also occur. Forced emesis may be

beneficial if done within 2 h of ingestion of oral cyclosporine. Treatment is symptom-directed and supportive. Cyclosporine is not dialyzable.

Compatible diluent/Administration
I.V. cyclosporine diluted in D_5W is stable for 6 h in PVC containers and 24 h in non-PVC containers or glass at room temperature; I.V. cyclosporine may bind to the plastic tubing in I.V. administration sets; non-PVC containers and administration sets should be used [3].

10.4   Antimetabolites (Mycophenolate Mofetil; Mycophenolic Acid; Azathioprine)

Most children receive some form of antimetabolite or antiproliferative agent. Azathioprine (AZA) was the most commonly used adjunctive therapy throughout the 1980s and 1990s, but in recent years, its use has dramatically decreased in favor of mycophenolate mofetil (MMF) [12]. A phase III study in adults after cardiac transplantation showed a survival benefit for MMF over AZA [13].

10.4.1   Mycophenolate Mofetil

Indication
Used as an immunosuppressive agent in conjunction with a calcineurin inhibitor with or without corticosteroids.

Mechanism of Action
A prodrug that is rapidly hydrolyzed to the active drug, mycophenolic acid (MPA), a selective, noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a critical rate-limiting enzyme in the *de novo* synthesis of the purine biosynthesis pathway. Inhibition of this enzyme results in a depletion of guanosine triphosphate and deoxyguanosine triphosphate and reduction of

T and B cell proliferation, cytotoxic T cell generation, and antibody production [14].

Dosing

Children: Oral, I.V., initial: 600 mg/m^2/dose twice daily; Alternative dose: 30–45 mg/kg/day divided every 12 h (some pediatric patients require every 8 h dosing due to rapid clearance). GI side effects often less noticeable if dosing started lower (e.g., 20 mg/kg/day divided every 12 h) and is gradually increased as tolerated.

Adults: Oral, I.V., initial: 1 g twice daily; dosages as high as 3–3.5 g/day were used in clinical trials, but no consistent efficacy advantage could be established with the higher doses and side effects were more common [3].

Pharmacokinetics

Rapid and extensive absorption and bioavailability of active metabolite MPA is 94 %. Metabolized to MPA after oral or intravenous administration and MPA, in turn, is metabolized to the inactive mycophenolic acid glucuronide (MPAG). MPAG is converted to MPA via enterohepatic recirculation. Parent drug cleared from blood within minutes. Half-life of MPA ~ 16 h. Most of the drug (87 %) excreted in urine as MPAG [3].

Presence of food decreases mycophenolate peak concentration by 40 % following mycophenolate mofetil, but has no effect on the extent of absorption [14].

Monitoring Parameters

CBC with differential and platelet count, renal and hepatic function, and MPA trough levels with target range of 2–4 mcg/mL (use of therapeutic drug monitoring remains controversial).

Drug-Drug Interactions [3]

Avoid concomitant use of mycophenolate with any of the following: azathioprine, cholestyramine resin, rifamycin derivatives, and vaccines (live).

Mycophenolate may increase the levels/effects of acyclovir, valacyclovir, ganciclovir, and valganciclovir.

The levels/effects of mycophenolate may be increased by acyclovir, valacyclovir, belatacept, ganciclovir, valganciclovir and probenecid.

Mycophenolate may decrease the levels/effects of estrogen/progestin containing contraceptives and vaccines (inactivated).

The levels/effects of mycophenolate may be decreased by antacids, cyclosporine, magnesium salts, metronidazole, penicillins, proton pump inhibitors, quinolone antibiotics, rifamycin derivatives and sevelamer.

Adverse Effects

Principal adverse effects are gastrointestinal and hematologic and include leukopenia, diarrhea and vomiting [14].

GI: Constipation, dyspepsia, diarrhea and emesis

Hematologic: Leukopenia, anemia and thrombocytopenia

Hepatic: Ascites, abnormal LFTs

Miscellaneous: Increased risk of infection, malignancy and vaccine failure

Poisoning Information

Symptoms of mycophenolate overdose may include nausea, vomiting, diarrhea, increased incidence of infections, and unusual bleeding or bruising. Pursue symptomatic and supportive treatment.

10.4.2   *Mycophenolic Acid (Delayed Release Tablet Formulation)*

Mycophenolic acid is available as delayed-release tablets indicated for organ rejection prophylaxis in allogeneic renal transplant patients when prescribed in combination with cyclosporine and corticosteroids. It has the same mechanism of action, monitoring parameters and drug interactions as mycophenolate mofetil. The adverse event profile is similar to mycophenolate mofetil but is purported to have less gastrointestinal effects [15].

Dosing

Mycophenolate mofetil should **not** be interchanged with the delayed-release tablet formulation due to differences in the rate of absorption [15].

Children: Oral: Renal transplantation: 400–450 mg/m^2/dose twice daily; maximum dose: 720 mg

BSA <1.19 m^2: Use of this formulation is not recommended.

BSA 1.19–1.58 m^2: 540 mg twice daily

BSA >1.58 m^2: 720 mg twice daily; **Note:** Mycophenolate delayed release 720 mg twice daily was shown to be bio-equivalent to mycophenolate mofetil 1,000 mg twice daily

Adults:

Cardiac transplant: 1,080 mg twice daily (has been shown to be therapeutically similar to mycophenolate mofetil 1.5 g twice daily)

Renal transplant: 720 mg twice daily

10.4.3 Azathioprine

Indication

Used as an adjunctive immunosuppressive agent for the prevention of rejection in heart transplant patients. AZA is used in combination with other agents such as corticosteroids and calcineurin inhibitors.

Mechanism of Action

Converted to 6-mercaptopurine (6-MP) which is then metabolized to ribonucleotide thioinosinic acid, which becomes incorporated into nucleic acids causing chromosome breaks, suppression of guanine and adenine synthesis, and synthesis of fraudulent proteins. The ultimate immunosuppressive effect is inhibition of RNA and DNA synthesis, leading to decreased immune cell proliferation [2].

Dosing

AZA is available in oral and intravenous dosage forms. AZA dosages must be carefully adjusted and individualized according to patient responses. The dosage of AZA must

be adjusted in the presence of renal dysfunction and bone marrow suppression.

Oral, I.V.: Initial: 2–3 mg/kg/dose once daily. Maintenance: 1–2 mg/kg/day.

Pharmacokinetics

Extensive metabolism by hepatic xanthine oxidase to 6-MP (active); 50 % bioavailability; 30 % protein binding; crosses the placenta; half-life of parent 12 min and of 6-MP 0.7–3 h; with anuria, half-life increased to 50 h; a small amount eliminated as unchanged drug; metabolites eliminated eventually in the urine [3].

Monitoring Parameters

CBC with differential, platelet count, creatinine, total bilirubin, alkaline phosphatase and liver function.

Drug Interactions [3]

The myelosuppressive effect of AZA may be enhanced by ACE inhibitors, mercaptopurine, sulfamethoxazole and trimethoprim.

Allopurinol may decrease the metabolism of AZA.

Ribavirin may increase serum concentrations of the active metabolites of AZA.

AZA may diminish the anticoagulant effect of vitamin K antagonists.

AZA may diminish the therapeutic effect of vaccines (inactivated) and enhance the adverse/toxic effect of vaccines (live).

Adverse Effects [16]

Hematologic: Bone marrow suppression; leukopenia, macrocytic anemia, and thrombocytopenia. Hematologic effects are dose-related. During severe toxicity the WBC count and hemoglobin level drop first, followed by a decreasing platelet count. The WBC count will usually return to normal when the dose of AZA is decreased. Patients with a genetic deficiency of the enzyme thiopurine S-methyltransferase (homozygous state) may experience life-threatening bone marrow suppression when treated with azathioprine.

GI: Vomiting, anorexia, and diarrhea may occur in patients who are receiving large doses of AZA. These GI effects may be ameliorated by giving AZA in divided doses and/or with meals. Other GI manifestations of toxicity include ulceration of the oral mucous membranes, esophagitis and steatorrhea.

Infection: Increased risk, as with all immunosuppressants. Risk is further increased during leukopenia. When infection occurs, the dosage of AZA and other immunosuppressive agents should be reduced as much as possible and appropriate therapy for infection instituted.

Miscellaneous: Drug fever, rash, myopathy and pancreatitis.

Poisoning Information

Signs and symptoms of overdose: diarrhea, leukopenia (in 2–3 days) and vomiting. Decontamination: Lavage within 1 h; give activated charcoal. Slightly dialyzable (5–20 %).

Compatible diluents/Administration

Reconstituted 10 mg/mL injection is stable for 24 h at room temperature; stable in neutral or acid solutions, but is hydrolyzed to mercaptopurine in alkaline solutions [3].

10.5   Inhibitors of the Mammalian Target of Rapamycin (mTOR) (Sirolimus; Everolimus)

Calcineurin-free regimens based around use of high dose mTOR inhibitors (with mycophenolate mofetil and steroids) are not routinely used in thoracic transplantation, as their ability to prevent rejection is unproven. There is little experience with these agents in the pediatric population, especially following thoracic transplantation. The most interesting aspect of the use of mTOR inhibitors is their possible role in the prevention of post-transplant coronary artery disease in cardiac transplant recipients [17].

10.5.1   Sirolimus

Indication
Indicated for the prevention of organ rejection in patients receiving a calcineurin inhibitor.

Mechanism of Action
Inhibits T lymphocyte activation and proliferation after the activation of interleukin-2 (IL-2) and other T cell growth factors. The drug's action requires the formation of a complex with the immunophilin, FKBP-12, which will bind to and inhibit the mammalian kinase, mTOR, a key enzyme in cell-cycle progression to the S phase. In this way, sirolimus inhibits acute rejection of allografts and prolongs graft survival [18].

Dosing
- **Children**: *Dosing poorly defined*. Oral: Typical starting dose 1 mg/m^2/day given daily or as twice daily dosing (especially in infants and young children). Subsequent dosing adjusted to maintain therapeutic sirolimus trough levels. Doses should be taken consistently either with or without food [3].
- **Adults**: Oral: Initial dose: 2–5 mg/day (dependent upon degree of immunologic risk). Subsequent dosing adjusted to maintain therapeutic sirolimus trough levels.
- Higher target levels may be used when there is a clinical indication to maintain calcineurin inhibitor dosing at very low levels due to side effects [18]. Data from clinical trials suggest that SCr levels will be higher when cyclosporine is used with sirolimus than when used with MMF or AZA. Careful monitoring of renal function is therefore required. Due to impaired wound healing, sirolimus should not be started until surgical wounds are completely healed.

Pharmacokinetics
Absorbed rapidly and reaches a peak concentration within 1–3 h. Bioavailability is approximately 14 % for oral solution and 18 % for tablets with protein binding approximately 92 %. Hepatically metabolized by CYP3A4 and is

transported by P-glycoprotein. Seven major metabolites have been identified in whole blood, as well as in the urine and feces. Some of these metabolites are active; however, sirolimus remains the major component in the immuno-suppressive effect. Half-life is less than 24 h in children and a mean of 62 h in adults. Majority (91 %) is eliminated in the feces [3].

Monitoring Parameters

Whole blood sirolimus trough concentration, serum cholesterol and triglycerides, and SCr; CBC with differential, liver function tests (LFTs), platelet count, calcineurin inhibitor blood levels and healing of surgical wounds.

Reference Range

Target trough concentrations: 3–7 ng/mL has been used in heart transplantation. Higher levels up to 15 ng/ml have been used in calcineurin-sparing or avoidance regimens.

Drug-Drug Interactions

Note: Although not well documented, drug interactions, qualitatively, are expected to be similar to tacrolimus or cyclosporine. Sirolimus is a substrate of CYP3A4 [3].

Sirolimus may enhance the adverse/toxic effect of ACE inhibitors, hypoglycemic agents, tacrolimus and vaccines (live), cyclosporine (increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (TTP)/thrombotic microangiopathy has been described).

May increase the serum concentration of sirolimus: cyclosporine (specific concern with cyclosporine [modified]; administer oral doses of sirolimus 4 h after doses of cyclosporine), azole antifungals, macrolide antibiotics and tacrolimus.

May decrease the serum concentration of sirolimus: fosphenytoin, phenytoin and rifampin.

Sirolimus may diminish the therapeutic effect of vaccines (inactivated).

Adverse Effects

Common: hyperlipidemia, thrombocytopenia, and mouth ulcers [3].

CV: Hypertension, tachycardia and peripheral edema

Endocrine: Hypercholesterolemia, hypertriglyceridemia and hypokalemia

CNS: Fever, arthralgia and pain

Dermatologic: Acne, rash, pruritus and impaired wound healing

GI: Nausea, diarrhea, constipation and mouth ulceration

Hematologic: Anemia, hemolytic-uremic syndrome, leukopenia, thrombocytopenia and TTP

Hepatic: Abnormal LFTs, ascites

Renal: Albuminuria, increased BUN/SCr, hematuria and tubular necrosis

Respiratory: noninfectious pneumonitis, pleural effusion and pulmonary embolism

10.5.2 Everolimus

A second mTOR inhibitor, everolimus, has been recently approved for prophylaxis of organ rejection in patients at low-moderate immunologic risk. It has a similar mechanism of action, pharmacokinetics, monitoring parameters, drug interactions and adverse effects to those of sirolimus.

Dosing [3]

Children: *Limited data available*: Children and Adolescents ≥1 year: Initial: 0.8 mg/m^2/dose twice daily (maximum single dose: 1.5 mg); a trial evaluating use for 3 years in pediatric patients (<16 years), the mean reported dose was 1.53 mg/m^2/day. Subsequent dosing adjusted to maintain therapeutic everolimus serum levels.

Adults: Initial: 0.75 mg twice daily; adjust maintenance dose if needed at a 4- to 5-day interval (from prior dose adjustment) based on serum concentrations, tolerability, and response.

Reference Range

Target range is 3–6 ng/mL (in pediatric studies). Monitor serum trough concentrations 4–5 days after dose initiation or previous dose adjustment, especially in patients with

hepatic impairment, with concomitant CYP3A4 inhibitors and inducers [3].

Adverse Effects – similar to those mentioned above with sirolimus with the addition of:

Dermatologic: Alopecia

Endocrine and Metabolic: Acidosis, hyperglycemia, diabetes mellitus and pancreatitis

GI: Abdominal distention, ileus

Hematologic: Hemorrhage, leukocytosis, lymphocytopenia and neutropenia

Hepatic: Increased bilirubin

Neuromuscular and Skeletal: Arthralgia, osteopenia, osteoporosis and tremor

Renal: Interstitial nephritis, renal failure/impairment

Respiratory: Atelectasis, dyspnea, epistaxis and pneumonia

ID: Increased risk of BK virus infection, candidiasis and *Aspergillosis*

10.6   Polyclonal Antibodies (Rabbit Anti-thymocyte Globulin and Equine Anti-thymocyte Globulin)

Equine Anti-thymocyte Globulin is currently used much less frequently than Rabbit Anti-thymocyte Globulin. Information that is common to polyclonal antibodies is listed first followed by specific sections for rabbit and equine derivatives.

10.6.1   Indication

Used in the treatment of steroid-resistant acute cellular rejection (ACR) in kidney and other solid organ transplant recipients in conjunction with immunosuppressive agents. Thymoglobulin is also used for induction in the immediate post-transplant period to prevent acute rejection and to allow for lower initial dosing of CNI to reduce immediate post-transplant toxicities, especially renal [3].

10.6.2   Mechanism of Action

Elimination of T cells from the peripheral blood or altered T cell function. The exact mechanism of action is unknown. Polyclonal antibodies have broad antigen specificity, bind to various cellular antigens on T cells in addition to cellular antigens on platelets, erythrocytes, and leukocytes. Complete, or near complete, depletion of T cells from the peripheral circulation generally occurs after 2–3 doses. There may be variable depletion of T cells from peripheral lymphoid tissues also [3].

10.6.3   Warnings

Anaphylaxis (symptoms can include hypotension, respiratory distress, pain in the chest, rash, and tachycardia) may occur at any time during therapy. Epinephrine and oxygen should be readily available to treat anaphylaxis.

10.6.4   Drug-Drug Interactions [3]

Polyclonal antibodies may enhance the adverse/toxic effect of vaccines (live).

Polyclonal antibodies may diminish the therapeutic effect of vaccines (inactivated).

10.6.5   Poisoning Information

Excessive dosing for prolonged periods may increase the risk of opportunistic infection and lymphoproliferative disorders.

10.7   Rabbit Anti-thymocyte Globulin

10.7.1   Dosing

Administer premeds 30 min before dose: acetaminophen (10 mg/kg P.O.), diphenhydramine (1 mg/kg I.V.), and

methylprednisolone (1–2 mg/kg I.V.). With prolonged administration times (>6 h), acetaminophen and diphenhydramine can be repeated. If the first dose is well tolerated, the dose of steroid premedication is often reduced (or even eliminated) for subsequent doses.

Induction: 1.5 mg/kg/day I.V. once daily for 5 days (range 3–7); Rejection: 1.5 mg/kg/day once daily for 7–14 days [3].

10.7.2   Pharmacokinetics

Peak levels occur 4–8 h after I.V. doses of 1.25–1.5 mg/kg with an average concentration of 22 mcg/mL. Peak levels increase to an average of 87 mcg/mL after 7–10 days of continuous dosing. Serum half-life after the first dose is approximately 44 h and increases with subsequent doses up to 13 days. Duration: lymphopenia may persist greater than 1 year [3].

10.7.3   Monitoring Parameters

Lymphocyte profile, CBC with differential and platelet count; vital signs during administration; signs and symptoms of infection.

> Adverse Effects: Infusion-related reactions such as fever, chills, headache, and rash. To prevent or minimize febrile reactions, premedicate with an antipyretic, anthistamine, and/or corticosteroid. Some of these effects reflect a cytokine release syndrome [19].
>
> CV: Hyper-/hypotension, tachycardia and edema
>
> CNS: Seizures, fever, headache, aseptic meningitis, chills and pain
>
> Endocrine and Metabolic: Hyperkalemia
>
> GI: Abdominal pain, diarrhea, gastritis and nausea
>
> Hematologic: Leukopenia, thrombocytopenia
>
> ID: Pneumonia, primary or reactivation of cytomegalovirus (CMV) infection

Hypersensitivity: Hypersensitivity may reflect anaphylaxis and may be indicated by hypotension and acute respiratory distress. Delayed serum sickness reactions may also be observed.

10.7.4   Compatible Diluents/Administration

Reconstitute with the supplied diluent, sterile water for injection immediately before use. Dilute dosage in 0.9 % sodium chloride injection or 5 % dextrose injection to a final concentration of 0.5–2 mg/mL. Use admixture immediately. Final solution is stable up to 24 h after initial reconstitution. Use within 4 h if kept at room temperature [3].

10.8   Equine Anti-thymocyte Globulin

10.8.1   Dosing

Intradermal skin test is recommended prior to administration of the initial dose; use 0.1 mL of a 1:1,000 dilution in NS; observe the skin test every 15 min for 1 h; a local reaction = 10 mm diameter with a wheal or erythema or both should be considered a positive skin test [3].

Administer premeds 30 min before dose: acetaminophen (10 mg/kg P.O.), diphenhydramine (1 mg/kg I.V.), and methylprednisolone (1–2 mg/kg I.V.). With prolonged administration times (>6 h), acetaminophen and diphenhydramine can be repeated. If the first dose is well tolerated, the dose of steroid premedication is often reduced (or even eliminated) for subsequent doses.

Cardiac allograft: 10 mg/kg/day for 7 days; Rejection prevention: 15 mg/kg/day for 7–14 days; initial dose should be administered within 24 h of transplantation. Rejection treatment: 10–15 mg/kg/day for 14 days.

10.8.2   Pharmacokinetics

Poor distribution into lymphoid tissues; binds to circulating lymphocytes, granulocytes, platelets, and bone marrow cells. Plasma half-life is 1.5–12 days; 1 % of dose excreted in urine [3].

10.8.3   Monitoring Parameters

Lymphocyte profile, CBC with differential and platelet count, vital signs during administration.

10.8.4   Adverse Effects

Infusion-related reactions such as fever, chills, headache, and rash. To prevent or minimize febrile reactions, premedicate with an antipyretic, anthistamine, and/or corticosteroid. Some of these effects reflect a cytokine release syndrome [3, 20].

CV: Bradycardia, cardiac irregularity, edema, heart failure and hyper-/hypotension
CNS: Agitation, chills, fever, headache and seizure
Dermatologic: Pruritus, rash
GI: Diarrhea, vomiting
Hematologic: Leukopenia, thrombocytopenia, neutropenia and anemia
Hepatic: Hepatosplenomegaly, abnormal LFTs
Renal: Proteinuria, renal function tests abnormal and acute renal failure
Respiratory: Pleural effusion, respiratory distress

10.8.5   Compatible Diluents/Administration

Dilute in ½NS or NS; when diluted to concentrations up to 4 mg/mL stable for 24 h if refrigerated; use of dextrose solutions is not recommended as precipitation can occur in solutions with a low salt concentration [20].

10.9   Monoclonal Antibodies (Alemtuzumab)

Two monoclonal antibodies have been used for induction and maintenance therapy and for treatment of rejection in solid organ transplantation. Muromonab CD3 was previously widely used in transplant but is no longer manufactured and not available for clinical usage. Alemtuzumab is only available through the Campath® Distribution Program in the United States and may be requested by organizations for off-label indications related to solid organ transplantation.

10.9.1   Alemtuzumab

Indication
Primarily used in the treatment of B cell chronic lymphocytic leukemia and more recently multiple sclerosis [21]. Has been used as induction and rejection therapy in a small number of solid organ transplant programs but is not approved for transplant usage. Previous use in pediatric transplant is minimal.

Mechanism of Action
Binds to CD52 after which antibody-dependent lysis occurs [3].

Dosing (*for off-label indication of solid organ transplant induction/rejection*):

Children: *Dosing poorly defined*. Induction: 0.4–0.5 mg/kg/dose I.V. (maximum dose: 30 mg)

Adults: I.V. infusion of 30 mg/dose for 1–2 doses (pre-transplant with or without a second dose on day 1 post-transplant) have been used in adult solid organ transplantation [3].

Drug-Drug Interactions
Allergic reactions may be increased in patients who have received diagnostic or therapeutic monoclonal antibodies due to the presence of human antichimeric antibody (HACA).

Warning

U.S. Boxed Warning**: Cytopenias, infusion reactions, and infections** [21]

Cytopenias: Serious, including fatal, pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia can occur.

Infusion Reactions: Alemtuzumab administration can result in serious, including fatal, infusion reactions.

Infections: Serious, including fatal, bacterial, viral, fungal, and protozoan infections can occur in patients receiving alemtuzumab.

10.10   Monoclonal Antibodies to IL-2 Receptor (Basiliximab)

Two IL2R antagonists have been developed, daclizumab and basiliximab. Daclizumab was recently withdrawn from the market due to manufacturing costs leaving basiliximab as the sole agent for use as IL2R blockade.

10.10.1   Basiliximab

Indication

Used for prophylaxis of acute organ rejection. Experience with basiliximab in heart transplantation is limited. In a cohort study in children, two doses of basiliximab were associated with low acute rejection rates despite intentional sub-therapeutic dosing of calcineurin inhibitors in the immediate post transplant period [22].

Mechanism of Action

A chimeric (murine/human) monoclonal antibody which blocks the alpha-chain of the IL-2 receptor complex; this specific high affinity binding to IL-2 receptor competitively inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection [3].

Dosing

In pediatric patients weighing less than 35 kg, the recommended regimen is 10 mg I.V. within 2 h prior to transplantation surgery, followed by 10 mg I.V. 4 days after transplantation. In pediatric patients weighing greater than or equal to 35 kg, the recommended regimen is 20 mg I.V. within 2 h prior to transplantation surgery, followed by 20 mg I.V. 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to basiliximab occur [23]. No dose adjustment is necessary when basiliximab is added to triple immunosuppression regimens including cyclosporine, corticosteroids, and either AZA or MMF.

Pharmacokinetics

Mean duration: 36 days (determined by IL-2R alpha saturation); elimination half-life in children 1–11 years: 9.5 days; Adolescents 12–16 years: 9.1 days; Adults: 7.2 days [3].

Drug Interactions

Basiliximab may decrease the effect of vaccines (inactivated).

Basiliximab may increase the risk of vaccinial infection from vaccines (live).

Adverse Effects [3]

GI**:** Abdominal pain, vomiting, and GI hemorrhage

CV: Hyper-/hypotension, generalized edema and arrhythmia

CNS: Headache, insomnia, pain and fever

Endocrine and Metabolic: diabetes mellitus, hyper-/hypoglycemia, fluid overload, hypercholesterolemia, hyperlipemia, hypertriglyceridemia and electrolyte disturbances

Genitourinary: Dysuria, urinary frequency, urinary retention and urinary tract infection

Hematologic: Anemia, hemorrhage, leukopenia, thrombocytopenia and thrombosis

Neuromuscular & skeletal: Arthralgia, myalgia, neuropathy, paresthesia, rigors and tremor

Renal: Dysuria, abnormal renal function and renal tubular necrosis

Respiratory: Dyspnea, upper respiratory tract infection and pulmonary edema

Dermatologic: Surgical wound complications, rash

ID: Increased risk of CMV infection, herpes infection (simplex and zoster) and sepsis

Warning

Severe acute hypersensitivity reactions including anaphylaxis have been observed with initial exposure and subsequent doses. These reactions may include hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing. If a severe hypersensitivity reaction occurs, therapy with basiliximab should be permanently discontinued. Medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available for immediate use [24]. Allergic reactions may be increased in patients who have previously received monoclonal antibody therapy due to the development of human antimurine antibodies [3].

Stability/Administration

Diluted in 25–50 mL 0.9 % NaCl or D5W [23] and infused over 20–30 min; may use peripheral or central line [3].

10.11   Selective T-Cell Costimulation Blockers (Belatacept)

Belatacept blocks costimulation signals necessary for the activation of T cells. It has been explored as a biological therapy for chronic immunosuppression due to the lack of the usual toxicities associated with CNIs [25]. Belatacept is currently approved for use as part of immunosuppression regimens with basiliximab, mycophenolate, and corticosteroids in the setting of Epstein-Barr virus (EBV) seropositive kidney transplant recipients [26].

Dosing

Adult **(**Dosing is based on actual body weight at the time of transplantation; do not modify weight-based dosing during course of therapy unless the change in body weight is >10 %.)

Kidney transplant, prophylaxis of organ rejection: I.V.: The prescribed dose must be rounded so that it is evenly divisible by 12.5 mg to allow accurate preparation of the reconstituted solution using the provided required disposable syringe for preparation. *Initial phase*: 10 mg/kg/dose on Day 1 and on day 5 (~96 h after Day 1 dose), followed by 10 mg/kg/dose given at the end of Week 2, 4, 8, and 12 following transplantation *Maintenance phase*: 5 mg/kg/dose every 4 weeks (plus or minus 3 days) beginning at Week 16 following transplantation [3]

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Chapter 11
Anticoagulation for Mechanical Circulatory Support

David S. Cooper and Angela Lorts

Abstract   Clinically significant thromboembolic events continue to be a devastating complication during Ventricular Assist Device (VAD) support. Despite monumental advances in mechanical circulatory support technology, the monitoring and management of coagulation in the presence of substantial foreign material remains an ongoing challenge. Furthermore, the peculiarity of hemostasis in children places these patients at increased risk of devastating complications even in the presence of standard anticoagulation regimes. Pre-existing coagulation abnormalities due to renal and hepatic dysfunction, exacerbated with depletion of clotting factors secondary to cardiopulmonary bypass and altered rheological state all conspire to increase bleeding in the perioperative time period. These considerations must be weighted with the eminent risk of clot formation and thromboembolic events over time.

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D.S. Cooper, MD, MPH (✉)
Department of Pediatrics, Cardiac Intensive Care Unit,
The Heart Institute, Cincinnati Children's Hospital Medical Center,
University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: david.cooper@cchmc.org

A. Lorts, MD
Department of Pediatrics, Advanced Heart Failure,
The Heart Institute, Cincinnati Children's Hospital Medical Center,
University of Cincinnati College of Medicine, Cincinnati, OH, USA

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11.1   Introduction

Clinically significant thromboembolic events continue to be a devastating complication during Ventricular Assist Device (VAD) support. It remains difficult to characterize the true incidence of thromboembolic or hemorrhagic events with the multitude of different VAD systems, be it, pulsatile or continuous flow pumps [1–3]. Despite monumental advances in mechanical circulatory support (MCS) technology, the monitoring and management of coagulation in the presence of substantial foreign material remains an ongoing challenge. Furthermore, the peculiarity of hemostasis in children places these patients at increased risk of devastating complications even in the presence of standard anticoagulation regimes. For all patients, sepsis and other inflammatory states can greatly affect coagulation profiles, necessitating vigilant monitoring and adjustments of anticoagulation/antiplatelet (AC/AP) regimes. Current monitoring of AC/AP therapy has expanded past activated clotting time (ACT) traditionally used for ECMO, to include anti factor Xa or unfractionated heparin level, International Normalized Ratio (INR), Thromboelastograph (TEG®) and Platelet Mapping™. These tests are instrumental in providing the necessary information to monitor and adjust unfractionated heparin (UFH), low molecular weight heparin (LMWH) and antiplatelet therapy.

Pre-existing coagulation abnormalities due to renal and hepatic dysfunction, exacerbated with depletion of clotting factors secondary to cardiopulmonary bypass and altered rheological state all conspire to increase bleeding in the perioperative time period. These considerations must be weighted with the eminent risk of clot formation and thromboembolic events over time. As such, there have been a multitude of different algorithms for initiation and continuation of

anticoagulants in VAD patients. Outlined is a brief overview of the current recommendations for anticoagulation in four of the more common pediatric and adult VADs including the Berlin Heart *EXCOR® Pediatric* (Berlin Heart Inc. Woodlands, TX), the HeartMate II (Thoratec, Pleasanton, CA), the Levitronix PediVAS® and CentriMag® (Levitronix LLC, Waltham, Mass), and the HeartWare (HeartWare, Inc., Framingham, Mass) (Table 11.1)

11.2 Anticoagulation in Berlin Heart *Excor® Pediatric*

The Edmonton Anticoagulation and Platelet Inhibition Guidelines for Pediatric VADs© is currently applied for the anticoagulation management of the Berlin Heart EXCOR®. The guideline suggests no anticoagulation for the first 24 h post-implantation, followed by the initiation of age appropriate dosing of intravenous unfractionated heparin (UFH) at 24–48 h once bleeding has resolved (<2 ml/kg/day) and platelet count is >20,000/µl (Table 11.2). At 48 h following surgery, a hemostatically and hemodynamically stable patient may be transitioned from UFH to LMWH (Table 11.2). In patients older than 12 months of age, oral anticoagulation therapy with a vitamin K antagonist, warfarin, can be initiated (target INR 2.7–3.5) once they are hemodynamically stable and receiving adequate enteral feeds. Patients younger than 12 months of age are unstable on oral anticoagulation regimes due to difficulties monitoring the warfarin effect secondary to multiple drug and diet interactions. Based on results of TEG® and Platelet Mapping™, acetylsalicylic acid (ASA) may be started at 48 h and dipyridamole at 4 days post-implantation if the patient is hemodynamically stable, with no bleeding and a platelet count greater than 40,000/µl (Table 11.3). All anti-platelet inhibition therapy is dosed individually based on the patient's platelet mapping studies and the degree of ADP and AA inhibition. The TEG® MA value is also monitored and the goal MA to start acetylsalicylic acid

Table 11.1 Anticoagulation regimes in VADs

Device	Anticoagulation	Anticoagulation monitoring	Timing of anticoagulation
Berlin Heart	Peri-operative: UFH	UFH: antifactor-Xa level 0.35–0.5 U/ml	0–24 h: no anticoagulation
EXCOR Pediatric	Long term: LMWH or warfarin and antiplatelet	LMWH: antifactor-Xa level 0.6–1 U/ml	>24–48 h: UFH
		Warfarin: INR 2.5–3	>48 h: transition to LMWH or vitamin K antagonist[a] and ASA
		Antiplatelet: TEG® monitoring	>4 days: dipyridamole[b]
HeartMate II	Perioperative: UFH	UFH: aPTT 55–65 s or 1.5–1.8 times normal	0–24 h: no anticoagulation
	Long term: warfarin and antiplatelet	Warfarin: INR 1.5–2	>24 h: UFH
			>48 h: antiplatelet (ASA)
			Transition to warfarin
Levitronix	Heparin	aPTT 1.5–2 times normal	>6–12 hors post-op and for duration of support
		ACT 180–200 s	

(continued)

TABLE 11.1 (continued)

Device	Anticoagulation	Anticoagulation monitoring	Timing of anticoagulation
Heartware	Perioperative: UFH	UFH:	0–24 h: no anticoagulation
	Long term: warfarin and antiplatelet	Warfarin: INR 2–2.5	>24 h: UFH
		Antiplatelet: TEG® monitoring	>48 h: antiplatelet (ASA)
			No post op bleeding and enteral feeding, change to warfarin

UFH unfractionated heparin, *LMWH* low molecular weight heparin, *ASA* acetylsalicylic acid

[a]Vitamin K antagonist (warfarin) only used in children >1 year old with stable enteral nutrition

[b]Dipyridamole started if hemostatically stable, platlet count >40,000/μL

TABLE 11.2 Unfractionated heparin (UFH) dosing at 24–48 h post EXCOR pediatric

	≤12 months	≥12 months
Initial dose[a]	15 IU/kg/h	10 IU/kg/h
After 6 h[b]	28 IU/kg/h	20 IU/kg/h

[a]Criteria for UFH initiation
    Platelet count >20,000/μl
    Normal function on Platelet Mapping™ studies
    Minimal bleeding (<2 ml/kg/day)

[b]6 h after increase to therapeutic dose, obtain a PTT and anti-factor Xa level (desired range 0.35–0.7 U/ml or aPTT 1.5–2.5 times baseline if PTT correlates with anti-factor Xa, secondary target: TEG R_k 8–15 min)

TABLE 11.3 Low molecular weight heparin (LMWH) at 48 h post EXCOR pediatric

	≤3 months	≥3 months
LMWH dosing[a,b]	1.5 mg/kg sc	1 mg/kg sc

[a]Criteria for LMWH initiation
    No bleeding
    Patient is hemodynamically stable
    Normal renal function (normal creatinine and urea)
[b]Stop UFH and administer subcutaneous (sc) LMWH with antifactor Xa 4 h after second dose (therapeutic range 0.6–1 U/ml, secondary target: TEG R_k 8–15 min)

TABLE 11.4 Antiplatelet therapy post EXCOR pediatric

	Acetylsalicylic acid	Dipyridamole
First dose timing	>48 h	>4 days
Dosing	1 mg/kg/day divided into 2 doses[a]	4 mg/kg/day divided into 4 doses[b]

[a]Criteria for Acetylsalicylic acid initiation
    No bleeding and hemodynamically stable
    Platelet Mapping™ does not show significantly decreased platelet function: net ADP G ≥4 and AA inhibition >70 %
    Platelet count >40,000/μl
    TEG® MA >56 from a CKH sample
[b]Criteria for Dipyridamole initiation
    Platelet Mapping™ shows platelet inhibition in the presence of net ADP G >4
    TEG® MA ≥72 mm from a CKH sample

is >56 mm and the goal at the time of dipyridamole initiation is a TEG® MA >72 mm (Table 11.4).

Despite adherence to these guidelines, there remains a significant risk of thromboembolic or hemorrhagic events, and as such not only is strict monitoring of coagulation profiles necessary, but vigilant surveillance of the pump and cannulas is paramount. In the initiation and transition stages of AC/AP

therapy, frequent checking of the pump with a flashlight for any fibrin or clot formation must be done every few hours. Once the patient has stabilized, pump and cannula inspection can be completed twice daily. In the event of significant fibrin or clot formation, additional anticoagulation dosing may be given and consideration must be given to changing the pump depending on the location and size of the clot. Fibrin and clot formation tends to occur in areas of blood stasis and as such the valve leaflets are a nidus for growth. For LVADs, the presence of a clot in the pump dictates frequent neurological monitoring and decreases the threshold for a pump change.

11.3   Anticoagulation for the Heartmate II

The HeartMate II is a continuous-flow LVAD that has gained widespread acceptance due to its small size and ease of implantation. Furthermore, initial clinical results from the HeartMate II Pivotal bridge to transplant (BTT) trial demonstrated survival rates of 75 % at 6 months and 68 % at 1 year [4]. The HeartMate II Pivotal BTT trial outlined an anticoagulation strategy that consisted of UFH within 12–24 h following implantation. UFH was titrated using a goal PTT of 45–50 s for the first 24 h, 50–60 s for the second 24 h and then 55–65 s thereafter. Antiplatelet therapy is initiated on postoperative day 2–3 with aspirin 81 mg and dipyridamole 75 mg three times daily. Following removal of chest tubes on day 3–5 post-implantation UFH can be discontinued and transitioned to warfarin with target INR of 2–3. For the assessment of platelet function, the MA of the TEG® is the most useful parameter to help tailor therapy to the individual patient. In general, an MA in the 56 to 75 mm range has been used as an appropriate target range for platelet activity in HeartMate II patients with good results. An MA of less than 55 mm indicates a hypocoagulable state and is cause for concern for inadequate platelet activity, whereas an MA exceeding 75 mm indicates a hypercoagulable state, and more aggressive antiplatelet therapy should be instituted.

The higher than expected frequency of hemorrhagic events, especially gastrointestinal bleeds, has resulted in reexamination of the anticoagulation regime [5]. Boyle and colleagues examined the risk of thromboembolic and hemorrhagic events in relation to the INR [6]. In the 331 patients discharged, thrombotic events comprised only 3 %, while bleeding related complication were present in 17.5 %. The highest incidence of hemorrhagic events were at INRs >2.5 with the lowest risk of thromboembolic events with INRs >1.5. Therefore, the authors concluded that lowering the target INR to 1.5–2.5 might decrease the risk of devastating hemorrhagic complications while attenuating the risk for thromboembolism. Further insights into the effect of continuous-flow devices on coagulation cascade suggest that these changes to the anticoagulation regime alone may be insufficient. Acquired vonWillbrand syndrome has been universally demonstrated in patients supported with continuous-flow devices and predisposes them to increased morbidity during support and at time of transplantation [7].

11.4   Anticoagulation for the Levitronix

The Levitronix CentriMag® and PediVAS® systems are continuous-flow devices that can be used for left, right and biventricular support in adults and children. The device is generally used for short to intermediate term support as a bridge to decision or bridge to bridge with the exchange to a longer term VAD. Furthermore, Levitronix can function similar to ECMO with the placement of an oxygenator.

The suggested anticoagulation guidelines comprise of UFH infusion starting 6–12 h post cardiopulmonary bypass for implantation in the presence of chest tube drainage less than 50 ml/h or 2 ml/kg/h for 2–3 h. Anticoagulation is titrated to maintain target ACT of 160–180 s and aPTT 1.3–1.6 times baseline. The target ACT and aPTT is increased by 5 % per day to ACT of 190–210 and aPTT 1.5–1.8 times baseline by post-implantation day 4. An antiplatelet agent can be initiated after 4 days depending on the hemostatic conditions of the patient and the pump.

11.5   Anticoagulation for the Heartware

The HeartWare is one of the newest MCS devices with the purported advantages of being smaller and more durable than previous LVADs [8]. With a pump weight of only 140 g; it is implanted within the pericardial space. The pump is a continuous-flow impellar with communication to the external power and control panel via the driveline that is externalized through the abdominal wall.

Similar to the HeartMate II patients, continuous antico-agulation is recommended and can be somewhat tailored to specific patient risk factors. The initial multicenter evaluation of the HeartWare used an anticoagulation regime that con-sisted of UFH in the postoperative period once bleeding had decreased [9]. The UFH is titrated to an aPTT target of 50–60 s or an ACT of 140–160 s. Once the patient is hemody-namically stable and tolerating enteral nutrition, warfarin therapy is started with the discontinuation of UFH to main-tain target INRs of 2.0–3.0. Antiplatelet therapy can be initi-ated with warfarin.

The initial clinical experience of 50 patients using this anti-coagulation therapy demonstrates a relatively low incidence of thromboembolic events (2 ischemic stroke) and higher frequency of bleeding complications (4 hemorrhagic stroke, 3 deaths) [9]. Bleeding events occurred most frequently in the perioperative setting and all were observed less than 30 days post implantation.

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Chapter 12
Pharmacological Treatment of Pulmonary Hypertension

Shinichi Takatsuki, Jennifer Eshelman, Allyson Berg, and David Dunbar Ivy

Abstract Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. In the last decade, specific targeted therapies have been developed and have improved survival in adult patients with PAH. These therapies have also benefited children with PAH. Unfortunately, there are limited data on treatment strategies in children with PAH due to the small number of randomized controlled clinical trials evaluating the safety and efficacy of specific treatments. Currently

S. Takatsuki, MD
Department of Pediatrics, Children's Hospital Colorado,
University of Colorado School of Medicine, Aurora, CO USA

J. Eshelman, PharmD • A. Berg, PharmD
Department of Pharmacy, Children's Hospital Colorado,
Aurora, CO USA

D.D. Ivy, MD (✉)
Department of Pediatrics, Children's Hospital Colorado,
Pediatric Cardiology, University of Colorado School of Medicine,
Aurora, CO USA

Pediatric Cardiology, Children's Hospital Colorado,
13123 East 16th Avenue, B100, Aurora, CO 80045, USA
e-mail: dunbar.ivy@childrenscolorado.org

approved PAH therapies impact one of three endothelial-based pathways including nitric oxide, prostaglandin, or endothelin-1. This chapter summarizes currently available therapies based on adult data and a limited number of clinical trials in children with PAH.

Keywords Prostacyclin • Epoprostenol • Iloprost • Treprostinil • Phosphodiesterase type 5 inhibitors • Sildenafil • Tadalafil • Endothelin receptor antagonists • Bosentan • Ambrisentan • Macitentan • Soluble guanylate cyclase stimulators • Riociguat

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. In the last decade, specific targeted therapies have been developed and have improved survival in adult patients with PAH. These therapies have also benefited children with PAH. The most common etiologies of PAH in children differ from the adult population. PAH is associated with congenital heart disease, idiopathic PAH (formerly known as primary PH), and heritable PAH in the majority of children. Unrepaired congenital heart diseases, such as ventricular septal defects or a patent ductus arteriosus and more complex diseases like truncus arteriosus or single ventricle physiology may cause PAH. Although PAH associated with congenital heart disease resolves in most children after early surgical correction, some children develop irreversible pulmonary vascular disease. Thus, the natural history of PAH due to congenital heart disease has a wide range of survival. In contrast to congenital heart disease, the survival rate in children with idiopathic or heritable PAH is worse. The diagnosis of idiopathic PAH is difficult as the symptoms are non-specific and include breathlessness, syncope, or seizures. Unfortunately, there are limited data on treatment strategies in children with PAH due to the small number of randomized controlled clinical trials evaluating the safety and efficacy of specific treatments. Currently
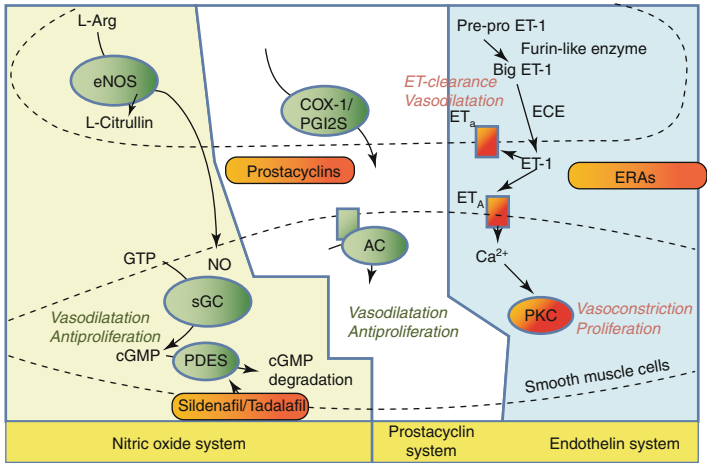
FIGURE 12.1 Pulmonary arterial hypertension therapies including nitric oxide, prostaglandin, or endothelin-1 pathways

approved PAH therapies impact one of three endothelial-based pathways including nitric oxide, prostaglandin, or endothelin-1 (Fig. 12.1) [1]. This chapter summarizes currently available therapies based on adult data and a limited number of clinical trials in children with PAH.

12.1 Calcium Channel Blockers

12.1.1 Indication and Clinical Trials

In the past, calcium channel blockers (CCBs) were used primarily due to the absence of other available therapy. Recent data suggests, CCB treatment for PAH is only indicated and efficacious in 10–30 % of children [2]. "Responders" to vaso-reactivity testing at cardiac catheterization may have a good response to treatment with calcium channel blockers, but "nonresponders" should not be treated with CCBs as they are associated with worse survival and may lower cardiac output. Although the exact definition of vasoreactivity in

children is not known, more children are considered vasore-active than adults using the revised pediatric definition (a fall in mean pulmonary artery pressure and pulmonary vascular resistance index by 20 % with no change or an increase in cardiac output) as opposed to the current adult definition (fall in mean pulmonary artery pressure of at least 10 mmHg to a value below 40 mmHg). The beneficial effects of CCBs have been reported in pediatric and adult patients with PAH [2, 3], but patients should be monitored closely as they may deteriorate later in the disease process.

12.1.2   Mechanism of Action

Calcium channel antagonists inhibit calcium flux into cardiac and smooth muscle by binding to the calcium channels and may decrease cardiac contractility. The effects on systemic blood pressure are consequence of a dose-related decrease of systemic vascular resistance.

12.1.3   Dosing

Nifedipine, diltiazem, and amlodipine are used as PAH therapy, while verapamil is contraindicated in PAH. In pediatric patients, oral nifedipine is initiated at 0.5–1.0 mg/kg/day divided three times daily with a maximum dose of 2–5 mg/kg/day divided three times daily if tolerated. Oral diltiazem is initiated at 1.5–2.0 mg/kg/day divided three times daily with a maintenance dose of 3–5 mg/kg/day divided three times daily if tolerated. Oral amlodipine is initiated at 0.1–0.3 mg/kg/day with maintenance dose of 2.5–5.0 mg/day daily to twice daily.

12.1.4   Pharmacokinetics

Pharmacokinetic data is available only for the children with pulmonary hypertension and bronchopulmonary dysplasia

[4]. In children who treated with nifedipine (single oral dose of 0.5 mg/kg), the mean time to maximum plasma concentration were 1.0 ± 0.8 h and the mean $t_{1/2}$ was 1.8 ± 0.8 h. All three CCBs undergo significant hepatic metabolism via the CYP3A4 enzyme system [5].

12.1.5   Monitoring Parameters

High dose CCBs have a potential risk for systemic hypotension.

12.1.6   Adverse Effects

The side effects include headache, constipation, dizziness, fatigue, nausea, edema, rash, gum hyperplasia, bradycardia, and systemic hypotension.

12.1.7   Precautions

Children who have low blood pressure should not receive CCBs. Do not use in patients with low cardiac output or high right atrial pressure. Use in neonates and infants is controversial.

12.1.8   Drug-to-Drug Interactions

Concomitant use of nifedipine with inhibitors of CYP3A4 should be cautioned.

12.1.9   Administration

Although nifedipine, amlodipine, and diltiazem have been used for treatment of pulmonary hypertension, there are no large series of patients comparing these three agents.

12.2   Prostacyclin

Prostacyclin, a member of the endogenous prostanoid family, is a potent vasodilator and has anti-thrombotic, anti-proliferative, and anti-inflammatory effects. Prostacyclin is produced from arachidonic acid in the vascular endothelium [6]. The elaborated prostacyclin has an extremely short biological half-life of between 2 and 3 min in the pulmonary circulation. The biological functions of prostacyclin are mediated by cell-surface G-protein receptors on pulmonary endothelial cells or platelets and increased intracellular cyclic adenosine monophosphate, leading to activation of protein kinase A. Protein kinase A contributes to smooth muscle relaxation and inhibition of platelet aggregation [7]. Prostacyclin metabolites and prostacyclin synthase are decreased in PAH [8–10].

12.3   Epoprostenol

12.3.1   Indication and Clinical Trials

Epoprostenol was Food and Drug Administration (FDA) approved in 1995 and is indicated for the treatment of adult PAH patients to improve exercise tolerance and survival. The pivotal randomized, open-label studies included primarily patients with idiopathic PAH or PAH associated with connective tissue disease with New York Heart Association (NYHA) functional class III-IV symptoms [11–13]. Although epoprostenol is not approved in children, continuous intravenous epoprostenol therapy is effective for improving symptoms, hemodynamics, and survival in children with idiopathic PAH or PAH associated with congenital heart disease [2, 14–16].

12.3.2   Mechanism of Action

Epoprostenol is a prostacyclin analogue with anti-proliferative, anti-platelet and vasodilatory effects on the pulmonary and systemic vascular beds.

12.3.3   Dosing

Intravenous epoprostenol is initiated at 1–3 ng/kg/min and the dose is rapidly increased over the first few days, then steadily increased by 1–2 ng/kg/min every 1–2 weeks if tolerated [17]. Due to the complicated nature of dose titration, epoprostenol therapy should be initiated during hospitalization by a pulmonary hypertension specialist. Further dose titration can be managed on an outpatient basis with the goal to maximize efficacy while side effects remain tolerable. Stable doses in children of 50–80 ng/kg/min are usually attained around 1 year after therapy initiation, with further up titration on an individual basis.

12.3.4   Pharmacokinetics

Epoprostenol has a rapid onset of action, reaching plasma steady-state concentrations within 15 min. Epoprostenol is obligated to a continuous intravenous therapy due to the elimination half-life of approximately 2–3 min. In human blood, epoprostenol is rapidly hydrolyzed and metabolized to 6-keto-PGF1α. This metabolite is biologically inactive and eliminated in the urine [18, 19].

12.3.5   Monitoring Parameters

Systemic blood pressure, heart rate, and side effects should be monitored at initiation of administration.

12.3.6   Adverse Effects

Side effects are generally related to vasodilation and are dose-dependent. The most common side effects include flushing, headache, nausea, diarrhea, jaw discomfort with first bite when eating, foot pain, rash, and thrombocytopenia [20, 21]. Although these symptoms are well tolerated in most cases, the severity is variable.

12.3.7   Precautions

Severe adverse events such as bradycardia, systemic hypotension, and thrombocytopenia resulting from insufficient or excessive dosage of epoprostenol may occur. Patients with pulmonary veno-occlusive disease or pulmonary vein disease may develop life threatening pulmonary edema. Patients with pneumonia or other parenchymal lung disease may develop worsening ventilation-perfusion matching.

12.3.8   Drug-to-Drug Interactions

Epoprostenol inhibits platelet aggregation and has antihypertensive effects. Therefore, co-administration of epoprostenol with anticoagulants or platelet inhibitors may exacerbate bleeding, and use with other vasodilators may worsen hypotension.

12.3.9   Administration

Epoprostenol is administered as a continuous intravenous infusion. Due to rapid biotransformation, epoprostenol requires a permanent central venous catheter and a portable infusion pump. The drug powder is mixed with an alkaline buffer (pH of 10.2–10.8) and requires daily preparation. The solution is stable for 8 h at room temperature, and 24 h if kept cold with ice packs. A formulation of epoprostenol that is stable at room temperature was FDA approved in 2010. Serious complications of epoprostenol include sepsis, resulting from infection of the indwelling catheter, and "rebound" pulmonary hypertension on acute discontinuation. Dyspnea, chest pain, pallor, and syncope may result from insufficient drug delivery. Patients with marked improvement in hemodynamics to normal or near normal levels have been successfully transitioned from intravenous epoprostenol to oral or inhaled targeted PAH therapy

without deterioration of clinical and hemodynamic parameters [16, 22]. Concomitant use of bosentan has allowed a reduction of epoprostenol dose and decreased its associated side effects with stabilization of hemodynamics [16]. In an adult randomized trial of epoprostenol with or without sildenafil, the addition of sildenafil to epoprostenol therapy improved exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life, although increased rates of headache and dyspepsia occurred with the addition of sildenafil [23].

12.4   Iloprost

12.4.1   Indication and Clinical Trials

Inhaled iloprost was FDA approved in 2004 for the treatment of adults with PAH to improve a composite endpoint consisting of exercise tolerance, functional class symptoms, and lack of deterioration [24]. Studies establishing efficacy were conducted primarily in adult patients with NYHA functional Class III and IV symptoms and etiologies of idiopathic/heritable PAH or PAH associated with connective tissue disease. Although iloprost is not approved in children, several studies have evaluated the use of aerosolized iloprost in children with PAH [17, 25–30]. There is currently only one study showing chronic iloprost efficacy in children with idiopathic PAH or PAH associated with congenital heart disease [25]. In this study, iloprost caused sustained functional improvement in select children with PAH, however, bronchoconstriction led to discontinuation in some patients.

12.4.2   Mechanism of Action

Iloprost is a synthetic prostacyclin analogue which has vasodilatory and platelet inhibitory properties with an elimination half-life of 20–25 min [31].

12.4.3   Dosing

The recommended starting dose is 2.5 mcg of inhaled iloprost and may be increased to 5.0 mcg per inhalation in adult patients. Iloprost should not be taken less than 6 times per day and is allowed up to a maximum of 9 times per day (no more than every 2 h while awake). Although the clinically effective dose of inhaled iloprost is not established in children, a recent study suggested that the initial dose of iloprost 2.5 mcg inhaled 5–9 times daily, could be increased to 5 mcg per inhalation, and could be maintained at that dose for chronic therapy [25]. Some patients have tolerated 7.5 mcg per inhalation. Compliance in children may be difficult given the frequency of dosing and time to deliver each treatment.

12.4.4   Pharmacokinetics

The maximum serum concentration is achieved at 5–10 min after inhalation. The serum elimination half-life of inhaled iloprost is 6.5–9.4 min with a pharmacodynamic half-life of 21–25 min [32]. Approximately 80–90 % of metabolites are eliminated in the kidney.

12.4.5   Monitoring Parameters

Bronchospasm and cough should be monitored after administration.

12.4.6   Adverse Effects

Common adverse events include headache, cough, flushing, jaw pain, and diarrhea [24, 25, 32, 33]. Less common adverse events include rash, and hypotension. Lower airway reactivity is a problem in some children. In most cases, these side effects are mild-to-moderate in severity and do not require discontinuation of therapy [25, 34].

12.4.7   Precautions

Inhaled iloprost requires caution in patients with concomitant pulmonary disease such as asthma and interstitial lung disease. The liver and kidney metabolize iloprost, and dosage adjustments may be necessary in hepatic or renal insufficiency. However, there is a lack of dosing and safety data for the use of iloprost in patients with bilirubin level greater than 3-mg/dl or creatinine clearance less than 30 ml/min.

12.4.8   Drug-to-Drug Interactions

No serious bleeding events have been noted in patients during co-administration with warfarin. There are no significant drug-to-drug pharmacokinetic interactions between iloprost and other pulmonary vasodilators [2].

12.4.9   Administration

Inhaled iloprost is provided in glass ampules containing 10 or 20 mcg/ml and remains stable at room temperature in ambient light at a pH of 7.4. The medication is inhaled over 10 min using the breath actuated I-neb Adaptive Aerosol Delivery System (Philips Respironics, Respiratory Drug Delivery Ltd., Chichester, UK). The 20 mcg/ml extracts 5 mcg from one ampule, whereas the 10 mcg/ml extracts 2.5 mcg or 5 mcg based on the computer disc chip slotted into front of the I-neb device.

12.5   Treprostinil

12.5.1   Indication and Clinical Trials

Treprostinil has four delivery options and is FDA approved for subcutaneous (2002), intravenous (2004), inhaled (2009), and oral (2013) administration in adults with PAH to diminish

symptoms associated with exercise [35–38]. The pivotal subcutaneous study was conducted primarily in patients with NYHA Class II-IV symptoms and etiologies of idiopathic or heritable PAH, PAH associated with connective tissue disease or congenital systemic-to-pulmonary shunts [35]. Intravenous treprostinil therapy received FDA approval based upon bioequivalence. The inhaled treprostinil study included primarily NYHA Class III patients with idiopathic PAH or PAH associated with connective tissue disease [36]. Treprostinil therapy is not approved in the pediatric population. However, recent studies have demonstrated safety in transitioning pediatric patients from epoprostenol to subcutaneous or intravenous treprostinil therapy for the advantages of stability at room temperature and a longer half-life as compared to epoprostenol [39, 40]. Inhaled treprostinil has been studied acutely and in the long-term in children [41, 42]. Oral treprostinil improved exercise capacity in adult PAH patients not receiving other treatment [113], but not in those on background ERA and PDE-5 therapy [114].

12.5.2   Mechanism of Action

Treprostinil is a prostacyclin analogue with anti-proliferative, anti-platelet and vasodilatory effects on the pulmonary and systemic vascular beds.

12.5.3   Dosing

Intravenous and Subcutaneous Infusion

Intravenous and subcutaneous treprostinil are generally initiated at 1.25–2 ng/kg/min and the dose is gradually increased based upon signs and symptoms of PAH and side effects. A stable dose is usually in the range of 50–80 ng/kg/min. Typically, doses of intravenous treprostinil are higher than intravenous epoprostenol [40, 43].

Inhaled

Inhaled treprostinil is dosed in breaths (1 breath = 6 mcg treprostinil). In adults, the starting dose of inhaled treprostinil is 3 breaths (18 mcg) 4 times per day, given approximately 4 h apart during waking hours. The dose is generally increased by an additional 3 breaths every 1–2 weeks as tolerated to a target maintenance dose of 9 breaths (54 mcg) per treatment. Smaller children (<20 kg) should be monitored for systemic hypotension and may require slower up titration of 1 breath every 2–4 weeks with an initial target maintenance dose of 5–6 breaths (30–36 mcg) per treatment [41, 42].

Oral

Oral treprostinil has not been studied in children. In adults, the starting dose is 0.25 mg twice a day with food. Increase as tolerated by clinical response by increments of 0.25–0.5 mg twice a day every 3–4 days; if 0.25 mg increase4s are not tolerated, increase by 0.125 mg. The total daily dose can be divided and given three times a day with food. The maximum dose is determined by tolerability. The maximum doses studied were 12 mg twice a day the the 12-week blinded study and 21 mg twice a day in the open-label long term study. Tablets should be swallowed whole and not crushed or chewed or split.

12.5.4   *Pharmacokinetics*

Intravenous and Subcutaneous Infusion

Intravenous and subcutaneous treprostinil are bioequivalent with a terminal elimination half-life of approximately 4.5 h. Treprostinil is rapidly and completely absorbed with subcutaneous infusion. Steady-state concentrations occur in 10 h. Ninety-one percent of treprostinil is bound to human plasma protein [44–47].

Inhaled

> The terminal elimination half-life of inhaled treprostinil cannot be estimated given the low plasma concentration achieved as compared with parenteral treprostinil due to direct lung delivery. Patients requiring high dose parenteral treprostinil ≥15 ng/kg/min should not be transitioned to inhaled treprostinil given the decreased exposure. Inhaled treprostinil T_{max} is achieved in 5–10 min.

Oral

> The oral bioavailability of oral treprostinil is 17 %. Maximum treprostinil concentrations occur between approximately 4 and 6 hours following oral treprostinil administration. The absorption of oral treprostinil is affected by food. A three times a day regimen reduces peak-to-trough fluctuations.

12.5.5   Monitoring Parameters

Systemic blood pressure, heart rate, and side effects should be monitored with intravenous treprostinil initiation, thus requiring in hospital initiation. In contrast, inhaled treprostinil has less systemic effects and has been started in the outpatient setting in stable patients as add-on therapy.

12.5.6   Adverse Effects

Intravenous Infusion

> Major side effects of treprostinil include headache, diarrhea, nausea, rash, flushing, jaw pain, and foot pain. Following transition from epoprostenol to IV treprostinil, children exhibited less prostanoid side effects, with the exception of leg muscle pain [40].

Subcutaneous

> Prostanoid side effects noted with intravenous treprostinil are similar to subcutaneous administration. In addition, infusion site pain and reaction are the most common side effects, which can negatively impact tolerability.

Incidence and severity of site pain appears to improve 5–7 days after subcutaneous catheter placement and by maintaining the infusion volume as low as possible (<1 ml/24 h). Additional pain mitigation techniques may also include: initiation of systemic H1 and H2 histamine blockers, such as famotidine and cetirizine, placing a "dry" site without medication 24 h prior to infusion start, application of topical anti-inflammatory agents such as fluticasone prior to site initiation, and administration of oral analgesics during the first 5–7 days of a new site.

Inhaled

The most common side effects include cough, headache, throat irritation, nausea, and flushing. Inhaled treprostinil has potential risk of worsening respiratory symptoms in patients with reactive airway disease [24].

Oral

The most common side effects of oral treprostinil are headache, nausea, and diarrhea.

12.5.7   Precautions

The clearance of treprostinil is decreased in patients with hepatic insufficiency. Therefore, cautious dosing may be required in patients with liver disease. Gram- negative bacteremia has been associated with intravenous treprostinil therapy. The use of protected connections and an alkaline buffer may decrease the risk [48, 49].

12.5.8   Drug-to-Drug Interactions

Treprostinil has no pharmacokinetic interactions with endothelin receptor antagonists or phosphodiesterase inhibitors. Treprostinil inhibits platelet aggregation and has hypotensive effects. Therefore, co-administration of treprostinil may have a potential risk of bleeding and systemic hypotension in children receiving concomitant drugs [50].

12.5.9   Administration

Treprostinil may be given subcutaneously, intravenously, inhaled or orally. Intravenous treprostinil requires a permanent central venous catheter and may be infused with one of three ambulatory pumps. The stability at room temperature (no ice packs), longer half-life, and smaller pump options are seen as advantages. Subcutaneous treprostinil offers the advantage of no central venous catheter. A single vial of treprostinil may be used up to 30 days after initial use. Inhaled treprostinil must be administered with the Optineb-ir device and is supplied in plastic 2.9 ml ampules containing 1.74 mg of treprostinil (0.6 mg per ml). One ampule is utilized daily.

12.6   Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 (PDE-5) is abundantly expressed in lung and penile tissue; in PAH the PDE-5 enzyme is increased in the lung vasculature. PDE-5 inactivates cyclic guanosine monophosphate (cGMP) leading to attenuated vasodilation [51]. PDE-5 inhibitors have antiproliferative, proapoptotic, and vasodilating effects in pulmonary vasculature through an increase in cGMP [52]. PDE-5 inhibitors, including sildenafil and tadalafil, have been approved for PAH in adult patients.

12.7   Sildenafil

12.7.1   Indication and Clinical Trials

Sildenafil citrate was FDA approved in 2005 for the treatment of adult PAH to improve exercise ability and delay time to clinical worsening at a dose of 20 mg three times daily. The pivotal study included primarily patients with WHO Functional Class II-III symptoms with idiopathic PAH or PAH associated with connective tissue disease [53]. Although sildenafil is approved for use in children with PAH in Europe, sildenafil is not approved for children with PAH in the

United States. The *STARTS-1* trial was a worldwide randomized, double blind, placebo-controlled study of 234 treatment naïve children [54]. In the 16-week study, children received low, medium or high doses of sildenafil or placebo orally three times daily. The primary endpoint, estimated mean ± standard error percent change in peak oxygen uptake (VO_2) during cycle ergometry, for the low, medium and high doses combined versus placebo was 7.7 % ±4.0 % (95 % CI, –0.2–15.6 %; $p = 0.056$). Thus, the pre-specified primary outcome measure was not statistically significant. Peak VO_2 only improved with the medium dose. Secondary outcomes showed a varied response to sildenafil. Functional capacity only improved with high dose sildenafil. PVRI improved with medium and high dose sildenafil, but mean PAP was lower only with medium dose sildenafil. A long-term extension study (*STARTS-2*) has been completed in children on sildenafil monotherapy [55, 56]. For the first 2 years, survival on sildenafil monotherapy was similar for all dosage groups. At 3 years, an increase in mortality was noted at the higher doses, and the data safety monitoring board requested a decrease in the dose of any child receiving high dose. Deaths in the extension study were related to etiology and baseline disease severity. The majority of deaths occurred in patients with idiopathic PAH and familial PAH, and most had baseline values above median values for pulmonary vascular resistance, mean pulmonary artery pressure, and right atrial pressure. Intravenous sildenafil has also been studied in children. A double-blind, multicenter, placebo-controlled study of intravenous sildenafil in pediatric patients with congenital heart disease and postoperative pulmonary hypertension showed favorable results such as shorter time to extubation and intensive care unit stay, although the study was stopped early due to poor enrollment [57].

12.7.2   Mechanism of Action

Sildenafil is a potent PDE-5 inhibitor that increases cGMP in the pulmonary smooth muscle vasculature. PDE-6 is also inhibited at therapeutic doses.

12.7.3   Dosing

Oral sildenafil, 20 mg three times daily, was approved for the treatment of adults with PAH. Although there is no recommended dosage for children with PAH, the dose approved in Europe is 10 mg three times a day for children under 20 kg, and 20 mg three times a day for children over 20 kg. Definitive dosing guidelines have not been established in the United States, but doses of 0.5–2.0 mg/kg TID are considered to provide significant therapeutic benefit in children [3, 9, 10]. Some centers have dosed neonates QID. An oral suspension of sildenafil (2.5 mg/ml) is stable for 91 days at room temperature with no change in pH, odor, or physical appearance [11]. Intravenous infusions of sildenafil at 0.07–1.64 mg/kg/day have been use in neonates [12]. Intravenous sildenafil is supplied as 0.8 mg/ ml [13].

12.7.4   Pharmacokinetics

Oral sildenafil citrate is absorbed rapidly after oral administration during fasting. The mean absolute bioavailability is 40 % [10]. Maximum plasma concentrations are achieved 60 min after administration, with a half-life of approximately 4 h in adults. When taken with food, the rate of absorption is slowed, with time to C max delayed by 1 h. Metabolism of sildenafil occurs primarily by hepatic cytochrome P450 (CYP) enzymes such as CYP3A4 and CYP2C9. CYP3A4 inducers, and medications such as bosentan, decrease the levels of sildenafil, thus monitoring may be advisable with co-administration with CYP3A4 inducers [14]. Alternatively, CYP3A4 inhibitors increase serum concentrations of sildenafil. N-desmethyl sildenafil is an active metabolite of sildenafil is believed to account for 20 % of its pharmacological effects. Sildenafil and its metabolite are 96 % bound to plasma proteins.

12.7.5   Monitoring Parameters

Oral sildenafil has less systemic effects and has been started in the outpatient setting. Eye screening in extremely premature

infants should be considered. In addition, hearing evaluation should be considered.

12.7.6   Adverse Effects

The most frequent adverse events include headache, agitation, flushing, rhinitis, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, back pain, and visual disturbances [53]. Serious adverse effects requiring drug discontinuation occur infrequently [58, 59]. Inhibition of PDE-6 at therapeutic sildenafil levels produce dose-related ocular effects including blurred vision, changes in light perception, and transient blue-green visual abnormalities [58, 59]. Sildenafil has been associated with hearing loss [60–63]. The association between use of high-dose sildenafil and late death in children on sildenafil monotherapy is being explored [55].

12.7.7   Precautions

Patients with a creatinine clearance less than 30 ml/min, hepatic cirrhosis, or concomitant use of CYP3A4 inhibitors may require a reduction in their sildenafil dose [64]. Although serum levels can rise in severe impairment of renal or hepatic function, dosage adjustments are usually not necessary. Sildenafil should not be used concomitantly with systemic nitrates.

12.7.8   Drug-to-Drug Interactions

Co-administration of sildenafil with bosentan leads to decreased sildenafil plasma concentrations and increased bosentan concentrations [65]. Bosentan decreases the maximum plasma concentration (Cmax) of sildenafil by 55.4 % and the area under the plasma concentration versus time curve over a dosing interval (AUC) by 62.6 %, whereas sildenafil increases the Cmax of bosentan by 42.0 % and AUC by 49.8 %. The recommendations of dose adjustment are not

available, but caution is advised. There is no significant pharmacokinetic interaction between sildenafil and warfarin.

12.7.9 Administration

Sildenafil is administered orally. Due to the short half-life, sildenafil may require multi-dose regimens and the currently approved dose of 20 mg 3 times daily for adult patients may be inadequate for some patients.

12.8 Tadalafil

12.8.1 Indication and Clinical Trials

Tadalafil, a long-acting PDE-5 inhibitor, is a once-daily alternative to sildenafil and was FDA approved for adults in 2009. Tadalafil is currently approved for the treatment of adult PAH (World Health Organization (WHO) Group 1) to improve exercise ability. A double-blind, placebo-controlled study demonstrated that tadalafil improved exercise capacity, decreased time to clinical worsening, and improved health-related quality of life in adult patients with primarily idiopathic PAH or PAH associated with connective tissue disease and NYHA functional class II-III symptoms [66]. While little is known of the use of tadalafil in children with PAH, a recent retrospective study suggested clinical efficacy and safety in children with PAH [67]. In this study, 33 pediatric patients with PAH were retrospectively evaluated and 29 of 33 patients who transitioned from sildenafil (3.4 ± 1.1 mg/kg/day) to tadalafil (1.0 ± 0.4 mg/kg/day) successfully continued tadalafil therapy without the need to return back to sildenafil. Only 2 patients stopped tadalafil due to side effects including migraine and allergic reaction (discontinuation rate 6 %). Furthermore, tadalafil statistically improved hemodynamic data including mean pulmonary arterial pressure (53.2 ± 18.3 versus 47.4 ± 13.7, $p < 0.05$) and pulmonary vascular resistance index (12.2 ± 7.0 versus 10.6 ± 7.2, $p < 0.05$) compared with sildenafil in

14 of 29 patients with repeated catheterization. An oral suspension (5 mg/ml) is stable for 91 days at room temperature [68].

12.8.2   Mechanism of Action

Tadalafil is a potent inhibitor of PDE-5 and increases the concentration of cGMP, which results in pulmonary vasodilation.

12.8.3   Dosing

Oral tadalafil, 40 mg once daily, was approved for the treatment of adults with PAH. Although pediatric dosing is not available, a retrospective study reported 1.0 mg/kg/day of tadalafil appears to be well tolerated in children [67].

12.8.4   Pharmacokinetics

After a 20 mg tablet was administered in healthy adult subjects, tadalafil was absorbed rapidly with the median time to maximal concentration of 4 h and a half-life of 35 h [69]. Steady-state plasma concentrations are achieved within 5 days of initiation of tadalafil at 20 mg or 40 mg daily. Unlike sildenafil, there does not seem to be any effect from food intake. The hepatic CYP3A4 pathway metabolizes tadalafil.

12.8.5   Monitoring Parameters

Tadalafil has less systemic effects and has been started in the outpatient setting. Use in children less than 4 years has not been described.

12.8.6   Adverse Effects

The most common adverse events include headache, flushing, nasal congestion, dyspepsia, nausea, and myalgia, and were

reported as mild to moderate in severity [66, 67]. Tadalafil has little effect on PDE-6, thus has a minimal influence on visual effects.

12.8.7   Precautions

Co-administration of PDE-5 inhibitors with other vasodilators may lead to hypotension. Concomitant use of potent inducers or inhibitors of CYP3A is not recommended. The dose should be reduced in patients with mild to moderate renal or hepatic impairment. Tadalafil is not recommended in patients with severe renal or hepatic disease, and should not be used in patients taking nitrates. Use in neonates is contraindicated due to lack of maturation of glucuronidation pathway.

12.8.8   Drug-to-Drug Interactions

Tadalafil exposure is decreased with concomitant bosentan by 41.5 % in healthy adult volunteers [70]. No pharmacokinetic drug interactions between tadalafil and ambrisentan have been noted [71].

12.8.9   Administration

Tadalafil administered orally once daily may lead to overall improved compliance for pediatric patients with PAH [67]. Tadalafil can be compounded in suspension [68]. The suspension of tadalafil 5 mg/ml is stable for at least 91 days at room temperature and there are no detectable changes in color, odor, taste, and pH. The absorption and therapeutic effectiveness of a drug in a suspension compounded from crushed tablets are unlikely to differ appreciably from those of the original dosage form.

12.9   Soluble Guanylate Cyclase Stimulators

Soluble guanylate cyclase (SGC) is the only receptor for nitric oxide (NO). SGC is a heterodimer and NO leads to a marked increase in SGC activity. SGC stimulators directly stimulate sGC, both independently of NO and synergistically with NO.

12.10   Riociguat

12.10.1   Indication and Clinical Trials

In October 2013, Riociguat was FDA approved for the treatment of PAH and is the first drug to be approved for the treatment of PH associated with chronic thromboembolic PH. In *Patent-1*, 443 patients with symptomatic pulmonary arterial hypertension were randomized to receive placebo or riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg-maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg-maximum group). After 12 weeks, the 6-min walk distance increased by a mean of 30 m in the 2.5 mg-maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95 % confidence interval, 20–52; $P < 0.001$). Prespecified subgroup analyses showed that riociguat improved the 6-min walk distance both in patients who were receiving no other treatment for the disease and in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance ($P < 0.001$), NT-proBNP levels ($P < 0.001$), WHO functional class ($P = 0.003$), and time to clinical worsening ($P = 0.005$) [72]. In the *CHEST-1* study, 261 patients with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension

after pulmonary endarterectomy were randomized to receive placebo or riociguat. By week 16, the 6-min walk distance had increased by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95 % confidence interval [CI], 25–67; P < 0.001). Pulmonary vascular resistance decreased by 226 dyn.sec.cm (−5) in the riociguat group and increased by 23 dyn.sec.cm (−5) in the placebo group (least-squares mean difference, –246 dyn.sec.cm (−5); 95 % CI, −303 to −190; P < 0.001). Riociguat was also associated with significant improvements in the NT-proBNP level (P < 0.001) and WHO functional class (P = 0.003) [73].

12.10.2   Mechanism of Action

Riociguat stimulates sGC independently of NO and increases the sensitivity of sGC to NO, resulting in increased cGMP levels.

12.10.3   Dosing

Dosing in adults starts at 0.5–1.0 mg three times daily with increases of 0.5 mg three times a day every 2 weeks to a maximum of 2.5 mg three times daily both for PAH and CTEPH.

12.10.4   Pharmacokinetics

Riociguat is rapidly absorbed and maximum plasma concentration is reached between 0.5 and 1.5 h. The mean elimination half-life is 5–10 h.

12.10.5   Adverse Effects

In the *PATENT-1* study, the most common serious adverse event in the 2.5 mg-maximum group was syncope. In the *CHEST-1* study, the most common serious adverse events were right ventricular failure and syncope. Common side effects observed in patients treated with riociguat include

headache, dizziness, indigestion, peripheral edema, nausea, diarrhea and vomiting.

12.10.6   Precautions

Riociguat carries a boxed warning alerting patients and health care professionals that the drug should not be used in pregnant women because it can harm the developing fetus. Patients should not take riociguat with any nitrates or PDE-5 inhibitors as this combination may lead to severe hypotension. Riociguat alters the regulation of bone homeostasis in juvenile rats and the riociguat-related bone findings are of concern with respect to potential pediatric use, especially in infants and younger children. Avoid use in dialysis patients.

12.10.7   Drug-to-Drug Interactions

Riociguat (2.5 mg three times daily) has no pharmacodynamic interaction with warfarin [74].

12.10.8   Administration

Riociguat is given orally three times a day.

12.11   Inhaled Nitric Oxide

12.11.1   Indication and Clinical Trials

Inhaled nitric oxide (NO) is the first line vasodilator treatment for persistent pulmonary hypertension of the newborn [75–78]. NO inhalation therapy has been used for post-operative pediatric PAH associated with congenital heart disease, bronchopulmonary dysplasia, congenital diaphragmatic hernia, and the severe presentation of PAH requiring intensive management [79–82]. Multicenter, randomized clinical studies have demonstrated that inhaled NO reduces the need for extracorporeal membrane oxygenation [77]. Furthermore, inhaled NO is used for the acute vasoreactivity testing during

the assessment of pulmonary hemodynamics at cardiac catheterization [25, 42, 83–85]. Inhaled NO has been used in a few trials of home therapy of PAH [86, 87]. However, the FDA approval for inhaled NO therapy is restricted to newborns with hypoxemic respiratory failure.

12.11.2   Mechanism of Action

NO is produced endogenously from L-arginine by NO synthases. Inhaled NO diffuses rapidly across the alveolar-capillary membrane into the pulmonary smooth muscle. The pathophysiological effects of NO are mediated through the increased intracellular concentrations of cGMP, leading to smooth muscle relaxation.

12.11.3   Dosing

A randomized, placebo-controlled, dose–response trial compared 3 different doses of inhaled NO (5, 20 or 80 ppm) and placebo in term newborns with respiratory failure. In this study, all regimens of inhaled NO improved oxygenation compared to the placebo group, however, there was no difference in responses among the 3 regimens and 35 % of patients who received 80 ppm of inhaled NO had methemoglobinemia. The study suggested that 5–40 ppm of inhaled NO therapy may be appropriate and safe, while sustained treatment with 80 ppm NO increases the risk of adverse events.

12.11.4   Pharmacokinetics

No pharmacokinetic data is available.

12.11.5   Monitoring Parameters

Patients receiving inhaled NO should be monitored for formation of nitrogen dioxide (NO_2) and methemoglobinemia.

NO_2 is easily converted to nitric acid that is highly toxic to the respiratory tract.

12.11.6   Adverse Effects

Methemoglobinemia may occur with sustained high concentrations of inhaled NO (80 ppm) [14, 16]. Inhaled NO combines with hemoglobin and is rapidly oxidized to methemoglobin, leading to tissue hypoxia without cyanosis. The acute withdrawal of inhaled NO therapy may precipitate rebound PAH, which may be ameliorated with the use of PDE-5 inhibitors.

12.11.7   Precaution

NO_2 and methemoglobinemia should be monitored.

12.11.8   Drug to Drug Interaction

No interactions

12.11.9   Administration

NO is administered by mask, nasal cannula, or endotracheal tube. In addition, the monitoring devices for NO and NO_2 concentrations should be used during administration.

12.12   Endothelin Receptor Antagonists

There are three endothelin (ET) isoforms including ET-1, ET-2 and ET-3 [88]. ET-1 is considered the predominant pathophysiological isoform in PAH. The over-expression of ET-1 protein has been demonstrated in patients with PAH [89]. Plasma and lung tissue ET-1 expression are increased in PAH, and correlate with the degree of pulmonary remodeling.

ET-1 is a potent vasoconstrictor and is mediated by 2 types of endothelin receptors including type A (ET_A) and type B (ET_B). Bosentan shows an almost equal affinity for both receptors. In contrast, ambrisentan is highly selective for ET_A. Both ET receptor antagonists (ERA) can improve hemodynamics and survival in adult patients with PAH. Although the use of oral bosentan in pediatric patients with idiopathic or associated PAH has been reviewed previously [8–14], bosentan has not been approved in pediatric populations.

12.13   Bosentan

12.13.1   Indication and Clinical Trials

Bosentan, an oral endothelin ET_A/ET_B receptor antagonist, improves exercise capacity, hemodynamics, and survival in adult patients with PAH [90–92]. Bosentan was FDA approved in 2001 and is recommended as treatment for adult PAH patients. Although the use of oral bosentan in pediatric patients with idiopathic or associated PAH has shown clinical efficacy [93–98], bosentan has not been approved in pediatric populations in the United States. A pediatric formulation is approved in Europe.

In the *BREATHE*-5 study, bosentan was studied in paitens with Eisenmenger syndrome. Bosentan did not worsen systemic oxygen saturation, but reduced PVRI and increased exercise capacity [115].

12.13.2   Mechanism of Action

The ET_A receptor and ET_B receptor on vascular smooth muscle mediates vasoconstriction and cell proliferation in pulmonary vascular smooth muscle cells. The ET_B receptor on endothelial cells mediates vasodilation, antiproliferation, and ET-1 clearance. Bosentan is a highly specific, competitive, dual ET-1 receptor antagonist which binds to ET_A and ET_B receptors [89].

12.13.3   Dosing

Bosentan is available as 62.5 mg and 125 mg tablets for oral administration. In adult patients, bosentan is initiated at 62.5 mg bid with a maintenance dose of 125 mg bid if tolerated [89]. Bosentan doses of 31.25 mg, 62.5 mg, or 125 mg (10–20 kg, >20–40 kg, or >40 kg, respectively) twice daily for 12 weeks significantly improved hemodynamics in pediatric PAH patients (aged 3–15 years) with WHO functional class II or III in a noncomparative, multicenter, pharmacokinetic trial (*BREATHE-3*) [93].

12.13.4   Pharmacokinetics

Bosentan is rapidly absorbed after oral administration and is unaffected by food. In the prospective pharmacokinetic study (*FUTURE-1* trial), bosentan pharmacokinetics were studied after multiple dosages (2 or 4 mg/kg) twice daily in pediatric patients with PAH [99]. The median time to maximum plasma concentration was 3.0 h for both dosing regimens. The mean maximum plasma concentration was 583 and 649 ng/mL in patients receiving 2 or 4 mg/kg twice daily, respectively. In the *BREATHE 3* trial, the mean maximum plasma concentrations were 685, 1,136, and 1,200 ng/mL in children receiving bosentan doses of 31.25 mg, 62.5 mg, or 125 mg twice daily, respectively. The corresponding values for median time to maximum plasma concentration were 2.5, 1.0, and 1.8 h, respectively [93]. Bosentan is metabolized in the liver by CYP2C9 and CYP3A4.

12.13.5   Monitoring Parameters

Although the incidence of serum aminotransferase elevation due to bosentan therapy is low in children [95], liver function tests should be monitored monthly. As bosentan is teratogenic, pregnancy should be tested monthly. Bosentan may cause anemia.

12.13.6   Adverse Effects

Bosentan is generally well tolerated in the pediatric population. In the *FUTURE-1* trial, the most frequent adverse events included abdominal pain, vomiting, chest pain, extremity pain, fatigue, flushing, headache, and nasal congestion [99]. In *BREATHE-3*, the most common adverse events were flushing, edema, and headache [93]. Bosentan has the potential risk of the dose-dependent increases in aminotransaminase levels (>3 times the upper limit of normal (ULN) in 11–14 % and >8 times the ULN in 2–7 % of adults) [89]. In pediatric studies, the incidence of elevated aminotransaminase levels (>3x ULN) were 3 % in extended *FUTURE-2* trial and 16 % in the *BREATHE-3 trial* [93, 95, 99].

12.13.7   Precautions

Bosentan is not recommended in patients with moderate or severe hepatic impairment. Teratogenicity is a significant concern in pregnant women. Decreases in sperm count have been observed in patients taking ERAs. Bosentan may decrease the effectiveness of oral contraceptive agents. ERAs may cause anemia.

12.13.8   Drug-to-Drug Interactions

Concomitant use of bosentan with inhibitors of CYP2C9 or CYP3A4 should be cautioned [94]. The pharmacokinetics of bosentan was not affected by coadministration with warfarin. Because sildenafil inhibits CYP3A4 activity, the coadministration of sildenafil leads to an increase in bosentan concentrations [100]. Likewise, bosentan reduces the concentration of sildenafil. Therefore, adjusting the dose

of sildenafil or bosentan should be considered in patients treated with combination therapy.

12.13.9   Administration

Bosentan is administered orally, twice a day. Bosentan is available as 62.5 and 125 mg tablets.

12.14   Ambrisentan

12.14.1   Indication and Clinical Trials

Ambrisentan is an oral ERA with selective affinity for the ETA receptor and was approved as treatment for adult patients with WHO functional class in 2007. The *ARIES* trials demonstrated efficacy and safety of ambrisentan through improvements in exercise tolerance, WHO functional class, and Borg dyspnea score, with a good safety and tolerability profile [101, 102]. The clinical efficacy and safety of ambrisentan therapy has not been well studied in children with PAH. A recent retrospective study suggested clinical efficacy and safety of ambrisentan in 38 children with PAH [103]. In this study, 15 of 38 patients were switched from bosentan to ambrisentan. The remaining 23 children were treated with ambrisentan as adjunctive therapy due to disease progression. In the 23 patients who underwent catheterization, ambrisentan therapy improved pulmonary arterial pressure (transition; 55 ± 18 versus 45 ± 20 mmHg, n = 10, *p = 0.04*, add-on; 52 ± 17 versus 45 ± 19 mmHg, n = 13, *p = 0.03*) and WHO functional class in 31 % of patients with no elevation of aminotransferase levels. Furthermore, ambrisentan therapy allowed 14 of 15 patients to be successfully switched from bosentan to ambrisentan. In Eisenmenger syndrome, short-term use of ambrisentan in 17 patients improved 6-min walk distance without causing a decrease in systemic saturation [104].

12.14.2   Mechanism of Action

Affinity for the ET_A receptor by ambrisentan is 4,000-fold greater than its affinity for the ET_B receptor [102, 105]. The possible impact of higher selectivity for the ETA receptor includes greater vasodilation and preserved ET-1 clearance.

12.14.3   Dosing

In adult patients, ambrisentan is initiated at 5 mg once daily and may be increased to 10 mg once daily if tolerated [102, 105]. Although the pediatric dose is not available due to insufficient clinical data, a current retrospective study demonstrated pediatric patients could be started on ambrisentan at 2.5 mg (<20 kg) or 5 mg (≥20 kg) and considered for an up-titration to the 5–10 mg dose if tolerated.

12.14.4   Pharmacokinetics

Ambrisentan is rapidly absorbed after oral administration with mean time to maximal concentrations of 1.7–3.3 h [71, 106, 107]. The pharmacokinetics of ambrisentan is not affected by food intake. Steady state is achieved after 3–4 days of therapy. The half-life of ambrisentan is approximately 15 h for the 5 mg once daily dosing in adults patients. The primary metabolic pathway of ambrisentan is hepatic glucuronidation. Ambrisentan is also metabolized by CYP3A4 and CYP2C19 isozymes [71, 106, 107]. A current pediatric study evaluated exposure to ambrisentan at doses from 2.5 to 10 mg; the mean Cmax was 737.7 ± 451.5 ng/ml, mean time to peak plasma concentration was 3.2 ± 2.1 h, and mean AUC was 6656.8 ± 4245.5 ng·h/ml, which were similar to those in adult studies [103].

12.14.5   Monitoring Parameters

The incidence of elevated hepatic aminotransferase levels was 2.8 % in the *ARIES* study and was similar to the placebo group [102, 105]. Monthly liver function testing for ambrisentan is no longer on the FDA label, but most pediatric centers still perform routine monitoring, every 3–4 months. Pregnancy should be tested for monthly.

12.14.6   Adverse Effects

Ambrisentan was generally well tolerated in clinical studies. In the *ARIES* study, the most frequent adverse events included peripheral edema, nasal congestion, upper respiratory tract infection, headache, flushing, and nausea [102, 105]. Side effects were not dose-dependent. In the pediatric study, 5 of 38 patients (13 %) discontinued ambrisentan due to severe headache, lack of clinical efficacy, or near syncope [103].

12.14.7   Precautions

Ambrisentan is not recommended in patients with moderate or severe hepatic impairment. No pharmacokinetic change in ambrisentan levels was found in mild or moderate renal impairment (creatinine clearance, 20–150 ml/min). There is no information in patients with severely reduced renal function with creatinine clearance of <20 mL/min. Teratogenicity is another effect of ERAs. The effects of ambrisentan on embryo-fetal abnormalities were observed in animal model, but have not been evaluated or published in pregnant women. Ambrisentan is contraindicated in women who are or may become pregnant.

12.14.8   Drug-to-Drug Interactions

Ambrisentan is partially metabolized by CYP3A4 and CYP2C19 and caution should be exercised with concomitant use of medications that are strong inhibitors of CYP3A4 or CYP2C19. Administration of ambrisentan with warfarin does not have significant drug interactions. There are no drug-to-drug interactions between ambrisentan and sildenafil [71, 107–109].

12.14.9   Administration

Ambrisentan is administered orally, once daily. Ambrisentan is available as 5 and 10 mg tablets.

12.15   Macitentan

12.15.1   Indication and Clinical Trials

Macitentan, an oral endothelin ET_A/ET_B receptor antagonist was approved in october 2013 for the treatment of PAH. In the pivotal trial, patients were randomly assigned to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg [110]. Stable use of oral or inhaled therapy for pulmonary arterial hypertension, other than endothelin-receptor antagonists, was allowed at study entry. The primary end point was the time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension. A total of 250 patients were randomly assigned to placebo, 250 to the 3-mg macitentan dose, and 242 to the 10-mg

macitentan dose. The primary end point occurred in 46.4, 38.0, and 31.4 % of the patients in these groups, respectively. The hazard ratio for the 3-mg macitentan dose as compared with placebo was 0.70 (97.5 % confidence interval [CI], 0.52–0.96; $P = 0.01$), and the hazard ratio for the 10-mg macitentan dose as compared with placebo was 0.55 (97.5 % CI, 0.39–0.76; $P < 0.001$). Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The effect of macitentan on this end point was observed regardless of whether the patient was receiving therapy for pulmonary arterial hypertension at baseline. There are currently no studies in children.

12.15.2   Mechanism of Action

Macitentan is an orally active, non-peptide dual endothelin ET_A and ET_B receptor antagonist for the treatment of pulmonary arterial hypertension.

12.15.3   Dosing

In adult patients, macitentan is initiated at 10 mg once daily.

12.15.4   Pharmacokinetics

The dose-proportionality coefficient beta for C_{max} (95 % CI) was 0.83 (0.79, 0.87) indicating less than dose-proportional pharmacokinetics of macitentan. In plasma, a pharmacologically active oxidative depropyl metabolite, ACT-132577, was found whereas in urine two minor metabolites were detected [111, 112]. The pharmacokinetics of macitentan are dose proportional over a range from 1 to 30 mg after once daily administration.

12.15.5   Adverse Effects

Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, anemia, and bronchitis.

12.15.6   Precautions

ERAs are contraindicated in pregnancy. Obtain baseline liver enzymes and monitor as clinically indicated. ERAs can cause decreases in hemoglobin. Decreases in sperm count have been observed in patients taking ERAs. There are currently no studies in children with macitentan.

12.15.7   Drug Interactions

Strong CYP3A4 inducers (rifampin) reduce exposure to macitentan and should be avoided. Strong CYP3A4 inhibitors (ketoconazole, ritonavir) increase exposure to macitentan and should be avoided. Macitentan does not cause clinically relevant changes in sildenafil or warfarin exposure.

12.15.8   Administration

Macitentan is administered orally, once daily. Macitentan is available as 10 mg tablets.

Table 12.1 FDA approved vasodilator therapies for adult patients with PAH (WHO Group 1)

	Brand name	Route	Max FDA Approved dose
Prostacyclin			
Epoprostenol	Flolan® Veletri®	IV	Unknown
Iloprost	Ventavis®	Inhaled	5 µg per inhalation
			6–9 times per day
Treprostinil	Remodulin®	IV/SQ	Unknown
	Tyvaso®	Inhaled	9 breaths (54 µg)
			4 times per day
	Orinetram®	Oral	Unknown
PDE-5 inhibitors			
Sildenafil	Revatio®	Oral	20 mg TID
		IV	10 mg (12.5 ml) TID
Tadalafil	Adcira®	Oral	40 mg per day
sGC stimulators			
Riociguat	Adempas®	Oral	2.5 mg TID
ERA			
Bosentan	Tracleer®	Oral	125 mg BID
Ambrisentan	Letairis®	Oral	10 mg per day
Macitentan	Opsumit®	Oral	10 mg per day

BID two times a day, *ERA* endothelin receptor antagonists, *FDA* Food and Drug Administration, *IV* intravenous, *PAH* pulmonary arterial hypertension, *PDE* phosphodiesterase type 5, *sGC* soluble guanylate cyclase, *SQ* subcutaneous, *TID* three times a day, *WHO* World Health Organization

TABLE 12.2 Treatment options for pediatric PAH. Safety and dosing of these medications is not established in children. None of these drugs are FDA approved for children with PAH

Agent	Dose	Mechanism of action	Side effects	Cautions
Prostacyclin				
Epoprostenol	Initial dose: 1–3 ng/kg/min Maintenance dose: 50–80 ng/kg/min	Increases cAMP Pulmonary/systemic vasodilation Inhibition of vascular remodeling Antiplatelet aggregation	Flushing, headache, nausea, diarrhea, jaw discomfort, foot pain, rash, hypotension, thrombocytopenia	Potential risk of hypotension and bleeding in children receiving concomitant drugs such as anticoagulants, platelet inhibitors, or other vasodilators
Iloprost	Initial dose: 2.5 μg per inhalation, 6 times per day Maintenance dose: 5 μg per inhalation, maximum 9 times per day	Increases cAMP Pulmonary/systemic vasodilation Inhibition of vascular remodeling Antiplatelet aggregation	Cough, headache, flushing, jaw pain, diarrhea, rash, and hypotension	Reactive airway symptoms, hypotension possible at high dose

Treprostinil	*Intravenous/subcutaneous*	Increases cAMP	*Intravenous infusion*	*Intravenous/subcutaneous*
	Initial dose: 1.25–2 ng/ kg/min	Pulmonary/ systemic vasodilation	Similar to epoprostenol but may require higher doses	Similar to epoprostenol
	Maintenance dose: 50–80 ng/kg/min	Inhibition of vascular remodeling	*Subcutaneous*	*Inhaled*
	Inhaled	Antiplatelet aggregation	Pain at the infusion site	Reactive airway symptoms, hypotension possible at high dose
	Initial dose: 3 breaths (18 μg), 4 times per day		*Inhaled*	
	Maintenance dose: 9 breaths (54 μg), 4 times per day		Cough, headache, nausea, dizziness, flushing, throat irritation	
	Oral		*Oral*	
	In Adults, initial dose: 0.125 mmg twice a day or three times a day Three times daily dosing may be better tollerated		Nausea, diarrhea, headach, flushing, jaw pain, extremity pain, hypokalemia, abdominal discomfort	
	Maintenance dose: Increase by 0.125 or 0.25 mg Twice a day or three times a day			

(continued)

TABLE 12.2 (continued)

Agent	Dose	Mechanism of action	Side effects	Cautions
Phosphodiesterase type 5 inhibitor				
Sildenafil	*Oral*	Blocks PDE-5	Headache, flushing, rhinitis, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, back pain, visual disturbances, hearing changes	Caution in concomitant use of CYP3A4 inhibitors reduce clearance of sildenafil
	Initial dose: 0.5 mg/kg/dose	Pulmonary vasodilation		Co-administration of bosentan leads to decreased sildenafil concentrations and increased bosentan concentrations
	Maintenance dose: 1.0–2.0 mg/kg/dose tid	Inhibition of vascular remodeling		Co-administration of nitrates is contraindicated
	Europe:			
	<20 kg 10 mg tid			
	>20 kg 20 mg tid			
	Intravenous			
	0.4 mg bolus over 3 h			
	1.6 mg/kg/day: continuous infusion not to exceed 30 mg/day			

Tadalafil	Preliminary studies suggest 1 mg/kg/day	Blocks PDE-5	Similar to sildenafil	Concomitant use of CYP3A4 inhibitors reduce clearance of tadalafil
	The adult maximum is 40 mg/day	Pulmonary vasodilation	No significant influence on vision	No clinically significant alterations in co-administered bosentan or ambrisentan
		Inhibition of vascular remodeling		Co-administration of nitrates is contraindicated
Soluble guanylate cyclase stimulators				
Riociguat	In adults, initiate treatment at 0.5–1 mg three times a day	Stimulate sGC	Headache, dizziness, dyspepsia, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, constipation	Co-administration of nitrates is contraindicated
	Increase dosage by 0.5 mg/dose three times a day no sooner than every 2-weeks as tolerated to a maximum of 2.5 mg three times a day	Pulmonary vasodilation	Teratogenicity	Co-administration of PDE-5 inhibitors is contraindicated
		Inhibition of vascular remodeling		Contraindicated in females who are pregnant
				In growing rats effects on bone formation were observed, including thickening of the growth plates, disorganized bone formation, and hyperostosis
				There are no studies to date in children
				US: requires risk evaluation and mitigation strategy program for pregnancy

(continued)

TABLE 12.2 (continued)

Agent	Dose	Mechanism of action	Side effects	Cautions
Endothelin receptor antagonist				
Bosentan	2 mg/kg bid	ET_A/ET_B receptor antagonist	Abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, edema, nasal congestion	Monthly pregnancy testing is required for females of child bearing potential
	10–20 kg: 31.25 mg bid	Pulmonary vasodilation	Potential risk of dose-dependent increases in aminotransaminase levels	Monthly monitoring of liver enzymes required
	20–40 kg: 62.5 mg bid	Inhibition of vascular remodeling	Teratogenicity	Not recommended in patients with moderate or severe hepatic impairment
	>40 kg: 125 mg bid		May decrease effectiveness of birth control	Teratogenic; requires birth control
				Anemia
				Caution in concomitant use of CYP3A4 inducers and inducers
				Co-administration of sildenafil leads to decreased sildenafil concentrations and increased bosentan concentrations
				Decreases in sperm count have been observed in patients taking ERAs Requires risk evaluation and mitigation strategy program liver and pregnancy

Ambrisentan	5–10 mg daily	ET$_A$ receptor antagonist	Peripheral edema, nasal congestion, sinusitis, flushing, anemia, asthenia, dizziness, fatigue, fluid retention, heart failure (associated with fluid retention), hypersensitivity, nausea, and vomiting	Monthly pregnancy testing is required for females of child bearing potential
		Pulmonary vasodilation	In clinical trials The incidence of aminotransferase elevations >3 times the ULN were 0 % on ambrisentan and 2.3 % on placebo	Routine monitoring liver enzymes recommended in children, but not mandated in adults
		Inhibition of vascular remodeling	Teratogenicity	Not recommended in patients with moderate or severe hepatic impairment
				Teratogenic: requires birth control
				Anemia
				Caution in concomitant use of cyclosporine
				No drug to drug interactions between ambrisentan and sildenafil or tadalafil
				Decreases in sperm count have been observed in patients taking ERAs
				US: Requires risk evaluation and mitigation strategy program for pregnancy

(continued)

TABLE 12.2 (continued)

Agent	Dose	Mechanism of action	Side effects	Cautions
Macitentan	10 mg per day	ET_A/ET_B receptor antagonist	Nasal congestion, headache, flushing	Monthly pregnancy testing is required for females of child bearing potential
		Pulmonary vasodilation	Anemia	Obtain baseline liver enzymes and monitor as clinically indicated
		Inhibition of vascular remodeling	The incidence of serum aminotransferase elevation is similar to placebo	Strong CYP3A4 inducers (rifampin) reduce exposure to macitentan and should be avoided
			Teratogenicity	Strong CYP3A4 inhibitors (ketoconazole, ritonavir) increase exposure to macitentan and should be avoided
				Teratogenic: requires birth control
				Decreases in sperm count have been observed in patients taking ERAs
				Requires risk evaluation and mitigation strategy program for pregnancy
				No data in children yet

Table 12.3 Metabolism

	CYP3A4	CYP2C9	CYP2C19	Glucuron-idation
PED-5 inhibitors				
Sildenafil	+	+	−	−
Tadalafil	+	−	−	+
sGC stimulators				
Riociguat	+	−	−	−
ERA				
Bosentan	+	+	−	−
Ambrisentan	+	−	+	++
Macitentan	+	−	−	−

ERA endothelin receptor antagonists, *PDE* phosphodiesterase type 5

Table 12.4 Pharmacokinetic Interactions

	Drug to Drug interactions	Pharmacokinetics
Sildenafil	Bosentan	Sildenafil levels decrease by 50 %
	Statin	Bosentan levels increase by 50 %
	Erythromycin	Statin levels decrease
	Cimetidine	Sildenafil levels increase
	Ketoconazole	Sildenafil levels increase
	HIV protease inhibitor (ritonavir)	Sildenafil levels increase
		Sildenafil levels increase
Tadalafil	Bosentan	Tadalafil levels decrease
	Rifampin	Tadalafil levels decrease
	Ketoconazole	Tadalafil levels increase
	HIV protease inhibitor (ritonavir)	Tadalafil levels increase

TABLE 12.4 (continued)

	Drug to Drug interactions	Pharmacokinetics
Riociguat	Rifampin	Riociguat levels decrease
	Ketoconazole	Riociguat levels increase
	HIV protease inhibitor (ritonavir)	Riociguat levels increase
Bosentan	Sildenafil	Sildenafil levels decrease by 50 %
	Tadalafil	Bosentan levels increase by 50 %
	Statin	Tadalafil levels decrease by 42 %
	Erythromycin	Statin levels decrease
	Ketoconazole	Bosentan levels increase
	Hormonal contraceptives	Hormone levels decrease
	Cyclosporine (contraindicated)	Cyclosporin levels decrease by 50 % needs
	Warfarin	May decrease plasma warfarin
Ambrisentan	Sildenafil	No dose adjustment
	Tadalafil	No dose adjustment
	Ketoconazole	No dose adjustment
	Cyclosporine	Ambrisentan levels increase 2-fold
Macitentan	Ketoconazole	Macitentan levels increase
	HIV protease inhibitor (ritonavir)	Macitentan levels increase
	Rifampin	Macitentan levels decrease

ERA endothelin receptor antagonists, *PDE* phosphodiesterase type 5

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Chapter 13
Antithrombotics and Antifibrinolytics

Donald Berry and Sriya Gunawardena

Abstract Pediatric thromboembolic events are rare, but the incidence of thrombosis in children has dramatically increased over the last decade and appears to be an increasing problem in pediatric tertiary care hospitals. They usually occur as a complication of a primary disease or treatment. This chapter describes the indications, mechanisms of action, dose regimens, therapeutic ranges and monitoring requirements, pharmacokinetics, contraindications, adverse effects and warnings, drug interactions and side effects of antithrombotic (anticoagulant, antiplatelet, and thrombolytic) agents and antifibrinolytic agents.

Keywords Antithrombotics • Antifibrinolytics • Anticoagulant agents

D. Berry, BSPharm
Department of Pharmacy,
Children's Hospital of Pittsburgh of UPMC,
Pittsburgh, PA, USA
e-mail: donald.berry@chp.edu

S. Gunawardena, MBBS
Division of Hematology/Oncology, Department of Pediatrics,
Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA

13.1   Antithrombotics

Pediatric thromboembolic events are rare, but the incidence of thrombosis in children has dramatically increased over the last decade and appears to be an increasing problem in pediatric tertiary care hospitals [1]. They usually occur as a complication of a primary disease or treatment.

Thromboembolic events are a significant source of morbidity in survivors of congenital heart disease (CHD), and have a propensity to plague those with single ventricle physiology. Central venous catheters are a major cause of thromboembolic disease in these patients [2]. In addition, many cardiac surgical procedures also increase the risk of thrombosis. Therefore, prophylactic anticoagulant therapy is used in some settings [3]. The thromboembolic events seen in those with cardiac disease include deep venous thrombosis (DVT), intra-cardiac thrombosis, pulmonary embolism and embolism to the central nervous system (CNS).

Antithrombotic drugs, including anticoagulants, antiplatelet drugs and thrombolytics, are used for treatment and prevention of a wide range of thromboembolic events in children with cardiac disease. Because thrombosis episodes are rare in children as compared to adults, there are relatively few clinical trials to support evidence based therapy. Therefore, current treatment/prophylaxis regimens for pediatric thrombosis are either based upon small case series or are extrapolated from adult studies. In addition, some of the routinely used drugs are not approved for use in children and are used off label for these conditions [4].

Due to many factors, the use of antithrombotic drugs in children varies from use in adults. The developing hemostatic system in children affects how they respond to these drugs. The volume of distribution, binding, and clearance of these drugs are age-dependent. Due to limited vascular access, accurate monitoring and drug administration may be difficult. In addition, pediatric formulations of some commonly used antithrombotic drugs are currently not available. Thus, accurate dosing may be difficult in young children. Also, since

breast milk and infant formulas have different vitamin K levels, use of oral vitamin K antagonists such as warfarin may be challenging in neonates and infants.

All thrombi are made of platelets, fibrin, and trapped red blood cells. However, there are important differences between arterial and venous clots and these features are useful when choosing antithrombotic agents. Because arterial thrombi form under high-shear conditions, they are rich in platelets but contain very small amounts of fibrin. Conversely, venous thrombi, which form under low-shear conditions, have increased amounts of fibrin and red blood cells and have fewer platelets.

Antithrombotic drugs target components of both arterial and venous thrombi. Antiplatelet drugs are used mainly for prevention and treatment of arterial clots since they are composed primarily of platelets. Anticoagulants may also be effective in this setting, but they are not commonly used. Anticoagulants are typically used for treatment and prophylaxis of venous thromboembolism because venous clots are largely made of fibrin. Antiplatelet drugs are less effective in preventing venous thrombosis. Thrombolytic agents can be used for rapid restoration of blood flow if there is organ or limb threatening arterial or venous thrombosis [5].

13.2   Antifibrinolytics

Lysine analogs such as aminocaproic acid and tranexamic acid inhibit fibrinolysis. They interfere with the formation of plasmin, a fibrinolytic enzyme from its precursor plasminogen by plasminogen activators such as t-PA. Studies have shown that antifibrinolytics effectively decrease bleeding and the transfusion requirement of pediatric patients undergoing cardiac surgery [6]. The benefit appears to be more significant in certain high risk groups, such as cyanotic patients and those who have had complex surgery or reoperations.

This chapter describes the indications, mechanisms of action, dose regimens, therapeutic ranges and monitoring

requirements, pharmacokinetics, contraindications, adverse effects and warnings, drug interactions and side effects of antithrombotic (anticoagulant, antiplatelet, and thrombo-lytic) agents and antifibrinolytic agents.

13.3   Antithrombotics: Anticoagulants

13.3.1   Argatroban

Indication

> Argatroban is approved in the United States for prophy-laxis or treatment of thrombosis in adults with heparin-induced thrombocytopenia (HIT) and as an adjunct to percutaneous coronary intervention (PCI) in patients who have or are at risk of coronary artery thrombosis associated with HIT.
>
> Off-label use of argatroban includes treatment of cerebral thrombosis and myocardial infarction (MI). It has been used in patients with HIT for anticoagulation during extracorporeal membrane oxygenation (ECMO), con-tinuous renal replacement therapy (CRRT), cardiac catheterization, and hemodialysis.

Mechanism of Action

> Argatroban is a direct, highly selective thrombin inhibitor that reversibly binds to thrombin's active site, inhibiting fibrin formation, activation of coagulation factors V, VIII, and XIII, protein C activation, and platelet aggre-gation. This activity does not rely on antithrombin III as a co-factor.

Dosing

> **Heparin-induced thrombocytopenia treatment and prophylaxis**:
>
> IV Continuous infusion:
>
> **Infants and children ≤16 years**: Dosing information in the pediatric patient population is limited.

Initial dose: 0.75 mcg/kg/min. In patients with reduced hepatic function, start at 0.2 mcg/kg/min.

Maintenance dose: adjust in increments of 0.1–0.25 mcg/kg/min based on aPTT results. In patients with reduced hepatic function, adjust in increments of ≤0.05 mcg/kg/min. Hursting et al. reported a wide range of doses (0.1–12 mcg/kg/min) in pediatric patients for either the prophylaxis or treatment of thrombosis to achieve therapeutic levels of anticoagulation [7].

Adolescents >**16 years and Adults**:

Initial dose: 2 mcg/kg/min. In patients with reduced hepatic function, who are critically ill, or have multiple organ dysfunction, start at 0.5 mcg/kg/min.

Maintenance dose: range 0.1–10 mcg/kg/min.

Pharmacokinetics

Onset: the onset of action begins within 30 min, with peak effects occurring in 1–3 h

Distribution: volume of distribution 174 mL/kg

Protein binding: protein binding to albumin is 20 %, and to α1-acid glycoprotein is 35 %, for a total of 54 % protein binding

Metabolism: hepatic via hydroxylation and aromatization.

Half-life: the elimination half-life of argatroban is 30–51 min and can be as long as 181 min in patients with hepatic impairment. The time to steady state is 1–3 h.

Elimination: excretion is 65 % in feces and 22 % in the urine.

Contraindications

Contraindications to argatroban are hypersensitivity to argatroban or major bleeding.

Warnings

Discontinue other parenteral anticoagulants before starting therapy. Caution should be taken in administering argatroban to patients with increased risk of hemorrhage (immediately after lumbar puncture,

spinal anesthesia, or major surgery; with congenital or acquired bleeding disorders; severe hypertension; or with GI ulcers). Bleeding can occur at any site in the body. Use caution in critically ill patients and patients with hepatic dysfunction.

Adverse Effects

The major adverse effect seen with argatroban therapy is bleeding. Other potential adverse effects with argatroban administration are:

Cardiovascular: hypotension, vasodilation, cardiac arrest, ventricular tachycardia, bradycardia, MI, atrial fibrillation, angina, myocardial ischemia

Central Nervous System: intracranial bleeding, fever, headache, pain

Gastrointestinal: gastrointestinal bleeding, nausea, diarrhea, constipation, vomiting, abdominal pain

Hematologic: decreased hematocrit or hemoglobin,

Renal/GU: genitourinary bleeding, urinary tract infection, abnormal renal function

Other: hypokalemia, dyspnea, cough

Drug/Drug Interactions

Drugs that affect platelet function, such as aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), abciximab, anagrelide, cilostazol, clopidogrel, dipyridamole, eptifibatide, ticlopidine, and tirofiban may potentiate the risk of bleeding. Anticoagulant drugs, such as acenocoumarol, alteplase, antithrombin III, bivalirudin, dabigatran, dalteparin, danaparoid, drotrecogin alfa, enoxaparin, fondaparinux, heparin, hirudin, lepirudin, nadroparin, rivaroxaban, tinzaparin, and warfarin can also cause an increased risk of bleeding.

Monitoring Parameters

For HIT, obtain baseline aPTT before start of therapy and check aPTT every 2 h after initiation of therapy until therapeutic dose has been reached. Adjust the dose,

keeping the steady-state aPTT 1.5–3 times the initial baseline value (not exceeding 100 s). Hemoglobin, hematocrit, signs and symptoms of bleeding, liver function tests, and daily international normalized ratio (INR) (if receiving additional warfarin therapy) should be monitored.

Poisoning Information

A minimum toxic dose of argatroban in humans has not been established. Treatment of possible overdose is symptomatic and supportive, with no specific antidotes available. Monitor for signs of bleeding, vital signs, electrocardiogram, and renal and hepatic function in symptomatic patients. Discontinue or decrease infusion to control excessive anticoagulation with or without bleeding. Reversal of anticoagulant effects may be longer than 4 h in patients with hepatic impairment. Hemodialysis may remove up to 20 % of the drug; however, this is considered clinically insignificant.

Compatible Diluents/Administration

The final concentration for I.V. administration of argatroban is 1 mg/mL. The injectable solution of argatroban may be mixed with NS, D5W, or LR, and may briefly show slight haziness. Do not use if the solution is cloudy. Argatroban should not be mixed with other medications.

13.3.2   Enoxaparin

Indication

Enoxaparin is used for the treatment of thromboembolic disorders, including deep vein thrombosis (DVT), venous thromboembolism (VTE), and acute coronary syndromes. Enoxaparin is also used for thrombosis pro-

phylaxis following hip or knee replacement surgery, abdominal surgery or in any patient with reduced mobility with risk factors for thrombosis, during percutaneous coronary intervention, and as an anticoagulant bridge in patients who need a temporary interruption in vitamin K antagonist therapy.

Mechanism of Action

Enoxaparin is a low molecular weight heparin (LMWH) that potentiates the activity of antithrombin III which primarily inactivates coagulation Factor Xa. Factor IIa (thrombin) activity is also inhibited, but to a much lesser degree than with unfractionated heparin.

Dosing

Children:

(Note: Reference ranges for antifactor Xa levels are between 0.5 and 1 units/mL for treatment and 0.2–0.4 units/mL for prophylaxis) [4].

Initial subQ:

Chest 2012 recommendations:

Infants younger than 2 months:

Prophylaxis: 0.75 mg/kg/dose every 12 h
Treatment: 1.5 mg/kg/dose every 12 h

Infants older than 2 months and children at most 18 years:

Prophylaxis: 0.5 mg/kg/dose every 12 h
Treatment: 1 mg/kg/dose every 12 h

Several recent studies [8–10] suggest these higher initial doses for treatment in neonates:

Premature neonates: Treatment: 2 mg/kg/dose every 12 h
Full-term neonates: Treatment: 1.7 mg/kg/dose every 12 h

Maintenance (see below): Note: in a recent prospective study of 177 courses of enoxaparin in pediatric patients (146 treatment courses and 31 prophylactic courses), considerable variation in maintenance dosage requirements was observed [11, 12] (Table 13.1).

TABLE 13.1 Enoxaparin treatment dosage titration (pediatric)

Antifactor Xa	Dose titration	Time to repeat antifactor Xa level
<0.35 units/mL	Increase dose 25 %	4 h after next dose
0.35–0.49 units/mL	Increase dose 10 %	4 h after next dose
0.5–1 unit/mL	Keep same dose	Next day, then in 1 week, then monthly, each 4 h after dose
1.1–1.5 units/mL	Decrease dose 20 %	Before next dose
1.6–2 units/mL	Hold dose for 3 h and decrease dose 30 %	Before next dose, then 4 h after next dose
>2 units/mL	Hold further doses until antifactor Xa is 0.5 units/mL, then decrease dose 40 %	Before next dose and every 12 h until antifactor Xa measures <0.5 units/mL

Modified from Monagle et al. [13]

Adults: (consider lower doses for patients weighing less than 45 kg)

subQ:

Treatment of acute deep vein thrombosis (DVT) and pulmonary embolism: (initiate warfarin therapy on first or second day of treatment and continue enoxaparin until INR is therapeutic ($\geq$2) for at least 24 h (usually takes 5–7 days)).

Inpatient treatment of acute DVT with or without pulmonary embolism:
1 mg/kg/dose every 12 h or 1.5 mg/kg/dose once daily
Outpatient treatment of acute DVT without pulmonary embolism: 1 mg/kg/dose every 12 h

Prevention of DVT:

Hip or knee replacement surgery: 30 mg every 12 h beginning 12–24 h after surgery if adequate hemostasis obtained
Patients with restricted mobility during acute illness or after abdominal surgery: 40 mg given once daily.

Dosage adjustment in renal impairment: (adult data)

Creatinine clearance (ClCr) at least 30 mL/min: no specific adjustment recommended; monitor patients closely for bleeding

ClCr less than 30 mL/min: monitor antifactor Xa levels

DVT prophylaxis in abdominal surgery, hip replacement, knee replacement, or in medical patients during acute illness, 30 mg subQ once daily

DVT treatment in conjunction with warfarin (in inpatients with or without pulmonary embolism and in outpatients without pulmonary embolism): 1 mg/kg/dose subQ once daily

Pharmacokinetics

Bioavailability: Based on antifactor Xa, enoxaparin is 100 % bioavailable after subQ injection

Onset and Duration: peak activity in 3–5 h and a duration of approximately 12 h

Protein binding: does not cross the placental barrier and does not bind to most heparin-binding proteins

Metabolism: hepatic via desulfation and depolymerization

Half-life (**adults**): 4.5 h for a single dose and 7 h for repeat dosing

Excretion: renally excreted, 40 % as active and inactive fragments and 10 % as unchanged drug

Contraindications

Contraindications to enoxaparin use are hypersensitivity to enoxaparin, heparin, pork products, or benzyl alcohol; patients with active major bleeding; and patients with heparin or low molecular weight heparin induced thrombocytopenia.

Warnings

There is an increased risk of epidural or spinal hematoma with concomitant neuraxial or spinal puncture

and LMWHs; this risk is increased with concurrent use of drugs that impair hemostasis and/or postoperative use of indwelling epidural catheters; enoxaparin should be held for two doses prior to lumbar or epidural procedures. Bleeding or thrombocytopenia may occur with treatment. Use enoxaparin with caution in patients with any increased risk of hemorrhage, recent brain, spinal or ophthalmic surgery, platelet inhibitor therapy, uncontrolled hypertension, or renal impairment.

Adverse Effects

Cardiovascular: atrial fibrillation, heart failure
Central nervous system: fever, confusion, pain
Dermatologic: eczema, skin necrosis
Gastrointestinal: diarrhea, nausea
Hematologic: thrombocytopenia, anemia, bleeding, hemorrhage (major)
Hepatic: increased liver function tests
Local: injection site hematoma, local irritation
Other: anaphylactoid reaction, dyspnea, pneumonia, edema

Drug/Drug Interactions

Anticoagulants, thrombolytic agents (alteplase, streptokinase, and urokinase), and platelet inhibitors (aspirin, salicylates, NSAIDs, dipyridamole, and clopidogrel) may increase the risk of bleeding.

Monitoring Parameters

Baseline labs prior to starting enoxaparin therapy: CBC with platelets, PT/INR, PTT, creatinine, fibrinogen. After starting enoxaparin: Antifactor Xa 4 h after second dose, 4 h after each dose change, and weekly thereafter for inpatients, monthly for outpatients; occult blood daily; CBC with platelets twice weekly for 2 weeks, then every 2 weeks; creatinine twice weekly;

consider monitoring bone density in infants and children with long-term use.

Poisoning Information

Reference ranges for antifactor Xa levels are between 0.5 and 1 units/mL for treatment and 0.2–0.4 units/mL for prophylaxis [4]. Treatment of severe bleeding or an overdose of enoxaparin is supportive. Protamine may be used at a dosage of 1 mg of protamine for each 1 mg of enoxaparin administered if given within 8 h of enoxaparin administration or a dose of 0.5 mg protamine per 1 mg enoxaparin if enoxaparin was given >8 h prior to protamine. A second dose of 0.5 mg protamine per 1 mg enoxaparin may be given if the aPTT continues to be prolonged 2–4 h after the first dose of protamine.

Compatible Diluents/Administration

Do not administer enoxaparin I.M., only subQ.; do not rub injection site as bruising may occur; rotate sites between the left and right anterolateral and left and right posterolateral abdominal wall; enoxaparin dilutions of 20 mg/mL in NS have been used for smaller doses in neonates [14].

13.3.3   Heparin (Unfractionated)

Indication

Heparin is indicated for prophylaxis and treatment of thromboembolic disorders. It is also used for anticoagulation during extracorporeal and dialysis procedures.

Mechanism of Action

Anticoagulation by heparin is mediated by antithrombin III, which primarily inactivates thrombin. In addition, heparin also inactivates activated coagulation factors IX, X, XI, XII, and plasmin, and it also prevents the conversion of fibrinogen to fibrin.

Dosing

Prophylaxis for cardiac catheterization via an artery:

> **Newborns**, **infants and children**: bolus, 100–150 units/kg I.V. Further doses may be required for prolonged procedures.

Systemic heparinization: (loading and infusion dose can be modified based on preexisting conditions)

Neonates and infants <1 year old: I.V. : initial loading dose, 75 units/kg administered over 10 min; initial maintenance infusion dose, 28 units/kg/h; adjust dose to maintain aPTT of 60–85 s (assuming this reflects an antifactor Xa level of 0.3–0.7 units/mL); see also recommendations in Table 13.2.

Children >1 year old: I.V. : initial loading dose, 75 units/kg administered over 10 min; initial maintenance infusion dose, 20 units/kg/h; adjust dose to maintain aPTT of 60–85 s (assuming this reflects an antifactor Xa level of 0.3–0.7 units/mL); see also recommendations in Table 13.2.

TABLE 13.2 Pediatric dosage adjustment table. To be used after initial loading dose and maintenance infusion given as outlined above. Measure aPTT 4 h after infusion started and 4 h after every rate change. Target aPTT goal is 60–85 s assuming this reflects an antifactor Xa level range of 0.3–0.7 units/mL. Actual aPTT goal is institution/lab specific

aPTT (seconds)	Dosage adjustment	Time to repeat aPTT
<50	Give 50 units/kg IV bolus and increase infusion rate 10 %	4 h after rate change
50–59	Increase infusion rate 10 %	4 h after rate change
60–85	No change	Next day
86–95	Decrease infusion rate 10 %	4 h after rate change
96–120	Hold infusion for 30 min and decrease infusion rate 10 %	4 h after rate change
>120	Hold infusion for 60 min and decrease infusion rate 15 %	4 h after rate change

Modified from Monagle et al. [4]

Adults:

Prophylaxis (**low-dose heparin**): subQ, 5,000 units every 8–12 h

Treatment of DVT and PE: I.V.: initial loading dose, 80 units/kg (or 5,000 units); initial maintenance infusion dose, 18 units/kg/h (or 1,300 units/h), with dose adjusted to maintain aPTT of 60–85 s (assuming this reflects an antifactor Xa level of 0.3–0.7 units/mL); usual range, 10–30 units/kg/h

Pharmacokinetics

Bioavailability: absorption of drug when heparin is administered subQ or I.M. is erratic. Peak concentration is reached 2–4 h after subQ administration.

Onset of action: onset of anticoagulation when heparin is administered I.V. is immediate, and is 20–30 min when administered subQ

Distribution: does not cross the placenta and does not appear in breast milk

Protein binding: 95 %

Metabolism: via the liver and through the reticuloendothelial system

Half-life: mean of 90 min and a range of 1–2 h. Factors that can prolong the half-life include obesity, renal dysfunction, hepatic dysfunction, malignancy, infection, and the presence of pulmonary embolism.

Elimination: renally, with small amounts as unchanged drug

Contraindications

Contraindications for heparin use are hypersensitivity to heparin or any component; uncontrollable active bleeding (unless secondary to disseminated intravascular coagulation); severe thrombocytopenia; and suspected or confirmed intracranial hemorrhage.

Warnings

Preservative-free heparin should be used in neonates to prevent neonatal gasping syndrome caused by the preservative benzyl alcohol [15]. Confirm concentration

of heparin being used before administration to prevent medication errors. May cause thrombocytopenia, including heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT). Bleeding may occur at any site (GI, GU, adrenal, retroperitoneal). Use with caution in patients with enhanced bleeding risk. Consider reduced heparin dosage if: therapeutically anticoagulated or on antiplatelet medications; mild to moderate bleeding diathesis; uncontrolled hypertension; platelets <100,000 or 50 % decrease from baseline; high risk or suspicion of bleeding at the time of initiation of heparin therapy (recent surgery within the past 2 days, recent trauma, arterial ischemic stroke, or cerebral sinus venous thrombosis, end stage liver disease, renal failure, aneurysm (aortic or cerebral), GI/GU bleeding within the past 14 days; thrombolytic therapy in the previous 12 h; elevated baseline aPTT or INR; malnourished; sub acute bacterial endocarditis.

Adverse Effects

Cardiovascular: chest pain
Central nervous system: fever, headache, chills
Dermatologic: hematomas, erythema and pain at the injection site (subQ), cutaneous necrosis with subQ injections
Gastrointestinal/genitourinary: hematuria, tarry stools
Hematologic: hemorrhage, thrombocytopenia, epistaxis
Hepatic: increased liver aminotransferase level
Other: anaphylaxis, osteoporosis with long-term use

Drug/Drug Interactions

Anticoagulants, thrombolytic agents (alteplase, streptokinase, and urokinase), platelet inhibitors (aspirin, salicylates, NSAIDs, dipyridamole, and clopidogrel), SSRIs, SNRIs, and alprostadil may increase the risk of bleeding. I.V. nitroglycerin may decrease heparin's anticoagulant effect.

Monitoring Parameters

Baseline labs prior to starting heparin therapy: CBC with platelet, PT/INR, aPTT, and fibrinogen.

After starting heparin: aPTT 4 h after infusion started, 4 h after each rate change, then every day once in therapeutic range; CBC with platelets daily; stool occult blood daily.

Poisoning Information

Bleeding is the primary symptom of overdose. Heparin is not removed by dialysis. Manage hypotension with IV fluids and vasopressors if needed. For severe bleeding the antidote is protamine. One milligram of protamine neutralizes 100 Units of heparin (see protamine for details). In addition packed red blood cells and fresh frozen plasma may be indicated.

If HIT or HITT is suspected, discontinue all heparin and start an alternative non-heparin anticoagulant such as argatroban or lepirudin.

Compatible Diluents/Administration

Because of pain, irritation, and hematoma, it is recommended that heparin not be administered I.M.; continuous I.V. infusion should be administered via a controlled infusion device; rotate the subQ administration site; heparin is compatible with 0.9 % NaCl, dextrose solutions, and parenteral nutrition solutions.

13.3.4   Warfarin

Indication

Warfarin is used for treatment and prophylaxis of pulmonary embolism, venous thrombosis, and other thromboembolic disorders. It is used to prevent thrombosis in patients with atrial fibrillation or prosthetic cardiac valves, and to prevent recurrent MI or stroke after myocardial infarction.

Mechanism of Action

Warfarin inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X) and the anticoagulant

proteins C and S by blocking the regeneration of vita-min K [1] epoxide by vitamin K epoxide reductase complex 1 (VKORC1).

Dosing

Oral:
Infants and children: to maintain an INR between 2 and 3. Table 13.3 describes initial loading and maintenance doses

Table 13.3 Warfarin Dosing for infants and children to maintain an INR between 2 and 3

Day	Dose
Day 1 loading dose (if baseline INR is 1–1.3)	0.2 mg/kg (maximum dose of 10 mg); 0.1 mg/kg if patient has liver dysfunction

Days 2–4: loading dose is dependent on patient's INR

INR	Dose
1.1–1.3	Repeat initial loading dose
1.4–1.9	Administer 50 % of the initial loading dose
2–3	Administer 50 % of the initial loading dose
3.1–3.5	Administer 25 % of the initial loading dose
>3.5	Hold drug until INR is <3.5, then restart at 50 % less than the previous dose

Day 5 and beyond (maintenance dosing): dose is dependent on patient's INR

INR	Dose
1.1–1.4	Increase dose by 20 % of previous dose
1.5–1.9	Increase dose by 10 % of previous dose
2–3	Do not change the dose
3.1–3.5	Decrease dose by 10 % of previous dose
>3.5	Hold drug and check INR daily until INR is <3.5, then restart at 20 % less than the previous dose

Adapted from Monagle et al. [4]

Usual maintenance dose for infants and children is about 0.1 mg/kg/day, with a range of 0.05–0.34 mg/kg/day, with infants requiring doses in the higher end of the range.

Adults: Initial, 2–5 mg daily for 2 days **OR** 10 mg daily for 1–2 days (in healthy outpatients), then adjust dose according to INR (usual maintenance doses, 2–10 mg/day)

IV dosing is equivalent to oral dosing for patients unable to take medication orally

Pharmacokinetics

Bioavailability: rapidly and completely absorbed, with peak concentrations in 4 h

Onset of action: onset is in 24–72 h, with the peak effect in 5–7 days

Duration: the effects from a single dose last from 2–5 days

Protein binding: highly protein bound (99 %)

Metabolism: in the liver via CYP2C9

Half-life: approximately 40 h; highly variable among individuals (range 20–60 h), due to genetic variations in proteins CYP2C9 and VKORC1

Elimination: 92 % of the drug is excreted renally (mainly as metabolites), with the remaining excreted through the biliary tract.

Contraindications

Contraindications to warfarin use are hypersensitivity to warfarin or any component, severe renal or hepatic impairment, hemorrhagic tendencies, cerebral or dissecting aortic aneurysms, active ulceration or bleeding, malignant hypertension, bacterial endocarditis, pericarditis and pericardial effusions, recent or potential surgery of CNS or eye, spinal punctures or lumbar block, and pregnancy (severe birth defects have been associated with fetal exposure), patients with a high potential for noncompliance with medications or monitoring.

Warnings

Serious, potentially fatal, bleeding may occur. Risk is higher during treatment initiation and with high doses. Risk factors include high target INR (>4), age ≥65 years, history of GI bleeding, hypertension, cerebrovascular disease, congestive heart failure, anemia, diabetes, malignancy, trauma, renal insufficiency, hepatic impairment, history of peptic ulcer disease, indwelling catheters, drug-drug interactions, and prolonged course of therapy. Avoid use in neonates due to greater risk of bleeding.

Skin necrosis and gangrene or systemic cholesterol emboli may occur with warfarin use; use caution in patients with prolonged dietary insufficiencies such as Vitamin K deficiency; do not switch brands without close INR monitoring; do not use as monotherapy for heparin-induced thrombocytopenia as necrosis and gangrene may occur; INR must be monitored in all patients due to large interpatient variability due to differences in metabolism, diet and medications; acute infection, antibiotics, fever, and disruption of normal GI flora may alter patient response to warfarin.

For scheduled major surgery, discontinue warfarin approximately 5 days before surgery, and restart 12–24 h after surgery once adequate hemostasis is achieved. If patient has high risk of thromboembolism without anticoagulation, consider bridging warfarin therapy with unfractionated heparin or enoxaparin [16].

Adverse Effects

Central nervous system: fever, headache, dizziness (signs of bleeding)
Dermatologic: hair loss, rash, urticaria, pruritus
Hematologic: hemorrhage from any site, anemia
Hepatic: hepatitis
Other: skin and tissue necrosis, gangrene, intraocular hemorrhage, tracheal calcification, hemoptysis, "purple toes" syndrome, osteoporosis with long term use.

Drug-Drug Interactions

Warfarin has many drug-drug interactions. Only drugs that have significant/major interactions have been listed. Consult detailed reference for complete listing.

Drugs that can increase the effects/toxicities of warfarin include: rivaroxiban, tamoxifen, alcohol, allopurinol, aspirin, salicylates, NSAIDs,, gemfibrozil, phenytoin, sulfonylureas, statins, amiodarone, fluconazole, ketoconazole, miconazole, voriconazole, metronidazole, omeprazole, amoxicillin, piperacillin, chloral hydrate, chloramphenicol, cimetidine, clopidogrel, fluorouracil, fosphenytoin, levofloxacin, moxifloxacin, phenobarbital, prednisone, SSRIs, streptokinase, sulfamethoxazole and trimethoprim, urokinase, ritonavir, delavirdine, nicardipine, testosterone, and ginkgo biloba. Breast milk has decreased levels of vitamin K and therefore, breast-fed infants may be more sensitive to warfarin.

Drugs that can decrease the effects of warfarin include: St. John's Wort, cyclosporine, ritonavir, bosentan, nevirapine, nafcillin, rifampin, carbamazepine, cholestyramine, mesalamine, coenzyme Q10, phenobarbital, oral contraceptives, sucralfate, phytonadione, and foods containing vitamin K.

Monitoring Parameters

Baseline labs prior to starting therapy with warfarin should include CBC (for hemoglobin and hematocrit) with platelets, PT/INR, and fibrinogen. After starting warfarin, obtain PT/INR daily until therapeutic two times 24 h apart, then every 72 h thereafter while inpatient. Also monitor occult blood daily and CBC with platelets twice weekly during the first 2 weeks, then every 2–4 weeks thereafter.

Target therapeutic INR for most pediatric indications is 2–3. Target range for mechanical prosthetic valves is usually higher. The prophylactic target INR range is 1.5–1.9.

Poisoning Information

Vitamin K reverses the anticoagulation effects of warfarin. For an excessively prolonged INR (usually >8) without significant bleeding, phytonadione 0.03 mg/kg IV (maximum 1 mg/dose) can be given to pediatric patients. For significant bleeding, reversal with fresh frozen plasma or prothrombin complex concentrates or recombinant factor VIIa is recommended [4]. Use extreme care administering vitamin K or fresh-frozen plasma in patients with prosthetic valves, because valve thrombosis can occur.

Compatible Diluents/Administration

Protect warfarin from light. Warfarin for injection should be reconstituted with sterile water for injection to a final concentration of 2 mg/mL and used within 4 h. Administer I.V. over 1–2 min.

13.3.5   Protamine: Reversal Agent for Unfractionated Heparin or LMWH

Indication

Protamine is used for the treatment of heparin or low molecular weight heparin (LMWH) overdose. Protamine is also used to neutralize heparin during surgery or dialysis procedures.

Mechanism of Action

Protamine is a weak anticoagulant that combines with strongly acidic heparin or LMWH to form a stable salt complex that neutralizes the anticoagulant activity of both drugs.

Dosing

Protamine dose is dependent on most recent dosage of heparin or LMWH. One milligram of protamine will

neutralize 115 units of porcine intestinal heparin, 90 units of beef lung heparin, and 1 mg (100 units) of LMWH; the maximum dose is 50 mg. Based on these dosing guidelines, Table 13.4 shows the appropriate dose of protamine to be administered according to the time that has elapsed since heparin was administered [17].

TABLE 13.4 Protamine dosing for heparin reversal

Time since last dose	Dose of protamine
<30 min	100 % of above dosing recommendations
30–60 min	Administer 50–75 % of dose
60–120 min	Administer 37.5–50 % of dose
>120 min	Administer 25–37.5 % of dose

Source: Modified from Lee et al. [17]

Heparin administered by subQ injection: 1–1.5 mg protamine per 100 units of heparin administered as 25–50 mg infused via slow I.V. infusion followed by the remaining portion of the calculated dose over 8–16 h or the expected duration of absorption for the heparin.

LMWH: if LMWH was administered within the last 4 h, administer 1 mg protamine per 1 mg (100 units) LMWH; a second dose of 0.5 mg protamine per 1 mg (100 units) LMWH may be administered if the aPTT remains prolonged 2–4 h after the first dose

Pharmacokinetics

Onset: heparin neutralization occurs within 5 min after I.V. administration

Elimination: unknown.

Contraindications

Protamine use is contraindicated with hypersensitivity to protamine or any component.

Warnings

There is an increased risk of hypersensitivity reactions to protamine in patients who have been previously exposed to protamine or protamine-containing insulin, when high doses are used, in infertile or vasectomized men, in patients with severe left ventricular dysfunction, or in patients who have hypersensitivity to fish. Heparin rebound or bleeding have been reported 8–18 h after protamine administration in cardiac surgery patients. In operative settings or with rapid administration, protamine has been associated with acute hypotension.

Adverse Effects

Cardiovascular: bradycardia, flushing, hypotension, circulatory collapse, capillary leak
Gastrointestinal: nausea, vomiting
Respiratory: dyspnea, pulmonary hypertension, pulmonary edema
Other: hypersensitivity reactions

Drug/Drug Interactions

Protamine may prolong the effects of insulin.

Monitoring Parameters

Coagulation studies, including aPTT or ACT; cardiac monitoring and blood pressure monitoring must be performed.

Poisoning Information

Signs and symptoms of protamine overdose include hypotension and bleeding. Treatment of overdose is symptomatic and supportive. There is no antidote.

Compatible Diluents/Administration

Administer the solution I.V. without further dilution over 10 min, but do not exceed 5 mg/min. The solution may be further diluted with either D5W or 0.9 % NaCl. Rapid I.V. infusion may cause hypotension.

13.4   Anti-platelet Drugs

13.4.1   Aspirin

Indication

Aspirin is used to treat pain, inflammation and fever, and for thromboembolism prevention in a variety of situations. It is used for the prevention of mortality during suspected acute MI as well as prophylaxis of a recurrent MI; prevention of MI in patients with angina; prevention of recurrent stroke and mortality after a TIA or stroke; adjunctive therapy in coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and carotid endarterectomy; and prevention of thrombosis in patients supported with a ventricular assist device and in patients with endovascular stents. Aspirin is used in high doses in the management of rheumatic fever, gout, rheumatoid arthritis and osteoarthritis. Off-label use of aspirin includes the treatment of Kawasaki Disease and to prevent thrombosis in patients after single ventricle palliation with a Blalock-Taussig shunt, bidirectional Glenn, or Fontan procedure.

Mechanism of Action

Aspirin is a salicylic acid derivative that inhibits both prostaglandin synthesis and platelet aggregation through inactivation of cyclooxygenase enzymes. Aspirin acts on the hypothalamus heat-regulating center to reduce fever.

Dosing

Children:

Analgesic and antipyretic (oral, rectal): 10–15 mg/kg/dose every 4–6 h; maximum dose, 4 g/day

Anti-inflammatory (oral): initial, 60–90 mg/kg/day divided every 6–8 h, maintenance, 80–100 mg/kg/day divided every 6–8 h

Kawasaki Disease (oral): 80–100 mg/kg/day divided every 6 h for up to 2 weeks, then 3–5 mg/kg/day once daily for 6–8 weeks if no evidence of coronary changes. If coronary abnormalities develop, continue indefinitely.

Antiplatelet effects (oral): adequate pediatric studies have not been performed; therefore, the dose is not well established. Doses ranging from 1 to 5 mg/kg/day administered as a single daily dose are recommended [18]; doses up to 10 mg/kg/day have been used; doses are rounded to a convenient amount; maximum, 325 mg/dose

Blalock-Taussig shunt and following Fontan operation (oral): 1–5 mg/kg/day given once daily [18]

Arterial ischemic stroke: 1–5 mg/kg/day after discontinuation of anticoagulants

Adults:

Analgesic and antipyretic (oral): 325–650 mg every 4–6 h (up to 4 g/day) (rectal): 300–600 mg every 4–6 h (up to 4 g/day)

Anti-inflammatory (oral): initial: 2.4–3.6 g/day in divided doses; maintenance: 3.6–5.4 g/day in divided doses; monitor serum concentrations

CABG, **coronary artery disease**, **carotid artery stenosis**, **peripheral artery disease** (**thrombosis prophylaxis**): oral: 75–100 mg/day given once daily

Suspected acute MI (oral): initial, 162–325 mg as soon as MI is suspected; then 75–162 mg once daily indefinitely

Acute ischemic stroke/TIA (oral): 160–325 mg within 48 h of onset

Prevention of stroke after ischemic stroke or TIA (oral): 75–100 mg once daily

Pharmacokinetics

Bioavailability: absorption is from the stomach and small intestine. The immediate-release formulation is completely absorbed, whereas the enteric-coated form is erratically absorbed.

Peak concentration: time to peak serum concentration is 1–2 h (this may be delayed with controlled- or timed-release preparations)

Duration: duration of analgesic/antipyretic effects is 4–6 h

Distribution: widely distributed

Metabolism: hepatic

Half-life: the half-life of the active drug is 6 h

Elimination: renal; aspirin is 50–100 % dialyzable

Contraindications

Contraindications to aspirin use are hypersensitivity to salicylates or other NSAIDs, bleeding disorders, hepatic failure, and children with chickenpox or flu symptoms because of the risk of Reye's syndrome [19].

Warnings

Use caution in administering aspirin to patients with bleeding or platelet disorders, erosive gastritis, peptic ulcer disease, renal failure, and severe hepatic insufficiency. Patients with asthma, rhinitis, or nasal polyps may be more sensitive to the effects of salicylates.

Adverse Effects

Central Nervous System: tinnitus, headache, dizziness, confusion, hyperpyrexia

Dermatological: rash, urticaria, angioedema

Gastrointestinal: nausea, vomiting, dyspepsia, epigastric discomfort, gastrointestinal bleeding, occult bleeding

Hematologic: prolongation of prothrombin time, anemia, thrombocytopenia

Hepatic: hepatotoxicity

Other: bronchospasm, metabolic acidosis

Drug/Drug Interactions

Anticoagulants, including acenocoumarin, antithrombin III, argatroban, bivalirudin, dabigatran, dalteparin, danaparoid, drotrecogin alfa, enoxaparin, fondaparinux, heparin, hirudin, lepirudin, nadroparin, rivaroxiban,

tinzaparin, and warfarin, other salicylate medications, including aminosalicylic acid, choline magnesium tri-salicylate, and salsalate, and NSAIDs, can potentiate bleeding. Antiplatelet drugs including clopidogrel, dipyridamole, prasugrel, and ticlopidine may also increase the risk of bleeding.

- Combination therapy of salicylates and carbonic anhy-drase inhibitors such as acetazolamide has resulted in significant metabolic acidosis in pediatric and adult patients. Salicylates (high dose) may diminish the anti-hypertensive effect of ACE inhibitors and may enhance the hypoglycemic effect of sulfonylureas. Aspirin may enhance the adverse GI effects (ulceration or bleeding) of alendronate and systemic corticosteroids, whereas antacids may increase the excretion of salicylates.

- Nondihydropyridine calcium channel blockers (diltiazem and verapamil) may enhance the anticoagulant effect of salicylates. Salicylates may enhance the adverse/toxic effect of varicella virus-containing vaccines causing Reye's syndrome, and they may increase serum concen-tration of methotrexate.

Monitoring Parameters

CBC, chemistry profile, blood pressure, fecal occult blood test, liver function at initiation of therapy and every 6–12 months thereafter should be monitored. Obtain serum salicylate concentration with chronic use. Monitor salicylate levels when using high doses for anti-inflam-matory effect.

Poisoning Information

Salicylate serum concentrations correlate with the phar-macological actions of aspirin. Salicylate levels of 30–50 mcg/mL produce analgesic and antipyretic effects, while levels of 150–300 mcg/mL are needed for anti-inflammatory effects. Adverse effects can begin to be observed with serum salicylate levels of approximately 100 mcg/mL, with the most common being nausea,

vomiting and tinnitus. Patients with mild-to-moderate intoxication may develop fever, tachypnea, respiratory alkalosis, metabolic acidosis and lethargy. Severe intoxication may result in encephalopathy, coma, hypotension, pulmonary edema, seizures, acidemia, coagulopathy, cerebral edema, and dysrhythmias. Treatment of accidental or chronic ingestion is supportive and can include the use of activated charcoal and gastric lavage. Sodium bicarbonate is used to alkalinize the urine and prevent acidosis. Hemodialysis can be considered for patients with high blood salicylate levels (>800–1,000 mcg/mL after acute overdose, >500–600 mcg/mL after chronic overdose).

Compatible Diluents/Administration

For oral administration, administer aspirin with water, food, or milk to decrease GI upset. Do not crush or chew controlled-release, timed-release, or enteric-coated tablets; these are designed to be swallowed whole.

13.4.2   Clopidogrel

Indication

In the United States, clopidogrel is approved for thrombosis prophylaxis in adults with acute coronary syndrome, cerebrovascular accident, myocardial infarction (MI), percutaneous coronary intervention (PCI), and peripheral arterial occlusive disease. Clopidogrel has also been used in patients with atrial fibrillation and chronic heart failure. The safety and efficacy in pediatric patients have not yet been established.

Mechanism of Action

Clopidogrel is converted to an active metabolite which prevents binding of adenosine diphosphate (ADP) to platelet P2Y12 receptors. This irreversibly inhibits

platelet aggregation for the lifespan of the platelets (7–10 days).

Dosing

(Safety and efficacy in pediatric patients are not established; limited pediatric dosing information is available)

Infants and Children ≤24 months: oral: 0.2 mg/kg/dose given once daily (PICOLO study) [20]

Children >2 years old: oral: 1 mg/kg/day (maximum 75 mg) given once daily

Adults:

Recent MI, **cerebrovascular accident**, **or established peripheral arterial occlusive disease**: 75 mg by mouth once daily

Acute coronary syndrome:

Unstable angina, non-ST segment elevation MI: initial, 300 mg loading dose, followed by 75 mg once daily by mouth (in combination with 75–325 mg aspirin once daily)

ST segment elevation MI: 75 mg once daily by mouth (in combination with aspirin 162–325 mg once daily initially followed by 81–162 mg once daily)

Percutaneous coronary intervention (PCI): loading dose: 300–600 mg by mouth before or at the time of PCI, then 75 mg once daily by mouth (in combination with aspirin 81 mg once daily).

Dosage adjustment in renal or hepatic insufficiency: not necessary

Pharmacokinetics

Bioavailability: well absorbed, with a time-to-peak concentration of 1 h and at least 50 % bioavailability.

Onset of action: inhibition of platelet aggregation occurs 2 h after an oral dose is administered and is dose-dependent. Peak response of 40–60 % platelet inhibition occurs in 3–7 days.

Duration: complete recovery of platelet function occurs approximately 5–7 days after the last oral dose, when new platelets replace those irreversibly affected by clopidogrel.

Protein binding: clopidogrel is 98 % protein bound.

Metabolism: metabolized extensively through the liver via oxidation by the cytochrome P450 system to an inactive metabolite that is then metabolized to the active thiol metabolite.

Half-life: the elimination half-life is 6 h for the parent drug and 30 min for the active metabolite.

Elimination: 50 % renal excretion and 46 % fecal excretion.

Contraindications

Contraindications to clopidogrel administration are hypersensitivity to clopidogrel and active bleeding (e.g., peptic ulcer disease or intracranial hemorrhage).

Warnings

Use clopidogrel with caution in patients who may be at increased risk of bleeding. Clopidogrel should be discontinued 5 days before elective surgery. There is an increased risk of bleeding when clopidogrel is used concurrently with other antiplatelet drugs. Use clopidogrel with caution in patients with severe liver disease and renal impairment. Cases of life-threatening thrombotic thrombocytopenic purpura (TTP) have been reported, requiring urgent plasmapheresis. Some patients with genetic variants of the CYP2C19 enzyme may not respond to clopidogrel therapy.

Adverse Effects

With clopidogrel use, bleeding is the most common adverse effect, including GI hemorrhage and epistaxis.

Dermatologic: pruritus, rash

Other serious adverse effects:

Central Nervous System: intracranial hemorrhage

Dermatologic: Stevens-Johnson syndrome

Hematologic: coronary artery stent thrombosis, agranulocytosis, pancytopenia, thrombotic thrombocytopenic purpura

GI/Hepatic: colitis, hepatotoxicity

Ocular: intraocular hemorrhage

Respiratory: pulmonary edema, respiratory tract hemorrhage

Postmarketing and/or case reports: acute liver failure, aplastic anemia, angioedema, erythema multiforme, hypersensitivity reactions, hypotension, interstitial pneumonitis, lichen planus, pancreatitis, serum sickness, stomatitis, toxic epidermal necrolysis, and vasculitis.

Drug/Drug Interactions

Avoid use with omeprazole or esomeprazole as they inhibit the conversion to the active metabolite; lansoprazole and pantoprazole may have less effect on the active metabolite formation. Azole antifungals like fluconazole and voriconazole should also be avoided due to the same reason. Anticoagulants (i.e. warfarin, heparin, enoxaparin, dabigatran, rivaroxiban) or other antiplatelet agents (aspirin, dipyridamole) may increase the risk of bleeding. Concurrent use of NSAIDs may increase the risk of GI blood loss. Rifampin may increase the effects of clopidogrel. Thrombolytics may increase the risk of bleeding. Concurrent use of SSRIs and SRNIs may result in an increased bleeding risk.

Monitoring Parameters

For signs of bleeding, periodic hemoglobin and hematocrit should be monitored. For efficacy determination, consider testing platelet aggregation.

Poisoning Information

Treatment of clopidogrel overdose is supportive and symptomatic. There is no antidote. However, activated charcoal may be used to help decontaminate. Symptoms of acute toxicity include vomiting, dizziness, and GI

hemorrhage. Monitor ECG, hepatic enzymes, fluid and electrolytes, and CBC/platelet and coagulation studies if bleeding is severe.

Administration

Clopidogrel can be taken with or without food. Take with food if upset stomach occurs. An oral suspension can be made from the tablets with a final concentration of 5 mg/mL.

13.4.3   Dipyridamole

Indication

Dipyridamole has been used in myocardial imaging studies and for prophylaxis of prosthetic cardiac valve thrombosis and prosthetic cardiac valve-related embolism in combination with warfarin. Dipyridamole is also used as a diagnostic agent for coronary artery disease. Off-label indications include maintenance of patency after surgical grafting procedures, including coronary artery bypass (in combination with aspirin) and prevention of thromboembolic disorders.

Mechanism of Action

Dipyridamole inhibits the activity of adenosine deaminase and phosphodiesterase, causing an accumulation of adenosine, adenine nucleotides, and cyclic AMP that, together, inhibit platelet aggregation, cause vasodilation, and decrease platelet activation.

Dosing

Children: oral, 3–6 mg/kg/day in three divided doses.
Adults:
Prophylaxis of thromboembolism after cardiac valve replacement (**adjunctive use**): oral, 75–100 mg, four times per day
Dipyridamole stress test (**for evaluation of myocardial perfusion**): I.V., 0.142 mg/kg/min for a total of 4 min

(0.57 mg/kg total); maximum dose, 60 mg; inject thallium 201 within 5 min after the end of injection of dipyridamole

Pharmacokinetics

Bioavailability: slow systemic absorption, with 27–66 % bioavailability and peak serum concentration within 2–2.5 h.
Protein binding: 91–99 %.
Metabolism: hepatic
Half-life: 10–12 h
Elimination: biliary

Contraindications

Hypersensitivity to dipyridamole products.

Warnings

Use caution in administering dipyridamole to patients with hypotension or hepatic impairment, patients on antiplatelet agents or anticoagulation, or patients with severe coronary artery disease or abnormal cardiac rhythm. Use the I.V. form with caution in patients with bronchospastic disease or unstable angina.

Adverse Effects

Cardiovascular: flushing, angina pectoris
Central nervous system: headache (dose-related), dizziness, weakness
Dermatologic: rash, pruritus
Gastrointestinal: abdominal distress, diarrhea
Reported with IV use only: vasodilation, hypotension, ECG abnormalities, tachycardia, ventricular arrhythmia, MI, and bronchospasm.

Drug/Drug Interactions

Heparin, warfarin, streptokinase, urokinase, aspirin, alteplase, NSAIDs, SSRIs and SNRIs may increase risk of bleeding; decreased coronary artery vasodilation

from I.V. dipyridamole may occur in patients receiving theophylline or caffeine. Patients taking dipyridamole may need lower initial dose of adenosine.

Monitoring Parameters

Blood pressure, heart rate, electrocardiogram, and vital signs during I.V. infusion; hepatic function should be monitored with long-term use.

Poisoning Information

Use of the I.V. form of dipyridamole has been associated with bronchospasm and chest pain. Use with caution in patients with bronchospastic disease or unstable angina. Aminophylline should be available in case of severe adverse reactions with I.V. use. Treat hypotension with IV fluids or other supportive care.

Based on limited experience, signs, and symptoms of overdose include hypotension, dizziness, headache, weakness, facial flushing, and fainting. Ipecac, activated charcoal and gastric lavage can be used.

Compatible Diluents/Administration

Dilute I.V. dipyridamole in at least a 1:2 ratio with D5W, NS, or 0.45 % NaCl and infuse over 4 min.

13.5   Thrombolytic Drugs

13.5.1   Alteplase

Indication

Alteplase is used for treatment of acute myocardial infarction (MI), acute ischemic stroke, acute massive pulmonary embolism, prosthetic valve thrombosis and occluded central venous catheters. Alteplase has also been used in pediatric patients with systemic thrombosis or parapneumonic effusion (via chest tube instillation).

Mechanism of Action

Alteplase is a plasminogen activator that binds to fibrin within a thrombus and converts plasminogen to plasmin, the enzyme that provides thrombus dissolution by degrading fibrin and fibrinogen into fragments.

Dosing

Occluded IV catheters:
Dose is listed per lumen; if multiple lumens of a multilumen catheter are occluded, treat one lumen at a time.

Chest, 2008 recommendations [18]:

Central venous catheters:
Use a volume equal to the internal volume of the lumen; instill into lumen over 1–2 min, leave to dwell in catheter for 1–2 h, then aspirate drug out of the catheter after dwell time. DO NOT INFUSE INTO PATIENT. Flush catheter after aspirating with normal saline (NS).
Patients weighing at most 10 kg: 0.5 mg diluted in NS
Patients weighing more than 10 kg: 1 mg in 1 mL NS; maximum, 2 mg in 2 mL NS
Subcutaneous port:
Patients weighing at most 10 kg: 0.5 mg diluted with NS to 3 mL
Patients weighing more than 10 kg: 2 mg diluted with NS to 3 mL

Manufacturer's Recommendations (CathfloTM Activase®) for I.V. Catheter Clearance

Central venous catheters: instill the appropriate volume (volume that is equal to 110 % of the internal lumen volume of the catheter) into the occluded catheter and let it dwell in the lumen. Evaluate catheter function after 30 min; if the catheter is functional, aspirate 5 mL of blood out of the catheter to remove the drug and residual clot and then flush the catheter with NS. If the catheter is still occluded, leave to dwell in lumen and evaluate again after 120 min. If the catheter is functional, aspirate 5 mL of blood and flush with NS. If the catheter

remains occluded after 120 min, a second dose may be administered by repeating the procedure

Patients weighing at least 10 kg and less than 30 kg: 1 mg/mL concentration; do not exceed 2 mg in 2 mL

Patients weighing at least 30 kg: 2 mg in 2 mL

Systemic thrombosis: Initial dose: 0.1 mg/kg/h intravenously (I.V.) for 6 h while monitoring for bleeding and measuring fibrinogen levels. If sufficient response is not reached within 6 h, increase dose by 0.1 mg/kg/h at 6-h intervals, to a maximum of 0.5 mg/kg/h. Maintain fibrinogen levels greater than 100 mg/dL. Duration of therapy is based on clinical response.

Arterial thrombosis after cardiac catheterization: 0.1 mg/kg bolus followed by an infusion of 0.5 mg/kg/h for 2 h followed by a heparin infusion [21].

Venous thrombosis: Initial dose of 0.03 mg/kg/h (0.06 mg/kg/h in neonates) I.V. and adjust based on clinical response [22].

Parapneumonic effusion: Intrapleural: Children >3 months: instill 4 mg in 40 ml NS in chest tube and dwell for 1 h, repeat every 24 h for 3 doses; alternate dosing:

0.1 mg/kg (maximum 3 mg) in 10–30 ml NS instilled in chest tube and dwell for 45–60 min, repeat every 8 h for 9 doses [23].

Pharmacokinetics

Onset of action: For acute MI, the initial response is seen in 20–40 min.

Volume of distribution: approximates plasma volume

Metabolism: Liver

Half-life: (adults) 25–45 min following a 90 min infusion

Elimination: more than 50 % of drug is cleared within 5 min after the infusion has ended and 80 % is cleared within 10 min. Must be given by continuous infusion to maintain thrombolytic activity.

Contraindications

Hypersensitivity to alteplase, active internal bleeding, cerebrovascular accident, intracranial neoplasm or

hemorrhage, suspected aortic dissection, recent intracranial or instraspinal surgery, arteriovenous malformation or aneurysm, bleeding diathesis, severe hepatic or renal disease, hemostatic defects, seizure at stroke onset, and severe uncontrolled hypertension are contraindications for alteplase use.

Warnings

Alteplase may cause bleeding; concurrent use of unfractionated heparin, low molecular weight heparins, or oral anticoagulants may increase bleeding; arterial and venous puncture should be minimized; avoid intramuscular (I.M.) injections; recent major surgery, recent trauma, recent genitourinary or gastroinstestinal bleeding, pregnancy, cerebrovascular disease, hypertension, patients with left heart thrombus, acute pericarditis, subacute bacterial endocarditis, hemostatic defects, significant hepatic or renal dysfunction, hypertension, septic thrombophlebitis or occluded IV cannula at an infected site and advanced age have an increased bleeding risk. Risks of alteplase therapy may be increased in patients with major early signs of infarct on computed tomographic (CT) scan and in those with severe neurological deficit at presentation.

Adverse Effects

Bleeding may occur at any site including gastrointestinal (GI) hemorrhage, genitourinary (GU) hemorrhage, ecchymosis, retroperitoneal hemorrhage, epistaxis, gingival hemorrhage, intracranial hemorrhage, pericardial hemorrhage and catheter insertion sites.

Adverse non-bleeding events may include:

Cardiovascular: hypotension

GI: nausea, vomiting

Other: fever, allergic reactions

Note: Doses used for catheter clearance have lower risk of adverse bleeding events.

Drug-Drug Interactions

Anticoagulants (unfractionated heparin, low molecular-weight heparins, direct thrombin inhibitors, and factor Xa inhibitors) and drugs that affect platelet function (aspirin, NSAIDS, clopidogrel) may increase the risk of bleeding. Safety of the concurrent use of aspirin or heparin with alteplase within the first 24 h after the onset of symptoms is unknown and should be considered with caution. Defibrotide may increase risk of bleeding. Antifibrinolytic agents may decrease effectiveness. Nitroglycerin may increase the hepatic clearance of alteplase.

Monitoring Parameters

Pretreatment labs for systemic use should include PT/PTT, platelet count, fibrinogen, fibrin degradation products, plasminogen, antithrombin, protein C and protein S. During infusion monitor for signs and symptoms of bleeding, renal and hepatic function, CBC with platelet count, reticulocytes, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, fibrin degredation products, D-dimer, plasminogen, antithrombin, and protein C levels.

Poisoning Information

Do not exceed recommended doses. Treatment for alteplase poisoning is symptomatic and supportive. Vital signs, renal and hepatic function, and potential bleeding sites should be monitored.

Compatible Diluents/Administration

Alteplase must be used within 8 h of reconstitution. Administer alteplase I.V. at a concentration of 1 mg/mL in sterile water for injection or dilute further to 0.5 mg/mL with NS or 5 % dextrose in water (D5W). When administered via a Y site alteplase is incompatible with dobutamine, dopamine, heparin, mor-

phine and nitroglycerin infusions, and is physically compatible with lidocaine, metoprolol, eptifibatide, and propranolol; alteplase is compatible with either D5W or NS.

13.6   Antifibrinolytics

13.6.1   Aminocaproic Acid

Indication

In the United States, aminocaproic acid has been used in the treatment of excessive hemorrhage caused by fibrinolysis and as prophylaxis for intraventricular hemorrhage in neonates supported on extracorporeal membrane oxygenation (ECMO) [24–26].

Mechanism of Action

Aminocaproic acid competitively inhibits activation of plasminogen, resulting in a decreased conversion of plasminogen to plasmin (fibrinolysin), an enzyme involved in fibrin clot degradation.

Dosing

Children: The I.V. route is the preferred route of administration in the intensive care setting. The oral route of administration is also available.
Acute Bleeding:
I.V/Oral:
Loading dose: 100–200 mg/kg/dose
Maintenance dose: 100 mg/kg/dose every 6 h OR as a continuous infusion of
30 mg/kg/h (daily maximum 30 g)
Prophylaxis of cardiac surgery associated bleeding:
I.V.: 100 mg/kg/dose given over 20–30 min prior to incision, 100 mg/kg/dose during cardiopulmonary bypass, and 100 mg/kg/dose over 3 h after heparin reversal [27].

Prophylaxis of extracorporeal membrane oxygenation (ECMO) associated bleeding:

I.V.: 100 mg/kg/dose prior to or immediately after starting ECMO, followed by a continuous infusion of 25–30 mg/kg/h for up to 72 h [28].

Adults:

Acute bleeding syndromes caused by elevated fibrinolytic activity:

I.V.: 4–5 g during first hour followed by continuous infusion at a rate of 1–1.25 g/h, continue for 8 h or until the bleeding stops

Oral: 5 g during the first hour, followed by 1–1.25 g/h for 8 h or until bleeding stops (maximum dose 30 g/day)

Dose adjustment for renal impairment: reduce dose to 15–25 % of normal dose in oliguria or end stage renal disease

Pharmacokinetics

Bioavailability: Absorption is rapid with 100 % oral bioavailability.

Distribution: Aminocaproic acid widely distributes through intravascular and extravascular compartments.

Metabolism: Hepatic metabolism is minimal, and half-life is 2 h.

Elimination: 40–60 % of aminocaproic acid is excreted as unchanged drug in the urine within 12 h.

Contraindications

Contraindications to aminocaproic acid use are hypersensitivity to aminocaproic acid, disseminated intravascular coagulation, and evidence of an intravascular clotting process; risk of thrombus may increase with use of Factor IX concentrate or anti-inhibitor coagulant concentrate.

Warnings

A definite diagnosis of primary fibrinolysis must be made before administration. Use injection form in premature neonates cautiously because of the presence of benzyl alcohol; use aminocaproic acid cautiously in patients

with cardiac, hepatic, or renal insufficiency (drug may accumulate in patients with decreased renal function and may require dosage adjustment); use cautiously in patients with hematuria of upper urinary tract origin or in patients at risk for venoocclusive disease of the liver.

Adverse Effects

Cardiovascular: hypotension, bradycardia, arrhythmias

Central Nervous System: headache, edema, seizures, stroke, confusion

Gastrointestinal: nausea, vomiting, abdominal pain, diarrhea

Hematologic: decreased platelet function, prolonged bleeding time, thrombosis, agranulocytosis, leukopenia

Musculoskeletal: myopathy, increased CPK, acute rhabdomyolysis

Renal: renal failure

Respiratory: dyspnea, pulmonary embolism

Other: rash, ocular discomfort, tinnitus

Drug/Drug Interactions

There is an increased risk of thrombosis with tretinoin, Factor IX, Factor IX complex, and anti-inhibitor coagulant complex.

Monitoring Parameters

Complete blood cell count (CBC) and coagulation panel initially and after treatment, fibrinogen, and fibrin split products; serum potassium, blood urea nitrogen (BUN) and creatinine should be monitored. Observe for bleeding, CNS changes, hypotension, arrhythmias, dyspnea, and myalgia.

Poisoning Information

The effective therapeutic concentration of aminocaproic acid is 130 mcg/mL. It is recommended that patients on therapy for longer than 2 weeks and with total doses of greater than 500 g should be monitored carefully for renal, hepatic, or muscle toxicity. Treatment is supportive

with no specific antidote. Monitor pulse oximetry and/or arterial blood gases (ABGs), chest x-ray, pulmonary function tests, CBC, urinalysis, and liver and kidney function.

Compatible Diluents/Administration

Rapid I.V. injection (I.V. push) of aminocaproic acid should be avoided because hypotension, bradycardia, and arrhythmia may result; administer loading doses over 15–60 min; I.V. infusion should be diluted with NS, D5W, or Lactated Ringer's solution (LR) to a final concentration of 20 mg/mL.

13.6.2   Tranexamic Acid

Indication

Tranexamic acid has off-label use in cardiac surgery for congenital heart disease to reduce perioperative blood loss in children and adults.

Mechanism of Action

Tranexamic acid competitively inhibits activation of plasminogen by forming a reversible complex that displaces plasminogen from fibrin, resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin.

Dosing

I.V.

Surgery for congenital heart disease in infants and children 2 months to 15 years old (limited data available; variable dosing regimens reported):

Loading dose: 10 mg/kg/dose, cardiopulmonary bypass circuit prime: 10 mg/kg/dose, post protamine: 10 mg/kg/dose [6, 27, 29].

OR

Loading dose: 100 mg/kg/dose, cardiopulmonary bypass circuit prime: 100 mg/kg/dose, then 10 mg/kg/h continuous infusion until transport to the intensive care unit [30].

Pharmacokinetics

Protein binding: 3 % protein bound, primarily to plasminogen
Half-life: elimination half-life is 2–11 h
Elimination: greater than 95 % of drug renally excreted as unchanged drug

Contraindications

Tranexamic acid is contraindicated with hypersensitivity to tranexamic acid or any component; subarachnoid hemorrhage; acquired defective color vision; or active intravascular clotting process.

Warnings

Do not administer tranexamic acid concomitantly with Factor IX complex concentrates or anti-inhibitor coagulant concentrate because of increase risk of thrombosis. Use tranexamic acid with caution in patients with disseminated intravascular coagulation, history of thromboembolic disease, and in patients with cardiovascular, renal, cerebrovascular disease, or transurethral prostatectomy. Changes in color vision or visual loss may occur. Seizures, thrombosis and ureteral obstruction due to clots have been reported with use.

Adverse Effects

Cardiovascular: hypotension (caused by rapid injection)
Gastrointestinal: nausea, diarrhea, vomiting
Hematologic: thrombosis
Other: anaphylaxis, visual disturbances (including color vision changes and vision loss)

Drug/Drug Interactions

Contraceptives (estrogen and progestins) or tretinoin may enhance the thrombogenic effect of tranexamic acid; coadministration of Factor IX complex, fibrinogen, or anti-inhibitor coagulant complex concentrates may increase risk of thrombosis.

Monitoring Parameters

> Reduction of bleeding with a reference range of 5–10 µg/mL is required to decrease fibrinolysis. Ophthalmic exam before therapy.

Poisoning Information

> With severe toxicity significant hypotension can develop, as well as seizures and CNS depression. Treatment of tranexamic acid overdose is symptomatic and supportive. There is no antidote.

Compatible Diluents/Administration

> Tranexamic acid may be administered by direct I.V. injection at a maximum rate of 100 mg/min (use plastic syringe only for I.V. push). Tranexamic acid is compatible with D5W and 0.9 % NaCl solutions.

13.7   Future Developments

Thrombosis, both venous and arterial, is a major cause of morbidity and mortality in children with cardiac disease. Although current antithrombotic drugs, such as unfractionated heparin, low-molecular-weight heparin, oral vitamin K antagonists, aspirin and clopidogrel, are the mainstay of treatment, they all have serious limitations. Hence, there is an ongoing need for further research to find new agents. A better understanding of biochemical pathways and molecular mechanisms underlying thrombus formation has helped identify new targets for antithrombotic agents [5].

A search for new oral anticoagulants has produced drugs such as dabigatran, rivaroxaban, and apixaban. Dabigatran is a direct thrombin inhibitor that binds to the active site of thrombin and inactivates fibrin-bound thrombin. Rivaroxaban and apixaban are both direct factor Xa inhibitors that block thrombin generation. A search for new antiplatelet agents has yielded drugs such as prasugrel, an ADP-receptor inhibitor.

Initial clinical studies in adults indicate that these new agents are at least as effective as or superior to currently available antithrombotics. Some of the new agents also have a better safety profile. Most of the new antithrombotic drugs do not require regular laboratory checks and frequent dose adjustments, providing another advantage over the currently used drugs. However, a notable disadvantage is the lack of a reversal agent for some of these drugs. Specific programs have been developed to evaluate some of the new antithrombotic agents in children and clinical trials are ongoing. It is expected that these studies will provide data on the safety and efficacy of the new agents as well as currently used anticoagulants in children.

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Chapter 14
Sedative Hypnotics and Anesthetic Agents

Erica P. Lin, James P. Spaeth, and David S. Cooper

Abstract   Pediatric patients with congenital and acquired heart disease comprise a unique population requiring frequent interventions that can require sedation or general anesthesia. They present in a variety of health states, be it as an outpatient or as a critically ill, intensive care unit (ICU) patient, and the regimen used must be tailored to the individual's specific pathophysiology, clinical status, and intended procedure. Generally speaking, the goal is to provide the appropriate sedation or anesthesia without compromising cardiac output and oxygen delivery, bearing in mind that these patients can have limited reserve.

Keywords   Anesthesia • Propofol • Etomidate

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E.P. Lin, MD (✉) • J.P. Spaeth, MD
Cardiovascular Anesthesia, The Heart Institute,
Cincinnati Children's Hospital Medical Center,
University of Cincinnati College of Medicine,
Cincinnati, OH, USA
e-mail: erica.lin@cchmc.org

D.S. Cooper, MD, MPH
Department of Pediatrics, Cardiac Intensive Care Unit,
The Heart Institute, Cincinnati Children's
Hospital Medical Center, University of Cincinnati
College of Medicine, Cincinnati, OH, USA

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Pediatric patients with congenital and acquired heart disease comprise a unique population requiring frequent interventions that can require sedation or general anesthesia. They present in a variety of health states, be it as an outpatient or as a critically ill, intensive care unit (ICU) patient, and the regimen used must be tailored to the individual's specific pathophysiology, clinical status, and intended procedure. Generally speaking, the goal is to provide the appropriate sedation or anesthesia without compromising cardiac output and oxygen delivery, bearing in mind that these patients can have limited reserve.

14.1   Propofol

14.1.1   Indications

Propofol is the most widely used intravenous (IV) anesthetic. It is a non-opioid, non-barbiturate sedative hypnotic agent that is commonly used for induction and maintenance of general anesthesia and as a sedative in the ICU. It has no analgesic properties. Additionally, propofol has an antiemetic effect and can be used in sub-hypnotic doses to treat nausea and vomiting in the postanesthesia care unit. Prompt recovery and lack of residual sedation make it an appropriate anesthetic for ambulatory surgery. Low/sub-hypnotic doses can also be used to treat pruritus induced by neuraxial opioids.

14.1.2   Mechanism of Action

Propofol's sedative-hypnotic effects are mediated by an interaction with γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system (CNS). By binding to the β-subunit of the GABA-receptor, propofol decreases the rate of dissociation of GABA from its receptor, thus enhancing inhibitory neurotransmission and depressing nervous system activity.

14.1.3   Dosing

Induction of Anesthesia

> *Healthy adults and children between 6 and 12 years of age*: 1.5–2.5 mg/kg IV
>
> *Younger children and infants*: 2.5–3.5 mg/kg IV

Premedication with opioid and/or benzodiazepine markedly reduces induction dose. Especially in sicker patients, induction should be performed in small, incremental doses.

Maintenance Dosing

> 125–300 mcg/kg/min continuous IV infusion, titrated to individual requirement and surgical stimulus. Typically, a higher dose is initiated immediately following the induction dose, then reduced by 30–50 % during the first half hour of maintenance. Concomitant administration of opioids, benzodiazepines, and/or ketamine can decrease infusion rate.

Sedation

> *Infusion*: 25–80 mcg/kg/min IV infusion, titrated individually to the desired effect.
>
> *Intermittent bolus*: 1 mg/kg IV bolus, followed by 0.5 mg/kg every 3–5 min as needed

When used for procedural sedation, consider adding a short-acting opioid, since propofol is non-analgesic. Infusions are not recommended for long-term ICU sedation due to multiple reports of otherwise unexplained metabolic acidosis, myocardial failure, and mortality after >48 h of high-dose infusion [1].

14.1.4   Pharmacokinetics

> **Onset**: Rapid onset of loss of consciousness after IV bolus dose, although time to onset varies with rate of administration

Distribution: Large volume of distribution; plasma levels initially decline rapidly as a result of both high metabolic clearance and rapid redistribution into muscle and fat

Protein binding: Highly protein-bound (97–99 %); pharmacokinetics may be affected by conditions that alter serum protein levels

Half-life : Elimination half-life is 30–90 min. Context-sensitive half-life for infusions lasting up to 8 h is <40 min.

Metabolism: Extensively metabolized in the liver by conjugation to inactive, water-soluble sulfate and glucuronic acid metabolites. High metabolic clearance exceeding hepatic blood flow suggests extra-hepatic metabolism (possibly in the lungs).

Clearance: Renal excretion of metabolites. Less than 0.3 % of a dose is excreted unchanged.

14.1.5   Drug Interactions

Coadministration of propofol with other premedication drugs, anesthetics, sedative-hypnotics, and opioids may result in enhancement of its effect on mean arterial blood pressure, cardiac output, and respiratory status. It does not significantly interact with neuromuscular blocking agents, local anesthetics, and non-opioid analgesics.

14.1.6   Systemic and Adverse Effects

Cardiovascular

Propofol causes a dose-related decrease in blood pressure (25–40 % reduction in systolic, diastolic, and mean blood pressure) that is associated with a 15 % decrease in cardiac output/cardiac index, stroke volume, and systemic vascular resistance (SVR) [2]. This is most pronounced during induction of anesthesia, but can persist in patients

maintained with a continuous infusion. This is caused by both vasodilation and myocardial depression, mediated by a reduction in sympathetic activity. Compared to other induction agents such as etomidate, propofol has greater negative inotropic effects on the heart. These effects may be exaggerated in hypovolemic patients and those with compromised left ventricular function. Adequate hydration before IV administration of propofol may ameliorate the hemodynamic effects of this drug. Despite decreases in systemic blood pressure, heart rate (HR) often remains unchanged during induction. Baroreceptor reflex control of HR may be depressed by propofol and seems to be more prominent in children younger than 2 years of age [3]. Profound bradycardia and asystole have been reported after induction of anesthesia with propofol, prompting the recommendation that anticholinergics be administered when vagal stimulation is more likely to occur. The risk of bradycardia-related death while undergoing propofol anesthesia is estimated at 1.4 in 100,000.

Propofol does not alter sinoatrial or atrioventricular node function and accessory pathway conduction [4, 5] and is a viable anesthetic during radiofrequency catheter ablation for most tachyarrhythmias, with the exception of ectopic atrial tachycardias which may be suppressed by propofol [6]. For patients with congenital heart disease (CHD), the decrease in SVR can have multiple ramifications including an increase in Qp:Qs, decreased left-to-right flow across left-to-right shunts, and/or increased right-to-left flow resulting in arterial desaturation in cyanotic patients with right-to-left shunts [7]. By coadministering propofol with ketamine, the mean arterial pressure (MAP) is better preserved, offering a viable sedation/anesthetic strategy for patients with less reserve [8].

Central Nervous System

Spontaneous, non-purposeful movements may occur during induction and recovery in younger children and infants. These excitatory movements are not associated with

cortical epileptic activity and are caused by depression of subcortical areas of the brain. Propofol decreases cerebral metabolic rate for oxygen consumption ($CMRO_2$), cerebral blood flow (CBF), and intracranial pressure (ICP) without affecting cerebral auto regulation or cerebral reactivity to carbon dioxide. At high doses, propofol produces electroencephalographic burst suppression. It can decrease the early component of somatosensory and motor evoked potentials, but does not alter brainstem auditory evoked potentials. At equal sedation, propofol produces the same degree of memory impairment as midazolam [9].

Respiratory

Propofol causes a dose-dependent respiratory depression with 25–35 % of patients becoming apneic after induction of anesthesia. Duration of apnea is prolonged by the addition of an opiate. In patients sedated with propofol infusion and breathing spontaneously, minute ventilation is altered, most noticeably by a decrease in tidal volume. Ventilatory responses to hypercarbia and hypoxia are blunted [10, 11]. Pharyngeal and laryngeal reactivity are also depressed by propofol, and it can be used to facilitate tracheal intubation in patients without the use of muscle relaxants. Propofol also produces some bronchodilation and can relieve bronchospasm. It does not affect hypoxic pulmonary vasoconstriction.

Hepatic and Renal

Propofol does not adversely affect hepatic or renal function. Prolonged infusions of propofol may result in excretion of green urine, reflecting the presence of phenols in the urine.

Other

Propofol has no effects on coagulation or platelet function. It does not trigger malignant hyperthermia, and has been

administered safely to patients with hereditary coproporphyria. It has no effect on adrenocortical function.

Propofol should not be administered to patients with a history of allergy to eggs, and should be used with caution in patients with multiple drug allergies, especially to neuromuscular blocking agents. Patients with peanut or soy allergies should not be administered the Fresenius Propoven formulation, which in recent years has been imported into the United States to address the critical shortage. Pain on injection is commonly reported and can be minimized by injection into a larger vein and/or pretreating with 1 % lidocaine or a short-acting opioid.

Poisoning Information

Propofol is classified as a pregnancy category B drug. It readily crosses the placenta and is excreted in human breast milk. It may be associated with neonatal depression, but is rapidly cleared from neonatal circulation. It should be used during pregnancy only if clearly needed.

Addiction to propofol has been described; the majority of abusers are medical professionals. Good dreams, amorous behavior, hallucinations, and a sense of well-being/euphoria have all been described during recovery from the effects of propofol [12].

Standard Concentrations and Compatible Diluents

Propofol (2,6-diisopropylphenol) is formulated in a slightly viscous, milky white emulsion for IV administration. It consists of 1 % propofol in 10 % soybean oil, 2.25 % glycerol, 1.2 % purified egg phosphatide with sodium hydroxide to adjust the pH. Disodium edetate (0.05 %) is added as a retardant to bacterial growth. Nevertheless, because propofol is still capable of supporting microbial growth (*E. coli* and *P. aeruginosa*), strict aseptic technique, with disinfection of the ampule neck surface or vial rubber stopper with 70 % isopropyl alcohol, should always be maintained. When withdrawn into

syringes, the medication should be administered or dis- carded within 6 h after removal from sterile packaging. IV infusions directly from the vial should be completed within 12 h after spiking; tubing and any unused portions should be discarded after 12 h.

The emulsion has a pH of 7–8.5 and a pKa of 11. It is avail- able in ready to use 20, 50 and 100 mL infusion vials con- taining 10 mg/mL propofol. It should be stored between 4 and 22 °C (40–72 °F), and never frozen. Propofol should not be coadministered through the same IV catheter with blood or plasma because aggregates of the globular com- ponent of the emulsion can occur with blood/plasma/ serum. It is compatible with 5 % dextrose (D5) injection, Lactated Ringer's (LR) injection, D5LR, D5 and 0.45 % Sodium Chloride (D5+ ½ NS) injection, and D5 and 0.2 % Sodium Chloride (D5+ ¼ NS) injection.

14.2   Etomidate

14.2.1   Indications

Etomidate is an anesthetic induction agent favored for its hemodynamic stability. It is a non-opioid, non-barbiturate sedative hypnotic without analgesic activity. It is employed both as a primary induction agent and as an adjunctive main- tenance agent for general anesthesia. While there is limited published evidence that supports its safety and efficacy in pediatric patients, its selective clinical application to patients with limited cardiac reserve would certainly include teenag- ers and adults with poorly compensated palliated congenital heart disease.

14.2.2   Mechanism of Action

Etomidate is a carboxylated imidazole derivative that was introduced into clinical practice in 1972. It exists as two iso- mers, with the (+) isomer being pharmacologically active.

Although the exact mechanism by which etomidate produces hypnosis is unclear, it presumably causes CNS depression by enhancing the effects of the CNS inhibitory neurotransmitter GABA.

14.2.3   Dosing

Induction of Anesthesia

Average dose 0.3 mg/kg IV (range 0.2–0.6 mg/kg)
Duration of anesthesia after a single induction dose is dose-dependent with each 0.1 mg/kg administered providing approximately 100 s of loss of consciousness [13]. Given its stable hemodynamic profile, it is a favored induction agent in patients with limited cardiac reserve.

Maintenance Dosing as an Adjunct

10–20 mcg/kg/min IV infusion, commonly with nitrous oxide and an opiate. Goal plasma level for hypnosis is 300–500 ng/mL. Infusion should be terminated approximately 10 min before desired awakening.

Sedation

Intermittent bolus: 0.1–0.2 mg/kg IV, followed by 0.05 mg/kg every 3–5 min as needed

Repeated bolus doses extend duration of hypnosis, but recovery after multiple doses remains rather rapid. Due to concerns for adrenocortical suppression, etomidate is no longer routinely used for prolonged sedation in the ICU setting. More commonly, it is used to provide sedation for short procedures, such as cardioversion.

14.2.4   Pharmacokinetics

Onset : Rapid onset of loss of consciousness after IV bolus dose, within one arm-to-brain circulation time

Distribution: Large volume of distribution, suggesting considerable tissue uptake

Protein Binding : Extensively protein-bound, mostly to albumin (75 %); conditions that alter plasma albumin concentrations can result in dramatic increases in unbound, pharmacologically active fraction of etomidate in the plasma

Half-life: Initial distribution half-life is 3 min. Redistribution half-life is 30 min. Elimination half-life is 2–5 h. Context-sensitive half-time is less likely to be increased by continuous infusion, as compared to thiopental.

Metabolism: Rapidly metabolized in the liver by ester hydrolysis and oxidative N-dealkylation to a water soluble, inactive carboxylic acid ester and mandelic and benzoic metabolites.

Clearance: Renal (85 %) and biliary (13 %) excretion. Less than 3 % of a dose is excreted unchanged.

14.2.5   Drug Interactions

It does not significantly interact with neuromuscular blocking agents, local anesthetics, and non-opioid analgesics. Premedication with opioids and/or benzodiazepines can reduce the dose necessary for induction of anesthesia.

14.2.6   Systemic and Adverse Effects

Cardiovascular

Etomidate is highly recommended for induction of anesthesia in patients with little or no cardiac reserve., as it has minimal effects on myocardial contractility at concentrations necessary to produce anesthesia. In vitro studies of failing and nonfailing human heart muscle demonstrate etomidate-induced negative inotropy only at doses that exceed the reaches of clinical use; furthermore, this effect

is reversible with beta-adrenergic stimulation [14]. In children presenting for cardiac catheterization, an induction dose of 0.3 mg/kg produced no significant changes in any hemodynamic parameter, including HR, MAP, right atrial, aortic, or pulmonary artery pressure (PAP), calculated Qp:Qs ratio, pulmonary vascular resistance (PVR), SVR, or mixed venous oxygen saturation [15]. A case report demonstrated stable hemodynamics with etomidate induction in a pediatric patient with end-stage cardiomyopathy who previously had cardiovascular collapse with ketamine induction [16]. This stability has been attributed to its lack of effect on both the sympathetic nervous system and baroreceptor function [17]. Myocardial oxygen supply-to-demand ratio is well preserved, with reduction of myocardial oxygen consumption and little effect on coronary perfusion pressure.

Central Nervous System

Etomidate causes direct cerebral vasoconstriction and decreases CBF by 34 % and $CMRO_2$ by 45 % without changes to MAP [18]. In adequate doses to produce EEG burst suppression, ICP is markedly reduced, while maintaining cerebral perfusion pressure [19]. Cerebral reactivity to CO_2 is maintained after etomidate administration, so hyperventilation can further reduce ICP. Interestingly, while higher doses have been associated with the onset of periodic EEG burst suppression, induction doses of etomidate have frequently been associated with involuntary myoclonic movements that manifest on EEG as excitatory spikes, prompting suggestions to use with caution in patients with a history of seizures [20]. These transient spontaneous movements are caused by disinhibition of subcortical structures that usually suppress extrapyramidal motor activity. Premedication with opioid or benzodiazepine may decrease the incidence of myoclonic excitatory movements. These skeletal movements also appear to be more frequent in patients who manifest venous pain on injection.

Given etomidate's propensity to increase epileptiform activity in some, although not all, chronic epileptics [21], it can facilitate intraoperative mapping of seizure foci in patients undergoing resection of epileptogenic tissue. Etomidate also augments the amplitude of somatosensory evoked potentials (SSEPs), rendering monitoring of these responses more reliable.

Respiratory

Etomidate has minimal effect on ventilation. On induction, it is rarely associated with apnea, and more commonly causes a decrease in tidal volume with a compensatory increase in respiratory rate, that lasts 3–5 min. The incidence of apnea is altered with premedication. Hiccups and coughing may also accompany induction. Etomidate may also directly stimulate ventilation independently of the medullary centers that respond to carbon dioxide tension. It is not associated with a histamine release, and can be used safely in patients with a history of reactive airway disease.

Gastrointestinal

Etomidate has been associated with nausea and vomiting, with an incidence of 30–40 %.

Hepatic and Renal

Etomidate is not been shown to cause hepatotoxicity.or nephrotoxicity.

Endocrine

The principal limiting factor in the clinical use of etomidate is its renowned ability to transiently suppress adrenocortical function. This effect is mediated by a dose-dependent reversible inhibition of the enzyme 11-β-hydroxylase and a minor inhibitory effect on 17-α-hydroxylase, resulting in an increase in cortisol precursors and adrenocorticotropic hormone (ACTH). In children undergoing cardiac surgery with cardiopulmonary

bypass, a single induction dose caused enzyme inhibition resulting in decreased plasma cortisol levels [22]. Theoretically, this adrenocortical suppression can become problematic in critically ill patients who require an intact cortisol response to counteract a major stress such as septic shock or major surgery.

Other

Pain on IV injection is common, occurring in up to 80 % of patients. The causative factor is the carrier preservative propylene glycol. Pain on injection can be reduced by pre-treatment with lidocaine in the same vein and injection into a larger vein. Superficial thrombophlebitis has been reported up to 48–72 h after etomidate injection. Accidental intra-arterial injection has not been associated with detrimental effect

14.2.7   Poisoning Information

Etomidate is categorized as a pregnancy category C drug. It is not known whether this drug is excreted in human milk. Although animal studies have not shown etomidate to be teratogenic, it has been shown to cause other unwanted effects such as fetal demise and maternal toxicity when administered in doses many times the usual human dose [23].

14.2.8   Standard Concentrations and Compatible Diluents

Etomidate is formulated as a 2 mg/mL solution with 35 % propylene glycol (pH 6.9). It is supplied in 20 mg (10 mL) and 40 mg (20 mL) single-dose vials. It should be stored at controlled room temperature, 15–30 °C (59–86 °F). When mixed with other commonly used anesthetics such as neuromuscular blockers, vasoactive drugs, or lidocaine, it does not cause precipitation.

14.3   Ketamine

14.3.1   Indications

Initially introduced for clinical use in 1970, ketamine is derived from phencyclidine and produces "dissociative anesthesia" that is characterized by a seemingly cataleptic state. The patient is generally noncommunicative, but wakefulness may be present. Eyes can remain open with a slow nystagmus, and there can be varying degrees of involuntary limb movements independent of surgical stimulation. Ketamine remains a commonly used agent in various settings, in part, because of its intense analgesic effect, unique among anesthetic induction agents. It retains significant analgesic effect even at subanesthetic doses, making it a popular medication for dressing changes and short debridement procedures. Satisfactory absorption and bioavailability following IM injection makes it an invaluable induction agent in the uncooperative pediatric patient. In the cardiac population, it is favored because it tends not to depress the cardiovascular and respiratory systems. Adverse psychological effects limit its use.

14.3.2   Mechanism of Action

Ketamine is available as a racemic mixture, consisting of two enantiomers. The S (+)-isomer is more potent and has a smoother recovery profile. It differs from other general anesthetic agents in that it does not interact with GABA receptors. Ketamine's effects are mediated by multiple mechanisms, including interactions with *N*-methyl-D-aspartate (NMDA) receptor, opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive calcium channels [24]. Noncompetitive antagonism at the NMDA receptor calcium-channel pore and interactions with phencyclidine-binding receptor sites lead to inhibition of NMDA receptor activity which is associated with both the general anesthesia and analgesic effects. Analgesic and dysphoric effects may be mediated by ketamine's action on opioid receptors (mu, delta, and kappa). Interaction with muscarinic receptors

accounts for its anticholinergic symptoms of emergence delirium, bronchodilation, and sympathomimesis. Antinociceptive action of ketamine may involve descending inhibitory monoaminergic pain pathways.

14.3.3   Dosing

Induction of Anesthesia

1–2 mg/kg IV; 4–8 mg/kg intramuscular (IM)
Lower doses should be considered if adjuvant medications such as midazolam are given. In small patients without intravenous access who cannot tolerate an inhalational induction, consider an IM ketamine injection mixed with glycopyrrolate as an antisialogogue to decrease the likelihood of coughing and/or laryngospasm from ketamine-induced salivary secretions. IM induction route is also appealing in difficult-to-manage, developmentally delayed patients.

Maintenance Dosing

30–90 mcg/kg/min IV infusion. Lower infusion rates (15–45 mcg/kg/min) can be used if other adjuncts are employed.

Sedation

Intermittent bolus: 0.5–2 mg/kg IV, may repeat 0.25–1 mg/kg IV (one-half of the initial dose) every 10–15 min, as needed. In patients without intravenous access, consider 2–5 mg/kg IM, followed by 2–4 mg/kg after 10 min, as needed. Oral dosing ranges from 3 to 10 mg/kg.

Premedication with benzodiazepine can reduce the dose requirement. Consider an antisialogogue to address troublesome salivation.

Pharmacokinetics

Onset: Rapid with peak plasma concentrations occurring within 1 min of IV administration and 5 min after IM injection; high lipid solubility ensures rapid transfer across the blood-brain barrier. There is less bioavailability

with oral administration, resulting in slower onset of action (6 mg/kg dose provides sedated conditions in 20–25 min).

Distribution: Large volume of distribution

Protein Binding : Not significantly protein-bound (12 %)

Half-life: Distribution half-life is 11–6 min. Elimination half-life is 2–5 h.

Metabolism: Metabolized by hepatic microsomal enzymes: *N*-demethylation produces norketamine which is then hydroxylated to hydroxynorketamine. This is eventually conjugated to a water-soluble, inactive glucuronide derivatives. Norketamine is an active metabolite with one-third to one-fifth the potency of ketamine and can contribute to its prolonged effect.

Clearance: High clearance. Water-soluble metabolites are excreted in the urine. Less than 4 % of a dose is excreted unchanged in the urine.

Drug Interactions

Prolonged recovery time occurs if barbiturates, benzodiazepines, and/or narcotics are used concurrently with ketamine. Benzodiazepines are frequently co-administered to attenuate emergence delirium; they may also blunt the cardiac-stimulating effects of ketamine. Diazepam seems to inhibit hepatic metabolism of ketamine, increasing its half-life. Ketamine enhances nondepolarizing neuromuscular-blocking drugs. Furthermore, pancuronium may enhance the cardiac-stimulatory effects of ketamine. Duration of apnea after administration of succinylcholine is also prolonged. Seizure threshold may be lowered in patients receiving aminophylline who are subsequently administered ketamine. In the presence of verapamil, the blood-pressure-elevating effects of ketamine may be attenuated, while increases in heart rate are enhanced.

14.3.4   Systemic and Adverse Effects

Cardiovascular

Ketamine's distinguishing feature is its stimulation of the cardiovascular system. This is characterized by increases in blood pressure, HR, and cardiac output. These increased hemodynamic variables correlate with both an increase in work and myocardial oxygen consumption; hence, ketamine should be used with caution in patients with coronary artery disease. Its sympathomimetic effect is centrally mediated by both direct stimulation of the CNS, resulting in an increased sympathetic nervous system outflow, and the inhibition of catecholamine reuptake. In vitro studies on failing and nonfailing human myocardium highlight a direct dose-dependent negative inotropic effect [25]. Generally, the centrally mediated sympathomimetic response to ketamine overrides the direct depressant effects of ketamine. In patients whose sympathomimetic response have been maximally stimulated, for instance in cardiomyopathy [16] or other conditions leading to poor myocardial reserve, the administration of ketamine can cause circulatory collapse because endogenous catecholamine stores have been depleted and the sympathetic nervous system compensatory mechanisms exhausted. Similarly, in patients treated chronically with β-adrenergic agonists, the downregulation of catecholamine receptors results in a limited response to endogenous catecholamine, thereby unmasking ketamine's direct myocardial depression.

Ketamine has been safely administered to patients with CHD for cardiac surgery and provided cardiovascular stability with only small increases in HR and BP after induction [26]. Ketamine anesthesia is also favored for patients with cardiac tamponade and restrictive pericarditis because it preserves HR and right atrial pressure. When administered to children with CHD undergoing

cardiac catheterization, a 2 mg/kg dose caused only a minimal (<10 %) increase in mean pulmonary artery pressure without significantly affecting systemic arterial pressure, SVR, Qp:Qs, or change in direction of shunting [27]. Subsequent studies have demonstrated that ketamine can be used safely in patients with pulmonary hypertension, with little change in pulmonary vascular resistance [28, 29]. Ketamine combined with propofol as a total intravenous anesthetic technique poses the advantages of maintenance of stable hemodynamics and minimal respiratory depression while allowing spontaneous ventilation.

Central Nervous System

Historically, the use of ketamine has been relatively contraindicated in patients with increased ICP because it was considered a potent cerebral vasodilator that increased cerebral blood flow (CBF) and ICP [30]. More recent review of data, however, suggests that this broad generalization is inaccurate. Ketamine does increase CBF in spontaneously breathing patients, but it is more likely that a rise in arterial pCO_2 contributes largely to vasodilation. Furthermore, Schwedler et al. directly injected ketamine directly into cerebral vessels and found no effects on cerebrovasculature [31]. Under conditions of controlled ventilation, ketamine has been used safely in neurologically at-risk patients without increases in ICP and may even improve cerebral perfusion [32, 33].

The distinct, behavioral effects of ketamine are mediated by depression of the sensory association areas of the cortex and thalamus, and enhancement of the extrapyramidal and limbic systems [34]. The functional disorganization of the thalamoneocortical and limbic systems render CNS centers unable to receive or process sensory information, and its emotional significance cannot be assessed [35]. This also factors into ketamine's analgesic properties, which are mediated both centrally and peripherally. The

EEG effects of ketamine manifest as a reduction in alpha-wave activity with concomitant increase in beta-, delta-, and theta-wave activity. Cortical seizure activity is absent, and ketamine is not known to lower seizure threshold in epileptic patients. At high doses, ketamine produces a burst suppression pattern. Ketamine also increases the cortical amplitude of SSEPs.

Unpleasant emergence reactions of varying severity are the most frequently reported adverse events. Visual, auditory, proprioceptive, and confusional illusions have been described as dreams with morbid content and in vivid color, the sensation of floating out of the body, alterations in mood and body image, hallucinations and delirium. They can be associated with excitement, confusion, euphoria and/or fear. They typically occur within an hour of emergence, but may have a delayed presentation up to 24 h after ketamine administration. These phenomena occur less frequently in children, and benzodiazepines may be used as a premedicant to decrease the incidence and lessen the severity of these symptoms or as a treatment to attenuate active ketamine emergence reactions.

Respiratory

When used as a sole agent, ketamine does not significantly depress central respiratory drive, although transient decreases in minute ventilation can occur after rapid IV bolus administration. Ventilatory response to CO_2 is maintained. Upper airway tone and protective airway reflexes such as cough, gag, sneeze, and swallow remain relatively intact, but silent aspiration can occur. A potential respiratory issue is the increase in salivary and tracheobronchial mucous gland secretions that can produce upper airway obstruction and contribute to laryngospasm. Thus, the routine use of an antisialagogue as a premedication is often recommended when use of ketamine is anticipated. Finally, ketamine is a potent bronchodilator that can

improve pulmonary compliance in anesthetized patients with reactive airway disease and bronchospasm [36].

Hepatic and Renal

Ketamine is not known to be hepatotoxic or nephrotoxic. However, chronic administration causes hepatic enzyme induction and tolerance.

Other

Ketamine is not associated with histamine release and is rarely implicated in allergic reactions.

14.3.5   Poisoning Information

Ketamine is a drug with high abuse potential. It is currently a Schedule III controlled substance in the United States. Precautions must be taken to avoid unauthorized nonmedical use. Recreationally, it is used as a psychedelic and for its dissociative effects. The preservative of the racemic mixture of ketamine is potentially neurotoxic, so epidural and subarachnoid administration is prohibited in the United States. Ketamine is an FDA pregnancy category B drug. There is no human data on teratogenicity available.

14.3.6   Standard Concentrations and Compatible Diluents

Ketamine is available as injectable solutions in 10, 50 and 100 mg/mL concentrations. Vials should be stored at controlled room temperature and protected from light. The 100 mg/mL solution should not be administered without proper dilution. It is recommended that the drug be diluted with at least equal volume of either sterile water for injection, NS, or D5W. Barbiturates and ketamine are physically incompatible and should not be injected from the same syringe because of precipitate formation.

14.4   Dexmedetomidine

14.4.1   Indications

Dexmedetomidine is a selective, α2-adrenergic agonist with sympatholytic, sedative, anxiolytic, and analgesic properties. It is currently used in pediatric patients for invasive and non-invasive procedures, intensive care unit sedation, and as an anesthetic adjunct during surgery. Dexmedetomidine is approved by the US Food and Drug Administration for use in adults, but is currently not approved for patients under the age of 18. Procedures for which dexmedetomidine has been utilized in pediatric patients include CT and magnetic resonance imaging, transthoracic and transesophageal echocardiography, cardiac catheterization, chest tube placement, and anterior mediastinal mass biopsy [37].

14.4.2   Mechanism of Action

The mechanism of action of dexmedetomidine differs from clonidine, another α_2-agonist, in that dexmedetomidine has an eightfold greater affinity for the α_2 versus α_1 receptor. The increased selectively for the α_2-receptor, especially the α_{2a}-subtype, makes this drug a much more effective sedative and analgesic agent than clonidine. Binding to the α_2-adrenoreceptor leads to a physiologic response via activation of G proteins. α_2-receptors are found in the central and peripheral nervous systems, vascular smooth muscle, and in many other organs including the liver, pancreas, and kidney [38]. They are located both prejunctionally and postjunctionally, and are generally inhibitory in nature. The sedative and anxiolytic effects of dexmedetomidine are primarily related to activation of postjunctional α_2-receptors in the locus coeruleus (LC), while the analgesic effects are primarily mediated through the spinal cord.

14.4.3   Dosing

Induction for Procedural Sedation
Infants and children: Loading dose: 1–2 mcg/kg over
   10 min

   Maintenance dose: 1–2 mcg/kg/h

Older teenagers and adults: Loading dose: 1 mcg/kg over
   10 min

   Maintenance dose: 0.4–1 mcg/kg/h

The use of dexmedetomidine for deep sedation during invasive procedures reduces the requirement for other sedative/anesthetic agents such as fentanyl, midazolam, or propofol, and reduces the incidence of respiratory depression and airway obstruction in spontaneously ventilating patients.

Intensive Care Unit Sedation
Infants and children: Loading dose: 1 mcg/kg over 10 min

   Maintenance dose: 0.3–.0.7 mcg/kg/h

Older teenagers and adults: Loading dose: 1 mcg/kg over
   10 min

   Maintenance dose: 0.2–0.7 mcg/kg/h

Dexmedetomidine lowers the dosage requirements for other sedatives during intensive care unit sedation in mechanically ventilated patients, and allows for these patients to be extubated earlier because it does not significantly depress ventilation.

14.4.4   Pharmacokinetics

Onset: Depends on whether a loading dose is utilized and/
   or the rate of infusion. When administering a bolus of 1
   mcg/kg over 10 min, sedative effects are usually seen
   within approximately 5 min. The use of other concomitant sedative drugs may shorten the time of onset.

Distribution Half-life (t1/2): Rapid (7 min)

Protein Binding: 93 % is protein bound. The unbound fraction is significantly decreased in patients with hepatic impairment.

Elimination Half-life (t1/2β): Approximately 2 h

Metabolism: Undergoes biotransformation in the liver by direct glucuronidation or oxidative metabolism via the cytochrome P450 system.

Elimination: The major excreted metabolites are N-glucuronides and N-methyl o-glucuronide dexmedetomidine. They are inactive and primarily excreted in the urine.

Clearance: May be reduced by as much as 50 % in neonates and infants under 1 year of age [39].

14.4.5   Drug Interactions

Administration of dexmedetomidine with anesthetics, sedative-hypnotics, and opioids likely leads to an enhancement of their effects. It does not appear to interact with neuromuscular blocking agents. Although highly protein bound, it does not result in protein-binding displacement of digoxin, phenytoin, warfarin, propranolol, theophylline, or ketorolac [40].

14.4.6   Systemic and Adverse Effects

Cardiovascular

Dexmedetomidine does not have any direct effects on the heart. A biphasic response in blood pressure has been described when administering a loading dose of 1 mcg/kg of dexmedetomidine to adults. Hypertension is first seen due to direct stimulation of peripheral postsynaptic α_{2b}-adrenergic receptors on vascular smooth muscle, followed by a longer period of hypotension caused by activation of central presynaptic α_{2a}-adrenergic

receptors. This central sympatholytic effect also causes a significant reduction in heart rate [41]. The hypertensive response to a dexmedetomidine bolus appears to be less common in children (5 %) than in adults (25 %), and is more often seen in infants compared to older children [42]. Dexmedetomidine causes a significant decrease in HR and cardiac index (CI) after a single bolus (2 mcg/kg) in children. After prolonged exposure (bolus + 1 mcg/kg/h infusion) in children there is an increase in the SVR, a decrease in HR, CI, and stroke index, and no significant change in blood pressure [43]. The hemodynamic effects of lower dose infusions for children in the intensive care unit setting are likely less pronounced but depend on many factors including the patient's illness, volume status, and the concomitant use of other sedatives. Hypotension and/or bradycardia may require treatment with intravenous fluids, elevation of the lower extremities, or the use of atropine or pressors. Dexmedetomidine has been associated with sinus arrest and disturbances in AV-node conduction in adults, and likely increases the risk of the development of heart block in children. The perioperative use of dexmedetomidine has been associated with a decreased incidence of ventricular and supraventricular tachycardia following congenital heart surgery [44].

Central Nervous System

Dexmedetomidine binds to α_2-receptors in the central nervous system causing dose-dependent sedation, anxiolysis, and analgesia. It reduces the doses of other sedatives required for intensive care unit sedation, and likely reduces the amount of anesthesia required during surgical procedures. This minimum alveolar concentration (MAC)-sparing effect has not been determined in children. Even when using higher doses of this drug,

patients are usually arousable to even gentle stimulation but quickly go back to their sleep-like state. Dexmedetomidine does not provide reliable amnesia, and it is important to administer other types of anesthetic agents during procedures to avoid recall. Dexmedetomidine has no direct effect on intracranial pressure, and in adult patients cerebral autoregulation is preserved [45]. This drug reduces the incidence of emergence delirium following anesthesia and surgery in children [46]. The perioperative use of dexmedetomidine in children after cardiac surgery appears to reduce the incidence of agitation and combative behavior, and decreases the need for benzodiazepines and opioids during the postoperative period. These properties have made this drug an ideal sedative agent for the many children being extubated immediately following cardiac surgery.

Respiratory

Compared to other sedative drugs, dexmedetomidine is unique in that it causes minimal respiratory depression in children; respiratory rate is maintained and there are only mild increases in the $PaCO_2$ [39]. Even in patients with severe obstructive sleep apnea, airway patency is maintained during deep sedation with dexmedetomidine. This unique property has made it possible to perform radiologic studies and minor procedures in children with abnormal airways without endotracheal intubation.

Hepatic and Renal

Liver disease significantly reduces the clearance of dexmedetomidine, and a reduction in dose may be necessary in patients with hepatic impairment. Dexmedetomidine pharmacokinetics are not significantly impacted in patients with severe renal disease when compared to healthy subjects.

14.4.7   Poisoning Information

Dexmedetomidine is a Pregnancy Category C drug, and placental transfer of the drug to the fetus does occur. It should only be used during pregnancy if the potential benefits justify the potential risks to the fetus. Overdoses of dexmedetomidine (i.e. 10 mcg/kg loading dose) have been reported in children, and despite a prolonged period of sedation cardiac and respiratory function remained Stable.

14.4.8   Standard Concentrations and Compatible Diluents

Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is highly lipophilic. It is supplied as a white powder that is freely soluble in water and has a pKa of 7.1. Dexmedetomidine must be diluted in NS to achieve a final concentration of 4 mcg/ml prior to administration. It is compatible when administered with LR, D5W, and 20 % Mannitol. Drugs with which dexmeditomidine is incompatible include amphotericin B and diazepam.

14.5   Remifentanil

14.5.1   Indications

Remifentanil is a potent opioid used for anesthesia, analgesia, and sedation. It is approved by the US Food and Drug Administration for use in children during the induction and maintenance of anesthesia. It has been utilized in pediatric patients during cardiac surgery, cardiac catheterization, transesophageal echocardiography, chest tube placement, and other types of invasive procedures. It is not routinely used for long-term sedation in the intensive care unit because of the development of acute tolerance [47].

14.5.2   Mechanism of Action

Remifentanil is a potent synthetic opioid which binds to the µ-receptor within the CNS and is competitively antagonized by naloxone. It has a rapid onset and offset, can be rapidly titrated to effect, and is not significantly impacted by liver or kidney disease. It allows the anesthesiologist to obtain a hemodynamic profile similar to that seen with a longer acting high-dose opioid technique, while still allowing for extubation of the trachea at the end of the procedure. It is important to administer other longer acting opioids such a morphine or fentanyl when postoperative pain is expected since remifentanil is rapidly metabolized.

14.5.3   Dosing (Based on Ideal Body Weight)

Neonates and Infants: 0.4–1 mcg/kg/min IV continuous infusion, supplement dose 1 mcg/kg IV
Children: 0.5–1.3 mcg/kg/min IV continuous infusion, supplement dose 1 mcg/kg IV
Adults: 0.05–2 mcg/kg/min IV continuous infusion, supplement dose 0.5–1 mcg/kg IV

Remifentanil should not be used as a single agent for general anesthesia because it does not reliably lead to loss of consciousness and/or amnesia, and the dose of other sedative/hypnotic agents may need to be reduced by as much as 75 % when administered with remifentanil. There is significant patient variability in regard to the clinical effects of this drug, and careful titration of the infusion rate based on the patient's individual response is vital. Clinically important side effects include apnea, muscle rigidity, bradycardia, and hypotension.

14.5.4   Pharmacokinetics

Onset: Rapid onset after initiation of a continuous IV infusion, although time to onset is dependent on the rate of infusion. Effects are usually seen with several minutes.

Distribution: Initial volume of distribution in adults of 100 mL/kg, and after distribution into peripheral tissues a steady-state V_d of 350 mL/kg. The steady-state V_d is increased in neonates and decreased in adolescents [48].

Protein Binding: Approximately 70 % of the drug is bound to plasma proteins, of which two-thirds is bound to α-1-acid-glycoprotein.

Half-life: Short elimination half-life of 3–10 min, which is independent of the length of the infusion or the dosed of the drug administered. There is no difference in neonates versus adolescents.

Metabolism: It undergoes rapid hydrolysis by non-specific esterases in blood and tissues, producing a carboxylic acid metabolite that is inactive. Renal and hepatic impairment do not impact the metabolism of remifentanil.

Clearance: Approximately 40 mL/min/kg in young adults. The clearance is increased in neonates (90 mL/min/kg) and in adolescents (57.2 mL/min/kg) [48].

14.5.5   Drug Interactions

Reminfentanil is synergistic with other anesthetic agents and decreases the dose required to achieve similar anesthetic effects. Failure to reduce the dose of other anesthetic agents may lead cardiovascular and/or respiratory compromise.

14.5.6   Systemic and Adverse Effects

Cardiovascular

Effects of remifentanil are similar to other opioids and include a decrease in heart rate, blood pressure, and cardiac index. The reduction in cardiac index is primarily related to a decrease in heart rate, and contractility and stroke volume are usually well maintained. Maintenance of stroke volume is dependent on preoperative volume status, and the cardiovascular effects may be accentuated in the setting of hypovolemia. Treatment with a vagolytic

agent such as atropine or glycopyrrolate prior to administration may ameliorate the reduction in cardiac index [49].

Central Nervous System

Remifentanil does not reliably lead to unconsciousness or amnesia and patient recall should be expected if not administered with other sedative-hypnotic drugs. Administration of remifentanil does not lead to increases in intracranial pressure and cerebrovascular reactivity to CO_2 remains intact. Cerebral perfusion pressure (CPP) does usually decrease due to a reduction in mean arterial pressure. Remifentanil does not significantly impact the monitoring of sensory and motor evoked potentials, and is commonly used as part of a balanced anesthetic technique for surgeries in which this type of monitoring is utilized [50] 2007)

Skeletal Muscle Rigidity

Occurs in as many as 20 % of patients undergoing general anesthesia and is related to the dose and speed of administration. It occurs more commonly with a bolus dose, and chest wall rigidity may make assisted ventilation difficult. Treatment includes discontinuing the continuous infusion, lowering the dose, or administering a neuromuscular blocking agent.

Respiratory

Remifentanil leads to dose-dependent respiratory depression which is augmented by the concomitant administration of other anesthetic agents. After discontinuation of even prolonged infusions the minute ventilation rapidly returns to baseline (<10 min).

Hepatic and Renal

Remifentanil does not have any significant effect on hepatic or renal function.

Other

Additional potential adverse effects include nausea, vomiting, pruritis, dizziness, headache, visual disturbances, and shivering.

14.5.7 Poisoning Information

Symptoms of a remifentanil overdose include apnea, brady-cardia, hypotension, and chest wall rigidity. Treatment is sup-portive and includes maintenance of the airway, administration of intravenous fluids, and atropine for management of brady-cardia. Naloxone, a μ-opioid antagonist, can be utilized to reverse the effects of drug.

14.5.8 Standard Concentrations and Compatible Diluents

Remifentanil is stable with the following diluents: sterile water, D5W, D5NS, NS, ½ NS, LR, and D5LR. The drug is stable for 24 h after reconstitution with all diluents except for LR, in which it is stable for 4 h. Remifentanil can be diluted to concentrations ranging from 20 to 250 mcg/mL [48].

14.6   Fentanyl

14.6.1 Indications

Fentanyl is a potent opioid used for anesthesia, analgesia, and sedation. It is approximately 100 times more potent than morphine sulfate, and can be used during the perioperative period as a premedication, a supplement to other sedative-hypnotic agents for induction and maintenance of anesthesia, and for postoperative analgesia.

14.6.2 Mechanism of Action

Fentanyl is a synthetic opioid with a strong affinity for the μ-receptor, which is located throughout the central nervous system. Fentanyl is extremely lipophilic and rapidly crosses the blood–brain barrier.

14.6.3   Dosing

Fentanyl is primarily administered intravenously, but can be delivered through a variety of routes which include intramuscular, transdermal, transmucosal, intranasal, epidural, and intrathecal. The dose of fentanyl utilized depends on the indication for administration (analgesia vs. anesthesia), airway management plan, and whether the patient is on chronic opioid therapy. There can be significant variability in an individual patient's response to fentanyl and careful titration to the desired effect by practitioners trained in airway management is important. Patients receiving chronic opioid therapy may require extremely high doses which may exceed the upper dose limits noted below.

Sedation and/or Analgesia

Neonates: 0.5–2 mcg/kg/dose
Infants: 1–2 mcg/kg/dose
Children: 0.5–2 mcg/kg/dose

Anesthesia (total dose depends on the length of surgery/type of procedure)

Neonates: 1–5 mcg/kg for inhalational anesthetic-based technique
20–100 mcg/kg for opioid-based technique

Infants: 2–10 mcg/kg for inhalational anesthetic-based technique
20–100 mcg/kg for opioid-based technique

Children: 3–10 mcg/kg for inhalational anesthetic-based technique
20–100 mcg/kg for opioid-based technique

Post-operative Analgesia/Sedation in ICU (depends on type of surgery/airway status)

Neonates: continuous infusion of 0.5–5 mcg/kg/h
Infants: continuous infusion of 1–5 mcg/kg/h
Children: continuous infusion of 1–5 mcg/kg/h

14.6.4   Pharmacokinetics

Onset: Rapid onset after IV bolus dose; maximal analgesic and respiratory depressant effects occur within several minutes

Distribution: High lipid solubility results in significant redistribution into muscle and fat. The V_d is greater in neonates, infants, and children compared to adults.

Protein Binding: At physiologic pH, 84 % is bound to erythrocytes, α_1-acid glycoprotein, and plasma albumin.

Elimination Half-life: Extremely variable and dependent on age and dose administered. In children receiving prolonged infusions the elimination half-life ranges from 11 to 36 h [51].

Metabolism: Fentanyl is primarily metabolized in the liver, and liver failure will significantly impact the clearance of this drug.

Clearance: Extremely variable and dependent on hepatic function, hepatic blood flow, and V_d. Clearance is markedly prolonged in pre-term neonates compared to neonates, and in neonates compared to infants [52, 53].

14.6.5   Drug Interactions

The use of other opioids, sedative-hypnotic drugs, and anesthetic agents will have additive effects. The dose of other anesthetic agents required may be decreased when fentanyl is utilized as part of a balanced anesthetic technique.

14.6.6   Systemic and Adverse Effects

Cardiovascular

Fentanyl is commonly used as the primary anesthetic agent in neonates and infants undergoing cardiac surgery. When administered as an induction agent (50–75 mcg/kg) with the non-depolarizing muscle relaxant pancuronium,

there are minimal effects on heart rate and arterial blood pressure and no significant response to endotracheal intubation [54]. In infants receiving a 25 mcg/kg bolus of fentanyl following congenital heart surgery, no significant change in heart rate, cardiac index, mean pulmonary artery pressure, and the pulmonary vascular resistance index were seen [55]. When high-dose fentanyl is administered to young children without a vagolytic drug, a significant reduction in heart rate, arterial blood pressure, and cardiac output may be seen. Fentanyl blunts the sympathetic nervous system and suppresses the hormonal and metabolic stress response to surgery, a factor which has been shown to improve outcomes following neonatal operations [56]. The addition of other sedative-hypnotic agents such as midazolam may lead to hypotension during anesthesia and sedation in neonates and older children with impaired cardiac function, and should be used with caution [57].

Respiratory

Fentanyl causes dose-dependent depression of ventilation with a reduction in respiratory rate and normal to increased tidal volume. Because fentanyl rapidly crosses the blood–brain barrier, it more commonly leads to apnea in young children compared to other opioids. Chest wall rigidity can occur in neonates after the administration of small bolus doses of fentanyl (1–2 mcg/kg), and can be alleviated by muscle relaxants or naloxone.

Central Nervous System

Fentanyl provides analgesia and sedation at lower doses (1–3 mcg/kg), and may lead to loss of consciousness at higher doses. Even at higher doses (10–100 mcg/kg), it does not provide reliable hypnosis or amnesia. The addition of some type of other hypnotic agent (benzodiazepine, ketamine, propofol, inhaled anesthetic agent) is recommended to avoid awareness. There is disagreement within the anesthesia community as to whether it is appropriate

to use fentanyl as the sole anesthetic agents in neonates and young infants undergoing cardiac surgery. Children receiving an infusion of fentanyl for postoperative analgesia can rapidly develop tolerance over 24–48 h requiring an escalation in the administered dose [58].

Other

Fentanyl can cause nausea, vomiting, pruritis, and miosis.

14.6.7   Poisoning Information

Symptoms are similar to an overdose of other opioid drugs and include apnea, bradycardia, hypotension, and chest wall rigidity. Treatment is supportive and includes maintenance of the airway, administration of intravenous fluids, and atropine for management of bradycardia. Naloxone, a μ-opioid antagonist, can be utilized to reverse the effects of drug.

14.6.8   Standard Concentrations and Compatible Diluents

Fentanyl citrate is preservative-free and available in a concentration of 50 mcg/mL. It is packaged in 2, 5, 20, and 50 mL ampules and/or vials. It is stable with the following diluents: sterile water injection, D5, and NS.

14.7   Benzodiazepines: Midazolam and Lorazepam

14.7.1   Indications

Benzodiazepines have anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and antegrade amnestic effects of varying degrees. Midazolam is the most commonly administered perioperative benzodiazepine, and is used for preoperative medication and intravenous sedation. It is often added to

fentanyl anesthesia as a sedative and amnestic in hemodynamically unstable patients and infants who cannot tolerate the myocardial depressant effects of volatile agents. Lorazepam is frequently used as an intermittently dosed sedative in the intensive care unit.

14.7.2   Mechanism of Action

Benzodiazepines bind specific $GABA_A$ receptor sites that almost exclusively exist on post-synaptic nerve endings in the CNS, thereby facilitating GABA inhibitory effects. The cerebral cortex has the highest density of these receptors, followed by the hypothalamus, cerebellum, midbrain, hippocampus, medulla, and spinal cord. It has been suggested that 20 % benzodiazepine receptor occupancy is associated with anxiolysis, 30–50 % occupancy produces sedation, and >60 % occupancy is necessary for loss of consciousness. For comparison, midazolam is 3–6 times, and lorazepam is 5–10 times, as potent as diazepam.

14.7.3   Midazolam Dosing

Anxiolysis, *Induction of Amnesia*, *Procedural Sedation*

- *6 months and older*: average single oral dose of 0.25–0.5 mg/kg (up to 1 mg/kg for younger patients 6 months to 6 years or uncooperative patients, with a maximum of 20 mg) administered 30 min prior to procedure. IM dose of 0.10.15 mg/kg is also effective when administered within 60 min of the procedure (up to 0.5 mg/kg IM in more anxious patients, with maximum dose of 10 mg).
- *6 months to 5 years*: initial dose of 0.05–0.1 mg/kg IV, titrated to desired effect (allowing 2–3 min after each increment for evaluation) to a total dose of 0.6 mg/kg. Maximum total dose 6 mg.
- *6–12 years*: initial dose of 0.025–0.05 mg/kg IV, titrated to desired effect (allowing 2–3 min after each increment for evaluation) to a total dose of 0.4 mg/kg. Maximum total dose 10 mg.

Healthy adults and children >12 years of age: 1–2 mg IV, may titrate using smaller increments with repeated dosing to desired level of effect. 0.07–0.08 mg/kg (usual dose 5 mg) IM administered up to an hour before procedure

Other routes of administration: Intranasal dose 0.2 mg/kg, can be repeated in 5–15 min, up to total 0.6 mg/kg.

Dose adjustment is necessary when administered with opioids to avoid respiratory depression and hypotension. When midazolam has been given as a premedication, IV anesthetic induction agent dose may be reduced.

Induction of Anesthesia

Healthy adults: in the absence of premedication, 0.3–0.35 mg/kg IV; after sedative or narcotic premedication, 0.15–0.25 mg/kg. Allow 2 min for effect, then additional increments of 25 % of initial dose may be used up to total 0.6 mg/kg in resistant cases.

Sedation in the Critical Care Setting for Mechanically Ventilated Patients:

Neonates: no IV loading dose; <32 weeks 0.03 mg/kg/h (0.5 mcg/kg/min), >32 weeks 0.06 mg/kg/h (1 mcg/kg/min) continuous IV infusion

Rapid IV injection should be avoided in neonates because severe hypotension and seizures have been noted.

Older infants and children: 0.05–0.2 mg/kg IV loading dose, followed by continuous IV infusion at 0.06–0.12 mg/kg/h (1–2 mcg/kg/min). Rate may be adjusted up or down by 25 % of initial or subsequent rate to achieve adequate sedation.

Healthy adults and children >12 years: 0.01–0.05 mg/kg IV loading dose, followed by continuous IV infusion of 0.02–0.1 mg/kg/h, titrated as needed.

Decreased infusion dosing required when concomitant narcotic analgesics are employed. Minimum effective infusion rate should be established to decrease potential accumulation and provide for rapid recovery when infusion is terminated.

14.7.4 Midazolam Pharmacokinetics

Onset: Short duration of action is due to high lipid solubility, leading to rapid restribution from brain to inactive tissue sites. There is high bioavailability (>90 %) with IM injection; time to peak onset after IM injection is 30 min. Oral premedication in children provides reliable amnesia and significant anxiolysis within 10 and 15 min respectively [59]. Following IV administration, peak effects occur within 2–3 min.

Distribution: V_d 0.4–4.2 L/kg (preterm infants); 1.24–.02 L/kg (infants and children 6 months to 16 years); 1–.1 L/kg (adults)

Protein binding: highly protein bound (96–98 %)

Half-life: Elimination half-life is 1–4 h; shorter context-sensitive half-life compared to diazepam and lorazepam

Metabolism: Extensive hepatic metabolism to hydroxylated metabolites that are conjugated before excretion. Only ~50 % of orally administered dose reaches systemic circulation due to substantial first-pass hepatic effect.

Clearance: Renal excretion of metabolites. α-hydroxymidazolam is an active metabolite, with estimated 20–30 % potency of midazolam; in healthy patients, it is rapidly cleared by the kidneys, but can accumulate in patients with renal impairment. <0.5 % unchanged midazolam is excreted by the kidneys.

14.7.5 Lorazepam Dosing

Premedication for Anxiolysis, **Induction of Amnesia**, **Sedation**: 0.05 mg/kg oral or IM (not to exceed 2 mg for pediatric patients 1 month to 12 years, 4 mg for patients ≥13 years); 0.01–0.04 mg/kg IV (up to 2 mg dose)

Sedation

Infusion: 0.01–0.1 mg/kg/h IV

Propylene glycol can accumulate significantly in patients receiving continuous lorazepam infusions [60]; therefore

patients should be monitored for signs and symptoms of propylene glycol toxicity, including metabolic acidosis, renal insufficiency or failure, mental status changes, hemolysis, and an elevated osmolar gap.

Intermittent bolus: 0.02–0.06 mg/kg IV every 2–6 h

Slow onset of action limits lorazepam's usefulness as an anesthetic induction agent.

14.7.6 *Lorazepam Pharmacokinetics*

Onset: Reliable absorption after oral and IM injection, but slow onset of action. Time to peak onset after oral administration is 1–2 h; for IM administration, peak onset occurs within 3 h. IV premedication should be administered 15–20 min before procedure.

Distribution: V_d 0.8–1.3 L/kg

Protein Binding: Highly protein bound (91 %)

Half-life: Elimination half-life is 10–20 h

Metabolism: Extensively conjugated in the liver to inactive metabolite lorazepam glucuronide; undergoes entero-hepatic recirculation

Clearance: Renal (88 %) and fecal (7 %) excretion of metabolites; 0.3 % of a dose is excreted unchanged.

14.7.7 *Drug Interactions*

The sedative effects of benzodiazepines are accentuated when administered concomitantly with any other CNS depressant, particularly narcotics. Decreased motor coordination and impaired cognitive function may also occur.

14.7.8 *Systemic and Adverse Effects*

Cardiovascular

The predominant hemodynamic effect of benzodiaze-pines is a reduction in arterial blood pressure as a result

of decreased SVR, with midazolam causing a slightly larger effect compared to lorazepam. HR increases slightly as a result of baroreflex activation. The hemodynamic effects are dose-related, with higher plasma levels causing a greater decrease in SBP; however, there is a plateau plasma drug effect above which there is little change in arterial blood pressure [61]. The combination of benzodiazepines and opiates produces a supra-additive hypotension. In children with congenital heart disease, fentanyl/midazolam caused a 22 % decrease in CO despite preservation of contractility [62]. Since this is predominantly due to a decrease in HR, coadministration of a vagolytic agent (atropine or pancuronium) may preserve CO.

Central Nervous System

Benzodiazepines produce a dose-related decrease in $CMRO_2$ and CBF. Cerebrovascular responsiveness to CO_2 is preserved. The effects on EEG include a decrease in alpha activity and an increase in rapid beta activity. Midazolam is unable to produce an isoelectric EEG. Benzodiazepines, specifically midazolam and diazepam, are potent anticonvulsants that can be used to treat both status epilepticus and grand mal seizures resulting from local anesthetic toxicity.

Respiratory

Benzodiazepines produce dose-related, central respiratory depression. The principal changes in ventilator mechanics include a decrease in tidal volume and increased respiratory rate and alveolar dead space. Apnea may also occur with rapid injection of higher doses (i.e. >0.15 mg/kg IV midazolam), especially if the patient has been premedicated with an opioid. Syngergistic respiratory depression has been observed when benzodiazepines and opioids are jointly used. Midazolam alone (0.05 mg/kg IV) produced no significant respiratory effects, but when given in combination with fentanyl (2 mcg/kg IV), the incidence of both hypoxemia and apnea increased significantly [63].

Benzodiazepines also depress the swallowing reflex and decrease upper airway activity.

Other

Although often administered for anxiolysis, benzodiazepines may elicit paradoxical reactions such as stimulation, irritability, restlessness, agitation, aggression, hostility, or rage [64]. These occur rarely and in an unpredictable fashion.

14.7.9 Poisoning Information

Both midazolam and lorazepam are Schedule IV controlled substances with potential for abuse and dependence. Even therapeutic doses can produce dependence, as evidenced by onset of physical and/or psychological symptoms after dosage is decreased or drug is discontinued. Withdrawal symptoms (irritability, insomnia, tremulousness) manifest within 1–2 days of discontinuation of short-acting benzodiazepines and within 2–5 days for longer-acting drugs. Flumazenil is a specific benzodiazepine-receptor antagonist that is indicated for reversal of the sedative and respiratory depressant effects of benzodiazepines. It has minimal intrinsic activity and functions as a competitive antagonist.

14.7.10 Standard Concentrations and Compatible Diluents

Lorazepam solution, available as 2 or 4 mg/mL, is compounded with 80 % polyethylene glycol with 2 % benzyl alcohol as a preservative. It should be stored in a refrigerator, protected from light. Undiluted solution is appropriate for IM injection. Prior to IV administration, it should be diluted with equal volume of compatible solution (sterile water for injection, NS, or D5W). Oral solution (2 mg/mL) and tablets (0.5, 1, 2 mg) are also available.

Midazolam injectable solution (1 or 5 mg/mL) is compounded with 0.8 % sodium chloride and 0.01 %

disodium edetate, with 1 % benzyl alcohol as a preservative. The pH is adjusted to 3 with hydrochloric acid and sodium hydroxide, to maintain water solubility. Compatible diluents include D5W, NS, LR. It may be mixed in the same syringe with the following commonly used premedications: morphine, meperidine, atropine or scopolamine. Midazolam is also available as a 2 mg/mL oral syrup.

14.8   Volatile Anesthetic Agents: Isoflurane, Sevoflurane, and Desflurane

14.8.1   Indications

These inhalational agents are used for general anesthesia. The two universal effects are immobility in response to noxious stimuli and amnesia.

14.8.2   Mechanism of Action

The mechanism of action of these agents is not entirely understood, but presumed to involve multiple sites of activity. Unconsciousness and amnesia may be mediated by cortical action, while ablation of movement in response to pain may be related to subcortical structures such as the spinal cord or brainstem. Synaptic transmission is more sensitive to general anesthetic agents than axonal conduction. On the molecular level, volatile anesthetics act directly on proteins, altering the function of ion channels [65] or the systems that regulate them. $GABA_A$, nicotinic acetylcholine receptors, glycine, and glutamate receptors have been implicated.

14.8.3   Dosing

The measure of inhalational anesthetic potency has traditionally been expressed in terms of the minimum alveolar concentration (MAC). This is defined as the concentration at 1 atm that prevents skeletal muscle movement in

response to surgical skin incision in 50 % of patients. Dose response curves for inhaled anesthetics, although not parallel, are all steep, emphasizing the fact that a modest increase to about 1.3 MAC prevents movement in at least 95 % of patients. The concomitant use of other agents (nitrous oxide, opiates, benzodiazepines, etc.) can decrease MAC requirements. Also, MAC decreases with increasing age [66]. Thus, infants require higher concentrations of anesthetic than older children and adults. Tables 14.1, 14.2, and 14.3 show MAC correlated with age for isoflurane, sevoflurane and desflurane.

TABLE 14.1 Isoflurane: MAC correlated with age

Age	MAC (% expired)
35 weeks	1.4
0–1 months	1.5
1–6 months	1.8
6–12 months	1.6
1–5 years	1.6
Adults	1.2

TABLE 14.2 Sevoflurane: MAC correlated with age

Age	MAC (% expired)
0–30 days	3.3
1–6 months	3.2
6–12 months	2.5
1–12 years	2.5
Adults	2.6
Elderly	1.5

TABLE 14.3 Desflurane: MAC correlated with age

Age	MAC (% expired)
0–30 days	9.16
1–6 months	9.42
6–12 months	9.98
1–3 years	8.72
3–5 years	8.62
5–12 years	7.98
>12 years	6

14.8.4   Pharmacokinetics

Uptake and Distribution

The uptake and distribution of inhalational agents is more rapid in infants and children than in adults. For any given anesthetic agent, the onset and recovery times are related to anesthetic solubility as well as the patient's minute ventilation and CO. Compared with adults, pediatric patients have more rapid respiratory rates, increased CI, and distribution of a greater proportion of the CO to vessel-rich organs. The presence of a right-to-left shunt has a diluting effect on the partial pressure of anesthetic in blood because a portion of systemic CO bypasses the lung. Volatile anesthetics that are initiated during cardiopulmonary bypass (CPB) take longer to equilibrate, while those same drugs present when CPB is initiated become diluted, potentially changing the anesthetic depth.

Elimination and Metabolism

Elimination of volatile anesthetic agents is by exhalation. It depends on the length of administration and the blood-gas solubility of the anesthetic agent. Generally speaking, the time needed for a 50 % decrease in anesthetic

concentration of isoflurane, sevoflurane, and desflurane is <5 min and does not significantly increase with anesthetic duration. The 80 % decrement times of both sevoflurane and desflurane are also small (<8 min) and do not increase significantly with anesthetic duration. In contrast, the 80 % decrement time of isoflurane increased to 30–35 min after approximately 60 min of anesthesia [67]. Hepatic metabolism plays a small role for all three agents.

14.8.5   Systemic and Adverse Effects

Cardiovascular

Decreases in SVR and sympathetic tone contribute to decreased arterial blood pressure in a dose-dependent fashion. All volatile anesthetic agents also directly depress myocardial contractility. It is important to note that neonates exhibit an exaggerated degree of depression of myocardial contractility in response to volatile agents [68]. Sevoflurane tends to increase HR only at concentrations of >1.5 MAC, whereas isoflurane and desflurane affect HR at lower concentrations. Volatile anesthetics appear to exert little predictable effect on pulmonary vascular resistance

Central Nervous System

Volatile anesthetics do not cause retrograde amnesia. $CMRO_2$ decreases in parallel with drug-induced decreases in cerebral activity. Cerebral vasodilation and decreased cerebral vascular resistance cause increased CBF that can increase ICP in patients with space-occupying lesions. Isoflurane, sevoflurane and desflurane do not produce evidence of epileptic activity on EEG. Volatile anesthetics, however, decrease the amplitude and increase the latency of somatosensory, visual, and auditory evoked potentials.

Respiratory

Generally, there is a rapid, shallow pattern of spontaneous breathing in patients under general anesthesia with

volatile agents. Increases in respiratory rate do not offset the decrease in tidal volume, resulting in net loss of minute ventilation and increases in $PaCO_2$. Ventilatory responses to both carbon dioxide and hypoxemia are also diminished. Volatile agents can dilate constricted bronchial muscles, but in the absence of bronchoconstriction, changes in airway resistance are hardly noticeable.

Other

Additional adverse effects include nausea, vomiting, and shivering.

14.8.6 Poisoning Information

Excessive concentrations of potent inhalational anesthetics can result in respiratory arrest and cardiovascular collapse. Treatment is discontinuation of the agent and supportive care with ventilatory support, IV fluids, and inotropic medications.

14.8.7 Standard Concentrations and Compatible Diluents

Isoflurane, sevoflurane, and desflurane are available as volatile liquids which are administered via agent-specific vaporizers. They are not diluted.

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Chapter 15
Medication Management in Patients with Multi-organ Failure

Kelli L. Crowley and Carol G. Vetterly

Abstract   Patients with multiple organ dysfunction syndrome (MODS) are severely ill and efficacy of medication therapies is crucial to outcomes. The physiologic changes that accompany MODS have many effects on medication dosage. Hemodynamic alterations and increased volume as well as organ function deterioration cause pharmacokinetic and pharmacodynamic modifications of drugs. Chemical properties of a medication dictate to what extent that medication is affected. There are many confounders present when tailoring medication management that will be especially as number of failing organ systems increases. Constant evaluation for efficacy and toxicity is imperative. Successful medication management involves maximizing efficacy while minimizing

K.L. Crowley, PharmD, BCPS (✉) • C.G. Vetterly, PharmD, BCPS
Department of Pharmacy Services, Children's Hospital of
Pittsburgh of UPMC, Pittsburgh, PA, USA

Department of Pharmacy and Therapeutics,
University of Pittsburgh School of Pharmacy,
Pittsburgh, PA, USA
e-mail: kelli.crowley@chp.edu; carol.vetterly@chp.edu

adverse effects. The objective of this chapter is to discuss concepts of pharmacodynamics and pharmacokinetics that affect medication management of patients experiencing MODS and practical applications of those concepts to persons receiving extracorporeal membrane oxygenation (ECMO) and/or renal replacement therapies.

Patients with multiple organ dysfunction syndrome (MODS) are severely ill and efficacy of medication therapies is crucial to outcomes. The physiologic changes that accompany MODS have many effects on medication dosage. Hemodynamic alterations and increased volume as well as organ function deterioration cause pharmacokinetic and pharmacodynamic modifications of drugs. Chemical properties of a medication dictate to what extent that medication is affected. There are many confounders when tailoring medication management that will be especially as number of failing organ systems increases. Constant evaluation for efficacy and toxicity is imperative. Successful medication management involves maximizing efficacy while minimizing adverse effects.

The objective of this chapter is to discuss concepts of pharmacodynamics and pharmacokinetics that affect medication management of patients experiencing MODS and practical applications of those concepts to persons receiving extracorporeal membrane oxygenation (ECMO) and/or renal replacement therapies.

15.1   Pathophysiology

Initially, MODS causes vasodilation and endothelial dysfunction resulting in capillary leakage into the extracellular space [1]. This shifting of fluid contributes to a dilutional effect on the serum. This is amplified by the fluid resuscitation that

most patients receive. Patients will experience edema as fluid accumulates. Often patients experience myocardial dysfunction producing hemodynamic variations which then cause hypoperfusion of the tissues and organs [1].

MODS often involves either renal dysfunction, hepatic dysfunction or both. Organ hypoperfusion may contribute to or worsen dysfunction. The rate of clearance declines as the function of the organ(s) responsible for metabolism and elimination declines. When a patient has renal dysfunction, congestive heart failure, ascites and/or inflammatory processes fluid will accumulate. When hepatic dysfunction is present, production of proteins such as albumin and glycoprotein is impaired decreasing binding of highly bound drugs [1].

15.2   Chemical Properties of Drugs

Distribution of medications is dependent on chemical properties of drugs. Ionic charge affects affinity for water versus lipid environment. Drugs will demonstrate either hydrophilic or lipophilic properties. A molecule that is hydrophilic will remain in the extracellular water of the intravascular and interstitial spaces without entering cell membranes. Examples of hydrophilic drugs include aminoglycosides [2] and beta-lactam antibiotics [1]. A lipophilic molecule will cross cell membranes allowing distribution into intracellular space and adipose tissues. Examples of lipophilic agents are benzodiazepines [2], amiodarone, phenytoin/fosphenytoin, fluoroquinolones and lincosamides. Molecular size also influences drug distribution with larger entities staying in the intravascular space but smaller ones being able to disperse more freely out of it [1]. Vancomycin would be an example of a drug that is considered to be a large molecule.

15.3   Pharmacodynamics

Pharmacodynamics describes the relationship between drug concentration at the site of action and the pharmacologic effect [2]. At the onset of MODS, there is a decline of serum

levels of medications observed with edema and fluid accumulation [2]. When cardiac dysfunction, vasodilation and capillary leak are present, circulation and consequently delivery of agents is compromised. Due to the increase in volume of distribution and decreased medication transport in the early stages of MODS, medications, particularly hydrophilic, will exhibit suboptimal efficacy because there is a subtherapeutic quantity reaching the target site(s) [3]. Subtherapeutic medication concentrations at the target sites may potentiate treatment failure.

In later stages of MODS, two potentially opposing pharmacodynamic effects may occur. Organ dysfunction ultimately decreases drug and metabolite elimination [1]. This leads to toxic pharmacologic effects of medications due to accumulation in the body and more specifically at the site(s) of action [3]. Active metabolites may also accumulate in this fashion further increasing drug effects and/or toxicities. The hemodilutional effect of excess fluid will still be present in later stage MODS. Declining cardiac, hepatic and renal function will exert the opposite effect on drug concentration causing subtherapeutic exposure at receptor sites [3]. Depending upon the specific patient situation and medication properties, these patients may experience decreased pharmacologic efficacy or increased toxicity [1].

15.4   Pharmacokinetics

Critically ill patients frequently experience pharmacokinetic alterations. Pharmacokinetics is defined as how the body affects a medication. Kinetic components include absorption, distribution, metabolism and excretion.

Absorption is affected by gastrointestinal function, pH and presence or absence of normal flora. In addition there will be hypoperfusion of the gut when patients are hemodynamically compromised [4]. Absorption is erratic and variable [5]. Gastric emptying is delayed in >20 % of critically ill

patients. There is no way to accurately and consistently measure gastric function and thereby medication absorption. While a patient may tolerate enteral feedings, that does not ensure medication absorption. The patient's physiologic response must be assessed when enteral drug formulations are used. It may be prudent to use parenteral administration if dysfunction is suspected [4].

Distribution of drugs is affected by hydration status, body composition (quantity of adipose tissue) and hypoalbuminemia. Hydration influences volume of distribution of medications. These patients tend to receive a large amount of fluid resuscitation resulting in a significant expansion of total volume in the body. Medications will have a larger volume of distribution and there will be a dilutional effect on drug serum concentration. Patients with larger ratios of adipose tissue to body weight exhibit greater distribution of lipophilic drugs into that adipose tissue and possibly away from target receptor sites [1].

Many drugs are bound in considerable proportion (>70 % of serum concentration) to serum proteins with just a small, free, or unbound, portion being available to work at the receptor site. Critically ill patients can be expected to have a striking reduction in serum albumin concentration, especially in the early stage of MODS [4]. If hypoalbuminemia is present, agents that are normally highly bound are then able to be present in the serum in elevated free fraction concentrations and are able to distribute more freely into the tissues to exert their physiologic effects. Also, there will be competition for binding by toxins and other protein bound medications which may cause displacement of highly bound drugs [4]. Significant toxicity can result especially when a medication has a narrow therapeutic free fraction serum level range. Some of these drugs include phenytoin/fosphenytoin, lidocaine, propranolol and warfarin [1].

Metabolism and clearance are largely reliant on hepatic and renal function and the blood flow to those organs [2]. This will be discussed in further detail in later sections of this chapter.

15.5   Cardiovascular Dysfunction

Cardiovascular dysfunction plays a role in suboptimal medication therapy in MODS. Deterioration in cardiac function impedes delivery of drugs by delaying distribution due to reduced output and through fluid accumulation. Improper functioning of the heart can also lead to renal impairment [6]. Microvascular alterations that manifest during MODS further obstructing delivery and achievement of pharmacologic effects [4].

15.6   Hepatic Dysfunction

Hepatic dysfunction affects medications through alterations in first pass effect, anatomic and physiologic changes. Liver damage may result from cholestasis, hepatocellular injury, hypoperfusion, hemolysis, or hepatotoxins. Residual hepatic function is variable depending on degree of failure [1]. It can only be assessed by clinical observation and evaluation of abnormalities in enzyme, bilirubin, albumin and coagulation laboratory values [4]. Cytochrome P450 enzymes are more sensitive to liver dysfunction than conjugation. Impairment of micro- and macrovasculature, fibrosis and cirrhosis inhibit metabolism and clearance of medications [1, 7]. Dose reduction is required for hepatically metabolized drugs and should be patient-specific.

First pass effect describes the metabolism of enterally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation. In the setting of MODS, decreased systemic circulation and thereby hepatic blood flow velocity decreases delivery of all medications to the liver [7]. A smaller fraction of a drug requiring hepatic metabolism or elimination reaching the liver will lead to accumulation and toxicity. In addition, hepatitis causes lower capacity of liver enzymes important to phase I and phase II metabolism. All of these factors contribute to accumulation, supratherapeutic systemic concentrations

and toxicity [1]. Propranolol is a medication in which hepatic metabolism and clearance is important [2].

15.7   Renal Failure

There are a multitude of challenges associated with identifying the most appropriate drug dosing for pediatric patients with renal failure. The most ideal method is to measure a urinary creatinine clearance (24 h) in critically ill patients. However, when that is not possible, an estimation of creatinine clearance is accomplished by using established formulas such as the Bedside Schwartz equation in children or the Cockroft-Gault equation for older adolescents and adults [3]. Careful extrapolation must be made when applying the formulas to critically ill children because the variation in plasma creatinine concentrations may be decreased due to immobility and decreased muscle mass [8].

Medication dose adjustments are necessary in critically ill patients with renal impairment. This is accomplished by a dose reduction or extended dose intervals to prevent drug accumulation and resulting adverse effects [9]. This is especially relevant when the medications are nephrotoxic and have a narrow therapeutic window. Careful attention must be made to ensure that there is a balance between efficacy and toxicity which can produce additional injury to already compromised kidneys [3].

Drug that have defined levels associated with optimal therapy are more easily adjusted because the doses or dosing intervals can be titrated based on the measured results. Examples of medications in these classes are vancomycin, aminoglycoside antibiotics (gentamicin, tobramycin, amikacin), antiepileptic drugs (phenytoin, phenobarbital). and cardiac medications (digoxin). These medications all have relatively narrow therapeutic windows and therapeutic drug monitoring is imperative in patients with renal compromise. Drugs that are concentration dependent should have the dose interval adjusted to ensure that the peak concentrations are obtained to achieve maximal effects [10].

Medications that do not have levels associated with them are more difficult to ascertain efficacy though and pharmaco-dynamics should be considered to provide optimal outcomes. For example, when considering antibiotics whose therapeutic effects are time dependant, a dose reduction would be the most prudent, rather than an a dose interval adjustment to ensure optimal time above the minimum inhibitory concentration of the drug [10].

There are many published dosing references available in the literature that provide recommendations for patients with impaired renal function or renal failure [3, 11–13]. Daily review of medication dosing in patients with compromised renal function is necessary to prevent toxicity and adverse events and ensure the desired therapeutic effects.

15.8   Renal Replacement Therapy

Drug dosing during renal replacement therapy (RRT) can also be challenging. Each mode of therapy is accomplished by different mechanisms. Drug clearance changes depending on which modality the patient is receiving.

In hemodialysis, blood flows on one side of a semipermi-able membrane as a crystalloid solution is pumped along the other side of the membrane in a countercurrent fashion. Large drug molecules, such as vancomycin, are expected to have slow rate of diffusion across the membrane [14]. Vancomycin dosing is determined by the timing of administration (during or after dialysis), the type of filter used, and the duration of dialysis.

Hemofiltration or continuous renal replacement therapy (CRRT), continuous arteriovenous hemofiltration (CAVH), or continuous veno-venous hemofiltration (CVVH) differs from hemodialysis in that blood is passed down one side of a highly permeable membrane under pressure which permits water and molecules with a high molecular weight to pass through the membrane by convection flow. Larger drug molecules such as heparin, insulin and vancomycin are cleared

more efficiently via this method [14]. Continuous venovenous hemofiltration with dialysis (CVVHD) is hemofiltration with the addition of dialysis to the system. Acute hyperkalemia or hyperammonemia are possible indications for this mode of dialysis [14].

Drug dosing can vary depending upon the type of renal replacement therapy a patient is receiving because each mode can affect the extent to which the drug is cleared. Factors that affect drug clearance include the molecular weight, pores of the membrane filter, adsorption of drug to the membrane filter, the percent of protein bound drug, the placement of the replacement fluid and the ultrafiltration rate [15]. In addition to information published in tertiary references, there are articles that provide information on the effects of specific renal replacement therapies on drug dosing [15].

15.9   Extracorporeal Membrane Oxygenation

ECMO can also have an effect on drug clearance and is utilized in critically patient with MODS. However, there are not an abundance of literature describing the effects of ECMO on drug metabolism and clearance in children.

ECMO alters the apparent volume of distribution of medications [16] because the circuit may potentially double the extracellular fluid volume of the patient. This effect is more pronounced with drugs with smaller volume of distribution, however it is unclear the degree to which this occurs [16]. Other factors in ECMO which can affect drug clearance include: decreases in drug protein binding, drug adherence to the pump tubing and oxygenator (and subsequent changes when the device binding sites are saturated), as well as if the drug is administered directly to the circuit as opposed to into the patient [16].

There is limited information on the effects of drug clearance and ECMO although some medications have been well studied. Antibiotics that have been studied include gentamicin and vancomycin. Some studies suggest that the half-life of

gentamicin is increased by two fold with ECMO [17]. Several study results recommended starting with an 18 h dosing regimen and measuring levels to determine the appropriate timing of the dose for avoidance of toxicity [17]. Vancomycin is often utilized in patients on ECMO in pediatric intensive care units. Altered vancomycin disposition was suggested in patients on ECMO receiving vancomycin [18]. Dosing intervals of every 18–24 h have been recommended based on studies [19]. Trough levels should be monitored closely to ensure appropriate therapeutic levels are maintained.

Patients have increased requirements of morphine and fentanyl when on ECMO. There is a loss of drug in the circuit. The extent of drug sequestered in the circuit is greater with fentanyl than with morphine. The ECMO membrane oxygenator appears to be the primary site of drug loss and the binding is irreversible [20].

Generally, there is a reduction in drug clearance in pediatric patients on ECMO support. There are many factors which may contribute to this decreased clearance including, organ function due to illness as well as organ perfusion [16]. The extent to which the drug adheres to the oxygenator and circuit also plays a large role in the medication's pharmacokinetic parameters. Pharmacoviligilance is vital to ensure that the desired therapeutic effects are achieved.

15.10   Conclusion

When approaching medication management issues in patients with MODS, it is necessary to evaluate the chemical characteristics of the drugs being prescribed as well as the specific influences on pharmacodynamics and pharmacokinetics that are exerted by the degree of organ dysfunction present. The physiologic effect of MODS may lead to plasma medication concentrations that are difficult to predict. Appropriate medication therapy is essential to maximizing patient outcomes in MODS.

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Chapter 16
Drug Therapy for Hypercholesterolemia and Dyslipidemia

Sarah D. de Ferranti

Abstract   The initial and primary treatment of abnormal lipid levels in children is to change diet and activity levels. Pharmacological treatment of lipid disorders is used according to guidelines published in 2011. In adults treatment cutpoints and goals for therapy are adjusted based on high risk populations and in the presence of other cardiovascular (CV) risk factors. Pediatric lipid guidelines also reflect this type of thinking, although the data on which treatment cutpoints are based is less robust than adults. Atherosclerosis is known to begin in childhood; however, extensive outcome data are lacking in pediatrics and parental and/or patient preference are usually included in the decision-making process.

Keywords   Hypercholesterolemia • Dyslipidemia • Bile acid sequestrants

S.D. de Ferranti, MD, MPH
Preventive Cardiology, Children's Hospital Boston,
Harvard Medical School, Boston, MA, USA
e-mail: sarah.deferranti@cardio.chboston.org

16.1 Treatment Criteria and Guidelines

The initial and primary treatment of abnormal lipid levels (Table 16.1) in children is to change diet and activity levels. Pharmacological treatment of lipid disorders is used according to guidelines published in 2011 (Table 16.2) [52]. In adults treatment cutpoints and goals for therapy are adjusted based on high risk populations and in the presence of other cardiovascular (CV) risk factors (Table 16.3). Pediatric lipid guidelines also reflect this type of thinking, although the data on which treatment cutpoints are based is less robust than adults. Extensive outcome data are lacking in pediatrics and parental and/or patient preference are usually included in the decision-making process.

Table 16.1 Categorization of lipid levels, shown in mg/dL

	TC	LDL	TG	HDL
Abnormal*	>200	>130	>150	<40
Borderline*	170–199	110–129	130–150	40–45
Acceptable	<170	<110	<130	<45
Ideal		70		<60

*>95th percentile from the Lipid Research Clinic. **>75th <95th percentile. Cutpoints for total cholesterol (TC) and low-density lipoprotein (LDL) are defined by the National Cholesterol Education Program (NCEP) and American Academy of Pediatrics (AAP) as published in 1992 and 1998 [1, 50]. The triglyceride (TG) and high-density lipoprotein (HDL) cutpoints are those used by the author in clinical practice and are based on normal values for children from the Lipid Research Clinics. School-aged children have lower TG and higher HDL than adolescents. Adolescent males have lower HDL after puberty likely due to increased testosterone

Table 16.2 AAP/NCEP recommendations for the initiation of pharmacotherapy

Indication for pharmacotherapy
Inadequate response to diet and lifestyle modification ≥6 months
Age ≥10 years
LDL ≥190 mg/dL
OR
1. LDL ≥160 mg/dL + family history of early coronary disease, OR
2. Two or more cardiovascular risk factors, OR
3. Coronary disease or equivalent (stroke, peripheral artery disease, diabetes)

Guidelines extracted from [52]

16.2   Non-pharmacological Lipid Lowering

16.2.1   Diet and Activity

Dietary counseling for abnormal lipid levels should be tailored to address the lipid profile of the child and the circumstances of the family. For elevated low-density lipoprotein (LDL), a low fat diet beginning at age 2 years is safe and moderately successful [1, 2]. The low fat Child 2 diet calls for reducing saturated fat to ≤7 % and total fat to 20–30 % of total calories, while dietary cholesterol is limited to <200 mg/day. Low fat dairy can be used in children starting at age 1 year if they have increased risk (high weight for length, family history of

TABLE 16.3 Conditions associated with cardiovascular risk that modify treatment cutpoints

At risk populations	Individual risk factors
Familial hypercholesterolemia – homozygous, heterozygous	Hypertension
Diabetes mellitus – Type 1 and Type 2	Obesity
Heart transplant	Insulin resistance, fasting glucose >100, Hb A1C >7 %
Kawasaki disease ± coronary aneurysms	Low HDL
Chronic kidney disease – Transplant, insufficiency	High TG
Chronic inflammatory disease – SLE, scleroderma	Elevated lipoprotein (a) with consistent family history
Previous chemotherapy or mediastinal radiation	Gender (male)
Congenital heart disease	1st or 2nd hand smoke exposure
	HIV treatment with protease inhibitors
	Marked inactivity
	Particularly severe family history

Abbreviations: *Hb* hemoglobin, *SLE* systemic lupus erythematosis, *HIV* human immunodeficiency virus

early atherosclerosis). For high triglycerides (TG), seen more frequently with the current epidemic in childhood obesity, lowering dietary carbohydrate content and/or glycemic load is generally effective [3], if it can be accomplished. Exercise is an important part of treatment that decreases total cholesterol (TC) and increases high-density lipoprotein (HDL). We recommend 60 min of exercise 5 days/week, increasing gradually from the child's starting level, consistent with national guidelines.

16.3   Pharmacotherapy

Lipid lowering medications are usually initiated if 6 or more months of diet and exercise changes fail to improve values sufficiently (Table 16.2). A summary of treatments is shown in Table 16.4.

TABLE 16.4 Standard adult doses and dosage forms, shown in mg unless otherwise noted

	Initial/day	Maximum/day	Dosage forms
Cholestyramine	2–4 g[a] Children: 240 mg/kg/day (of anhydrous resin) in 3 divided doses; may need to titrate dose OR <10 year: Initial 2 g/day, range 1–4 g/day	16 g	4 g/packet or scoop
Colestipol	2.5–5 g[a]	20 g	5 g/packet or scoop
Colesevelam	1.25 g[a]	4.375 g	0.625 g per tablet
Pravastatin	20	40	10, 20, 40
Atorvastatin	5–10	80	10, 20, 40, 80
Simvastatin	20	**40**	10, 20, 40, 80
Fluvastatin	20	80	10, 20, 40, 80
Rosuvastatin	5	40	5, 10, 20, 40
Lovastatin	20	80	10, 20, 40, 80
Ezetimibe	10	10	10
Gemfibrozil	900 in 2 divided doses	1,200	600
Fenofibrate	48	145	48, 145, 67, 134, 200 generic[b]

(continued)

TABLE 16.4 (continued)

	Initial/day	Maximum/day	Dosage forms
Niacin	500	2,000	500, 750, 1,000[c]
Omega-3 Fatty Acids	500	4,000	500, 1,000

[a]Cholestyramine, colestipol, and colesevelam should be divided into two daily doses. Each dose should be taken with 8 oz of liquid
[b]200 mg generic fenofibrate equivalent to 145 mg patent-protected drug
[c]Dosages are not interchangeable – three tablets of 500 mg each is not equivalent to two tablets of 750 mg. Doses of niacin higher than 2,000 mg give greater LDL decreases, but have higher risks of hepatotoxicity and are not recommended. See text for further information on all medications

16.3.1   Bile Acid Sequestrants: Cholestyramine, Colestipol, and Colesevelam

Bile acid sequestrants are safe medications that lower TC and LDL, and CV risk. They are, however, difficult to tolerate. The longest pediatric and adult experience is with these medications. The Lipid Research Clinic Program, one of the earliest reports on pharmacologic lipid lowering, showed that a 1 % reduction in TC due cholestyramine led to a 2 % decrease in coronary disease events [4]. Trials in children have demonstrated decreases in TC and LDL, and reasonable increases in HDL [5, 6].

Indications:

Elevated LDL AND:

1. Age <10 years
2. Age ≥10 years AND unable to tolerate statins, parental concern about statin, or as additional agent.

The safety and effectiveness of colestipol has not been evaluated in children.

Mechanism of Action:

Positively charged sequestrants bind to negatively charged bile acids in the intestines and prevent the re-absorption of cholesterol-containing bile. This increases bile production by the liver. When bile synthesis is increased, TG production is increased, which can lead to increased TG concentrations. Increased bile synthesis also increases LDL-C clearance through the liver and up-regulates LDL receptors, causing 3-hydroxy-3-methylbutaryl coenzyme A (HMG CoA) reductase activity to increase, so that using a bile acid binding resin with a statin is an effective combination.

Dosing:

See Table 16.4. Take each dose with 8 oz of fluid prior to a meal.

Pharmacokinetics:

Absorption: the sequestrants remain in the gut and are not systemically absorbed, thus the side effect profile is minimal. Maximal lipid lowering effect occurs in 2 weeks.

Drug-Drug Interactions:

Combines well with a statin or niacin to decrease LDL maximally. However, ingestion of other medications, including statins and multivitamins (MVI), should be separated from sequestrants either by 1 h before or 4 h after dosing to prevent a decrease in drug absorption.

Adverse Effects:

Gastrointestinal: bloating, constipation can be reduced by allowing the preparation to sit for several hours prior to taking it (should be refrigerated), and by increasing fiber (dietary or psyllium supplements) and liquid intake.

Decreased compliance: due to gritty powder or large pills. One study showed ~40 % non-compliance in children with familial hypercholesterolemia over 18 weeks of treatment [7].

Metabolic: hypertriglyceridemia
Other: rare reports of hyperchloremic acidosis

Poisoning Information:

Cholestyramine has been used as an agent to treat toxin poisonings.

Contraindications/Cautions:

- TG >400 mg/dL
- Inability to tolerate or understand prophylactic medications

16.3.2   HMG CoA Reductase Inhibitors: Pravastatin, Atorvastatin, Simvastatin, Fluvastatin, Rosuvastatin, Lovastatin

HMG CoA reductase inhibitors, commonly referred to as statins, are used widely in adults to reduce LDL in patients with and without CV disease, and have been shown to reduce CV events by 25–30 %. All drugs in this class seem to have similar efficacy, if the same reduction in LDL level is achieved [8]; however, there may be greater improvements in HDL with particular statins at maximal doses (rosuvastatin > simvastatin > atorvastatin) [9, 10]. There are eight published pediatric trials of HMG CoA reductase inhibitors ranging from 2 months to 2 years in length. Both males and females are included, and the subjects are primarily those with familial hypercholesterolemia. The trials are relatively small, with the largest including 214 participants, and the agents evaluated include simvastatin [11, 12], lovastatin [13, 14], pravastatin [15, 16], and atorvastatin [17, 18]. A rosuvastatin trial is presently ongoing. These trials have demonstrated good compliance (90 %) and effectiveness (Table 16.5), minimal side effects including no impact on growth and development despite some increases in (DHEA) and/or cortisol levels. However, there are no long-term safety data, and no trial specifically addressed whether

TABLE 16.5 Therapeutic effects of various interventions on lipid parameters, shown in percent change

Medication	TC	LDL	HDL	TG	Comments
Bile acid binding resin	↓ 7–17	↓ 10–20	↑ 2–8	↑6–12	
HMG CoA reductase inhibitors	↓ 13–30	↓ 17–41	↑ 3–11	↓ 2–18	
Ezetimibe		↓ 15–20	↑1–2	↓ 5	↓ Plant sterol absorption
Niacin		↓ 25	↑15–30	↓ 35–50	↓ Lp(a) 30–50 %
Fibrates	↓ 13	↓ 20	↑ 15	↓ 30–50	Can see ↑ LDL
Fish oil		? ↑		↓ 25–45	
Diet – low fat	↓17	↓ 25	↑ 2	↓ 6	
Diet – low carbohydrate	↓ 3	↑ 4	↑ 4	↓ 48	
Diet – low glycemic load	↓ 10	↓ 9	↑ 2	↓ 35	
Aerobic activity	↓ 5–30		↑		

Data extracted from Tonstad, de Jongh, Knipscheer, Weigman, Lambert, Stein, and McCrindle [7, 11–18]. Niacin and fibrate data are taken from adult experience due to the lack of pediatric data (Goodman and Gillman, 11th ed). Dietary data are from Sondike et al. [51] and [2, 52]

puberty is affected, a concern because cholesterol is a precursor for sex steroid hormones.

Indication:

> Elevated LDL-C and ≥10 years of age. There are Food and Drug Administration (FDA) indications for simvastatin, lovastatin and atorvastatin for children with heterozygous familial hypercholesterolemia >10 years old, and pravastatin for those >7 years old.

Mechanism of Action:

Competitive inhibition of the key step in cholesterol synthesis in the liver leads to greater synthesis of and reduced breakdown of LDL receptors, which causes increased uptake of LDL by the liver. Additionally, levels of (VLDL) and (IDL) precursors of LDL are reduced, which may explain LDL reductions seen in homozygous familial hypercholesterolemic patients who generally do not have functioning LDL receptors. Statins have other effects associated with reduced CV risk including anti-inflammatory effects lowering C-reactive protein, a risk factor for CV disease independent of cholesterol levels [19], greater atherosclerotic plaque stability [20], improved endothelial function [21, 22], and decreased platelet aggregation [23]. There is also evidence that statins may have a role in reducing the incidence of cancer [24] and in cataract formation [25]. The response to statins is likely mediated in part by genetic polymorphisms, although genetic testing is not yet used clinically [26].

Dosing:

See Table 16.4. Atorvastatin levels are increased in those drinking >1 quart/day of grapefruit juice.

Pharmacokinetics:

Absorption: in the upper intestines

Metabolism: in the liver, with all but pravastatin being processed by the cytochrome P450 (CYP450) system (pravastatin is sulfonated in hepatic cytosol). Simvastatin and lovastatin are more lipophilic and are converted beta-hydroxy acids, while rosuvastatin, atorvastatin, pravastatin, and fluvastatin are more hydrophilic.

Half-life: for most statins it is 1–4 h, aside from rosuvastatin and atorvastatin, which have half-lives of ~20 h [27]

Protein-binding: statins are primarily protein-bound, aside from pravastatin which is only half protein bound

Elimination: statins are primarily excreted through the GI track

The shorter acting statins should be taken at night because the highest rate of cholesterol synthesis is between 12 and 2 am. LDL reductions are seen within 7–10 days of initiating treatment or changing doses; dose efficacy is usually assessed ~4 weeks after initiation or dose change. Statins tend to increase intestinal absorption of cholesterol, which means they combine well with cholesterol absorption inhibitors [28].

Drug-Drug Interactions:

Interactions are well described with medications metabolized by the CYP450 system, including fibrates (gemfibrozil, fenofibrate), niacin, warfarin, digoxin, amiodarone, macrolides, mibefranil, antifungals, cyclosporine, nefazadone, and protease inhibitors. Most cases of rhabdomyolysis, the most serious side effect of HMG CoA reductase inhibitors, occur in the setting of possible drug-drug interactions [27]. Pravastatin may be less likely to interact with these drugs, as it is not metabolized by the CYP system. Concomitant dosing of any statin may be acceptable if the statin is given at 25 % of usual dose (maximum 20 mg for most statins, 10 mg for rosuvastatin) with careful monitoring [27]. Statins can also be combined with bile acid binding resins if given >4 h after the statin dose to prevent reduced activity of the statin. This combination produces an additional ~20 % decrease in LDL [29]. Combination with ezetimibe gives an additional 20 % LDL lowering without an increased risk of side effects [30].

Adverse Effects:

General data: Despite early reports of hepatotoxicity and myopathy, statin therapy is generally quite safe in adults. Pediatric trials are small, but they also have not shown significant side effects, including rhabdomyolysis. In 14,236 adults randomized to atorvastatin, there were no cases of serious liver complications or rhabdomyolysis, and rates of adverse events were similar in high dose, low dose and placebo arms, including liver function test (LFT) abnormalities and increases in

creatine kinase (CK) [31]. Chemical differences among the statins may be responsible for individual variation in tolerance; an adverse response to one statin does not predict a response to another. The author's convention, admittedly cautious, is to measure LFTs and creatinine kinase (CK) at baseline, at 6 and 12 weeks after every dose change, and every 6 months when on stable dosing.

Hepatic: Dose related reversible LFT elevations (>3 times the upper limit of normal) were initially reported in 0.3–1.9 % of adult users. However, later studies have shown rates of LFT elevations in 1.1 % of those on placebo as well. There are 30 cases of reported liver failure associated with statin use.

Muscular: CK elevations >10 times the upper limit of normal occur in 0.17 % of adults on statins, compared to 0.13 % of patients on placebo. Few with CK elevations reported symptoms of muscle ache. The muscle ache is similar to the myalgias accompanying influenza, starting in the extremities and accompanied by weakness and fatigue. If there are changes in the urine (dark brown color) or muscle aches, the patient should stop taking the statin and have a CK measured to assess whether this is indeed myopathy. Of those with true myopathy, >50 % are receiving other drugs that increase risk, have medical problems such as hepatic or renal insufficiency, older age (particularly >80 years), or are small in size (relevant for pediatrics) [32]. The incidence of rhabdomyolysis in hospitalized patients was 0.44 (95 % confidence interval [CI], 0.20–0.84) per 10,000 patient years for atorvastatin, simvastatin, and pravastatin; for fibrates it was 2.82 (95 % CI, 0.58–8.24). For individuals taking only a statin as a lipid lowering agent, 22,727 would need to be treated in a year to see 1 case of rhabdomyolysis requiring hospital admission [33].

Neurological: headache, case reports of peripheral neuropathy, sleep and mood disturbances and cognitive difficulties

Dermatological: rash, lichenoid skin eruption

Other: GI upset

Contraindications/cautions:

• Pregnancy (teratogenic)
• Liver disease, possible steatohepatitis
• See Drug-Drug Interactions

16.3.3   Cholesterol Absorption Inhibitor: Ezetimibe

Indication:

Elevated LDL with an inadequate response to statins as monotherapy; sitosterolemia.

Mechanism of Action:

Ezetimibe selectively inhibits absorption of dietary cholesterol by [by 54 % [34]] and plant sterols, and prevents re-absorption of bile acids via transport protein NPC1L1 in the jejunal brush border [35]. Decreased absorption leads to decreased cholesterol in chylomicrons circulating to the liver, which up-regulates the hepatic LDL receptor and diminishes circulating LDL levels. LDL synthesis increases in response, making this drug particularly effective when combined with a statin. HDL increases and TG decreases [36–38]. Ezetimibe also inhibits the absorption of the plant sterols campesterol and sitosterol by ~40 % [34], which may make it an effective agent for sitosterolemia, a rare disorder leading to early CV disease. In a 1-week multiple-dose trial, adolescents showed similar pharmacokinetics to those seen in adults. A pediatric study is ongoing. Because of ongoing safety concerns raised in some adult trial data, and lack of outcome data for CV event reduction, this agent is not used first line.

Dosing:

10 mg/day for all ages, taken with or without food.

Pharmacokinetics:

> **Absorption and metabolism**: glucuronidated in the intestinal wall and circulated enterohepatically; there is presumably minimal systemic exposure, which may explain the low side effect profile
>
> **Elimination**: most is excreted in the feces

Drug-Drug Interactions:

> Concomitant administration with cyclosporine or gemfibrozil raises the concentrations of both drugs.

Adverse Effects:

> **Gastrointestinal**: diarrhea, nausea, taste changes, pancreatitis, cholelithiasis
>
> **Muscular**: may potentiate statin-induced myopathy
>
> **Hepatic**: LFT elevations, probably not greater than placebo
>
> **Hamatological**: thrombocytopenia
>
> **Other**: angioedema, rash. No effect on fat soluble vitamin absorption

Contraindications/Cautions:

> Co-administration with bile acid binding resins causes inhibition of ezetimibe absorption. High doses given to pregnant rats and rabbits caused skeletal abnormalities; administration during pregnancy is contraindicated.

16.3.4   Fibrates: Fenofibrate and Gemfibrozil

Indication:

> Elevated TG unresponsive to diet with risk of pancreatitis (TG >500–1,000 mg/dL). Increases in HDL are greater with fenofibrate than gemfibrozil. LDL may increase with gemfibrozil. The greatest TG reductions are seen in those with Fredrickson Type III (dysbetalipoproteinemia); also effective in those with chylomicronemia, along with a low fat and alcohol-free diet. These agents may also increase fibrinolysis and inhibit coagulation

[39]. Reducing TGs reduces the risk of coronary artery disease in adults. Adults with a history of CV disease had 22 % fewer future events on fibrates without significant decrease in LDL or TC levels. The effect may be related to the anticoagulative effects or the increase in HDL. The safety and efficacy of gemfibrozil has not been established in pediatric patients, and their use is confined to severe cases and older adolescents.

Mechanism of Action:

Interacts with hepatic peroxisome proliferator activated receptor (PPAR) α to stimulate free fatty acid oxidation and increase the production of lipoprotein lipase, which aids in TG and VLDL clearance and HDL expression [40].

Dosing:

See Table 16.4

Pharmacokinetics:

Absorption: absorbed best when taken 3o minutes before food
Protein-binding: bound to albumin
Half-life: fenofibrate has a 20-h half-life while gemfibrozil has a 1-h half-life
Metabolism and elimination: both are glucuronidated and excreted in the urine

Drug-Drug Interactions:

Increased prothrombin time when co-administered with coumadin. Increased risk of myopathy if co-administered with a statin; if using both medications, decrease statin dose and follow CK level every 3 months until on a stable regimen. Myopathy is less common with fenofibrate than gemfibrozil. Cyclosporine levels increase ~3 fold with co-administration.

Adverse Effects:

Gastrointestinal: side effects in 5 % of adults; <u>elevated LFTs and CK,</u> less commonly than with statins

Metabolic: increased LDL, particularly in those with only mildly elevated TGs (metabolic syndrome).

A small pediatric trial (n = 14) showed minimal side effects in adolescents.

Contraindications/Cautions:

- Concurrent statin and gemfibrozil (fenofibrate safer) administration
- Renal insufficiency
- Pregnancy – category C, effect unknown

16.3.5   Niacin (Nicotinic Acid)

Indication:

Low HDL-C, hypertriglyceridemia, and possible use in those with elevated lipoprotein (a) with a concerning family history, but without clear hypercholesterolemia.

Mechanism of Action:

Pyridine-3-carboxylic acid or nicotinic acid is a B vitamin that in large doses decreases VLDL production and TG synthesis. It reduces TG lipolysis by lipoprotein lipase in adipose tissue and decreases free fatty acid circulation to the liver, thus leading to less TG synthesis by the liver. There may be some inhibition on the rate limiting enzyme of TG synthesis (diacyl-glycerol acetyltransferase 2) [41]. Less TG synthesis by the liver leads to lower VLDL levels and thus lower LDL levels. Clearance of TG from the blood is increased by niacin because it improves the function of lipoprotein lipase. Clearance of ApoA-I is reduced leading to increased HDL levels [42]. The ABCA 1 membrane cholesterol transporter is up-regulated by niacin [43]. Adult data show this agent gives the greatest increase in HDL levels of the pharmacologic agents [44, 45]. Furthermore, niacin is the

only agent that significantly decreases lipoprotein (a) (Lp(a)) (approximately 40 %), although there are some "non-responders". The effects on TG are seen within 1 week, while the LDL lowering occurs over 3–6 weeks. There is limited experience in pediatrics: one case series found 30 % reductions in LDL, with common reversible side effects in 76 % (16/21) of participants [46]. Because of the difficulty with tachyphylaxis and other side effects, niacin is rarely used.

Adult **Dosing**:

There are several preparations that are not interchangeable.

> **Regular preparation**: initiate at 100 mg orally twice a day and increase every 7 days by 100 mg up to 1.5–2 g. Check LFTs, albumin, glucose, and uric acid levelsand a fasting lipid panel every 2–4 weeks until on a stable dose, then follow with labs every 3–6 months.
>
> **Extended release form**: initiate at 500 mg once daily in the evening and increase no more frequently than every 4 weeks, adjusting with laboratory tests for efficacy and side effects up to a maximum of 2 g/day.
>
> Regular (crystalline) 50–500 mg, available over the counter, is not recommended by most practitioners.
>
> Sustained release (6–8 h) is available, as is extended release. The extended release form (Niaspan) uses once a day dosing and is the only FDA approved prescription form (See Table 16.4).

Pharmacokinetics:

> **Absorption**: water soluble
>
> **Onset of action**: regular preparation niacin results in rapid peak serum levels within 60 min
>
> **Metabolism**: processed in the liver
>
> **Elimination**: excreted in the urine, or excreted unchanged as nicotinic acid [47]

Drug-Drug Interactions:

Can be used effectively with a bile acid binding resin as long as dosing is timed appropriately. If given with a statin, watch carefully for increased risk of myopathy and use statin at 25 % of maximal statin dose. Flushing and dizziness is seen with nicotine and alcohol use.

Adverse Effects:

Tachyphylaxis: flushing, pruritus, and headache, which are mediated through prostaglandins and can be treated or prevented in some cases with antihistamines and/or aspirin, usually resolves over 1–2 weeks. Flushing is worse if taken with alcohol or hot beverages.

Hepatic: dose-related hepatotoxicity, particularly at more than 2 g/day, and with over the counter preparations, including liver failure with sustained release. Extended release form may cause less hepatotoxicity. Flu-like symptoms, very significant decreases in LDL (>50 %) may indicate liver failure. Maximal reported improvement in lipid levels are seen with doses of 4–6 g/day, but the risk of hepatotoxicity increases above 2 g/day.

Muscular: myopathy with CK elevations and muscle cramping and rhabdomyolysis with co-administration of a statin in a small number of reported cases

Cardiovascular: palpitations, atrial arrhythmias, hypotension

Metabolic: mild hyperglycemia, hyperuricemia

Dermatological: acanthosis nigricans (treat with topical salicylic acid preparations), dry skin

Ophtalmological: toxic amblyopia and toxic maculopathy (rare and reversible)

Other: upper GI distress (improves if taken with a meal)

Contraindications:

Liver disease, severe gout (increases uric acid levels), peptic ulcer, active bleeding, hypersensitivity to niacin, unstable angina, diabetes (may require an increase in hypoglycemic therapy), and pregnancy (birth defects in animals) [44, 48].

16.3.6   Omega-3 Fatty Acids

Indication:

Adjunctive therapy in adults with elevated TG >500 mg/dL. Safety and effectiveness have not been established in children.

Mechanism of Action:

Found in fatty fish (tuna, salmon, swordfish), omega-3 fatty acids appear to protect against thrombosis, arrhythmia, inflammation, and hypertension, and improve endothelial function. Some studies show they decrease the risk of recurrent CV events
(GISSI). Twenty children with mildly elevated TG levels treated with DHA had favorable lipid profile changes [49]. The precise mechanism is not clear, but may be related to decreased TG synthesis in the liver.

Dosing:

Adolescents: 1,000–4,000 mg/day
Adults: 4,000 mg/day or more

Pharmacokinetics:

Response generally seen within 1 month

Drug-Drug Interactions:

None known

Adverse Effects:

Metabolic: increase in LDL
Dermatological: rash
Cardiovascular: angina
Other: back pain, fishy odor to breath (lessened by freezing pills and taking at bedtime)

Poisoning Information:

Some concern about purity and mercury content in the over the counter forms, which are less regulated. One purified form is available by prescription and is approved by the FDA for use in severely elevated TG.

16.4   Summary

Lifestyle modification is the primary treatment modality for lipid disorders; however, pharmacotherapy should be considered in children with high LDL cholesterol and concerning risk factors or high TG at risk for pancreatitis. Medications to lower lipid levels are generally well tolerated and effective. However, there are gaps in our knowledge about long-term safety and efficacy, and each child should be considered in the context of the family's risk and attitudes towards pharmacotherapy. Improved understanding of the initiating factors of atherosclerosis and the non-invasive measurement of preclinical disease will allow us to target treatment more precisely and interpret lipid values more effectively in the context of other risk factors.

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Chapter 17
Drug Clearance on ECMO and Dialysis/CRRT

Stuart L. Goldstein and David S. Cooper

Abstract Use of extracorporeal membrane oxygenation (ECMO) in the pediatric, and particularly neonatal, population to support patients with cardiopulmonary failure has become increasingly commonplace over the past two decades. However, there has been a relative paucity of research into the effects of ECMO on drug metabolism and elimination in children. Extracorporeal clearance of medications imparts a significant clinical challenge to the medical team caring for critically ill children, particularly with acute kidney injury (AKI). Rational drug dosing in this situation requires knowledge of multiple properties of the specific medication, modality of renal supportive therapy (RST), dialysis membrane characteristics and the dialysis dose. However, minimal *in vitro* or *in vivo* measured pharmacokinetic data exist for

S.L. Goldstein, MD
Department of Pediatrics, Center for Acute Care Nephrology,
Cincinnati Children's Hospital Medical Center, University of
Cincinnati College of Medicine, Cincinnati, OH, USA

D.S. Cooper, MD, MPH (✉)
Department of Pediatrics, Cardiac Intensive Care Unit,
The Heart Institute, Cincinnati Children's Hospital
Medical Center, University of Cincinnati College of Medicine,
Cincinnati, OH, USA
e-mail: david.cooper@cchmc.org

cardiovascular drugs in the setting of pediatric RST. Given these tenants, frequent monitoring of drug levels and therapeutic effects are recommended to ensure proper dosing in the child receiving ECMO support.

Keywords   Extracorporeal Membrane Oxygenation • Renal supportive therapy • Drug clearance • Dialysis

17.1   Introduction

Use of extracorporeal membrane oxygenation (ECMO) in the pediatric, and particularly neonatal, population to support patients with cardiopulmonary failure has become increasingly commonplace over the past two decades. However, there has been a relative paucity of research into the effects of ECMO on drug metabolism and elimination in children. By its very nature, ECMO is used in the most critically ill children, those who are often already receiving maximal pharmacological support with multiple vasoactive agents to improve their circulation, high doses of sedatives and muscle relaxants and prophylactic or therapeutic antibiotics. Additionally, diuretics and renal replacement therapy are frequently used to maintain fluid balance.

Extracorporeal clearance of medications imparts a significant clinical challenge to the medical team caring for critically ill children, particularly with acute kidney injury (AKI). Rational drug dosing in this situation requires knowledge of multiple properties of the specific medication, modality of renal supportive therapy (RST), dialysis membrane characteristics and the dialysis dose. In addition, careful estimation of residual renal function and the potential for enhanced non-renal clearance of medications in the setting of AKI will help optimize medications with substantial renal clearance.

This chapter reviews the general ways in which ECMO may affect drug clearance, and the properties of renal replacement therapy and medications, which impact drug clearance.

17.2   General Principles

Both its volume of distribution and clearance affects the half-life of a drug. Drug clearance and the volume of distribution can be affected by a number of different mechanisms; these same mechanisms may be fundamentally altered during ECMO support. The volume of distribution relates the total amount of drug in the body to the concentration of the drug in blood or plasma. The volume of distribution is affected by the pKa of the drug, the degree to which the drug binds to plasma or tissue proteins, and how lipophilic or hydrophobic (partition coefficient) the drug is, among other properties. ECMO alters the apparent volume of distribution of drugs in a number of fashions. The most obvious of these is the degree to which the ECMO circuit changes the extracellular volume. With ECMO circuit priming volumes traditionally between 200 and 400 mL, the circulating blood volume of an infant (80–85 mL/kg) can be doubled acutely. The magnitude of this effect exerts a much greater influence on a drug with a small volume of distribution than on a drug with a greater volume of distribution. The dilutional effect of the prime is often exacerbated by the ongoing intravenous (I.V.) fluid requirements of a critically ill child. Additionally, bleeding complications often necessitate multiple transfusions of red blood cells, platelets, and plasma. Resultant, losses of fluid from the intravascular compartment requires repeated I.V. fluid boluses to maintain adequate levels of circuit flow [1]. Not surprisingly, a 30 % increase in the body weight of infants with respiratory failure placed on ECMO has been noted. The degree to which ECMO itself expands the intracellular and extracellular fluid compartments is debatable, and the increase is more likely related to the underlying disease process than to ECMO per se [2]. These effects are only exacerbated by the additional increase in volume and loss of existing drug during ECMO circuit changes. Conversely, the prime and multiple transfusions also dilute plasma proteins, resulting in decreased drug binding, increased free concentration of drug, and an apparent decreased volume of distribution. The increased fraction of free drug is, however, more likely to

result in redistribution to the tissues, which may increase the apparent volume of distribution. Additional effects on plasma proteins include binding of protein by heparin and potential denaturation of proteins passing through the membrane oxygenator. Oxygenators, because of their large surface areas, may in particular affect drug levels and apparent volume of distribution. Silicone oxygenators have been demonstrated to have a higher affinity for more lipophilic drugs [3]. Dagan and colleagues examined pre-oxygenator and post-oxygenator concentrations of several drugs in an in vitro model. These investigators used both new circuits and circuits that had been used to support patients. When examining drug loss in the new ECMO circuits, a significant decrease in the concentration of drugs was seen after flow through the oxygenator. Phenytoin decreased by 43 %, vancomycin and morphine by 36 %, phenobarbital by 17 %, and gentamicin by 10 %. In circuits that had been used in a patient for 5 days, the loss was significantly less; the decreases were morphine, 16 %; vancomycin, 11 %; and phenobarbital, 6 %. These findings suggested saturation of binding sites over several days in circuits used to support patients [4].

When drugs are administered directly to the circuit, different effects may be observed whether the drug is administered before or after the oxygenator, as well as with the type of oxygenator used. The partition coefficient has been demonstrated to be of particular importance in determining the amount of drug lost to the circuit [5].

There may also be incomplete mixing of drug in the circuit. Silicone venous reservoirs or bladders are often used as a safety measure. When there is inadequate return of blood, such as occurs with kinking of circuit tubing or hypovolemia, an alarm sounds and the pump shuts down to avoid entraining air. The venous reservoir is then subject to low and more laminar flow. It has been demonstrated that dye injected distal to the reservoir in the ECMO circuit mixes completely in 10 min. Drug injected proximal to the reservoir did not mix thoroughly. In the same study, flow rates less than 250 mL/min were associated with pooling in the system [6].

The clearance, or rate of elimination, of a drug is also affected during ECMO. Similar to the volume of distribution, the clearance of a drug can be affected by the degree to which ECMO impacts bound or unbound drug levels. Drugs generally are cleared as a result of processes in the liver and kidneys, but the lungs and other organs may also clear drugs. Clearance is intimately related to the amount of drug presented to these organs, i.e., the blood flow to each organ, the volume of distribution, and the bound and unbound fractions of the drug. ECMO can result in altered end organ perfusion, most prominently by a lack of pulsatility in venoarterial ECMO. The lack of pulsatile flow may result in an increase in systemic vascular resistance, decreased capillary flow, and decreased lymphatic flow [7, 8]. The renal response is altered in the absence of pulsatility, resulting in decreased function and activation of the renin-angiotensin system. Decreases in hepatic blood flow may also affect drug metabolism [9, 10]. Decreased capillary flow and decreased flow to skeletal muscles, adipose tissue, bone, and skin, as well as the liver and kidneys, will decrease the volume of distribution and clearance and alter the half-life. There also may be alterations in end organ perfusion related to the underlying disease state. If induced hypothermia is used for cerebral protection while on ECMO, there will be even more pronounced alterations in perfusion and enzymatic function. In venoarterial ECMO, only bronchial flow is delivered to the lungs; this profoundly alters drug binding or elimination of drugs that are distributed or metabolized by the lungs [11]. Importantly, the kidneys, liver, and other organs frequently have suffered an insult before the initiation of ECMO, and such an insult may affect their intrinsic ability to clear drug.

17.3   Medication Characteristics That Affect Clearance in RST

Each medication's individual pharmacokinetic and pharmacodynamic characteristics must be considered when dosing during CRRT to obtain the best possible outcome [12].

Relevant properties include the drug volume of distribution (V_d), molecular weight (MW) and protein binding to determine how much drug will be removed by CRRT. Drugs with large V_d (>1 L/kg of body weight), a MW larger than the pore size of the hemofilter, or high protein binding (>50 %) are less likely to be removed by intermittent hemodialysis (IHD) or continuous renal replacement therapy. It is important to remember that only the free, unbound percentage of the drug can be cleared by RST, which is calculated as 1 minus the protein-binding rate. In addition, drugs that are highly lipophilic are unlikely to be cleared by RST for similar reasons.

17.4   Mechanisms of Clearance

Dialysis therapies clear medications via two mechanisms, diffusion and convection. Both mechanisms require a semipermeable membrane that allows passage of the molecule from the vascular compartment. Diffusive clearance occurs down a concentration gradient from higher to lower concentration, with a rate that is inversely proportional to molecular size. Convective clearance occurs as part of a solvent drag, in which plasma water is pushed or sieves across the membrane, carrying with it all molecules dissolved in the volume that moves thorough the membrane. Convective clearance is therefore less affected by molecular size; larger molecules are more efficiently cleared by convection than diffusion [13]. All dialysis modalities can be configured to achieve either or both convective and diffusive clearance.

17.5   Renal Supportive Therapy Modality

Intermittent hemodialysis (IHD), peritoneal dialysis (PD) and continuous renal replacement therapy (CRRT) comprise the three most common renal supportive therapy (RST) modalities provided to acutely ill patients with acute kidney injury. Although PD is often provided continuously in the

ICU, especially early after infant cardiopulmonary bypass (CPB), CRRT generally refers to veno-venous modes of continuous extracorporeal clearance and will be used in this context for the purposes of this chapter. The modality choice depends upon numerous patient characteristics noted below.

17.6   Intermittent Hemodialysis

IHD is usually reserved for more stable and larger patients requiring RST. Each IHD session usually lasts 3–4 h in duration with a desired small solute clearance of 65–70 % per session, using blood urea nitrogen clearance as a surrogate. Clearance is primarily diffusive, with some convective clearance occurring with fluid removal, called ultrafiltration. Hemodialyzer membranes have various molecular weight cut-offs, above which larger molecules cannot pass (usually 15–30 kDa). High-flux membranes have larger pore sizes and may be used for pro-inflammatory cytokine removal, with a cut-off of 60 kDa. During a standard IHD procedure, significant clearance occurs for molecules with a MW of <1,000 Da (2,000 Da for high-flux membranes).

17.7   Peritoneal Dialysis

PD provides clearance via instillation of a balanced electrolyte solution into the peritoneal cavity, and employing the semipermeable properties of the peritoneal membrane to allow for mass transfer. Clearance rates are affected by the amount of fluid instilled in the cavity and the number of exchanges or cycles provided to the patient over the day. A cycle is defined as fluid filling, dwell time and drain time. Typically, cycles are prescribed as a 5 min fill, 45 min dwell and 10 min drain, although cycle time can be altered to meet the specific needs of the patient. PD ultrafiltration is achieved by varying the osmotic concentration (usually in terms of complex dextrose) of the PD fluid. PD is commonly used in

infants after cardiopulmonary bypass (CPB), as PD catheters can be placed in the operating room in high risk patients [14–16]. PD is ideal for such infants as it does not require the extracorporeal circuit needed for clearance with IHD or CRRT, which can lead to cardiovascular instability and blood exposure in smaller patients.

Clearance calculations for acute PD are based on small solute clearance, and are based on the total daily volume of PD fluid prescribed, which is normalized to patient body surface area. As opposed to IHD and CRRT membranes, the diffusive capacity of an individual patient's peritoneal membrane is unknown and rarely measured [17]. However, the peritoneal membrane surface area to body surface area ratio is relatively higher for a smaller patient, which would lead to greater relative diffusive clearance.

17.8   Continuous Renal Replacement Therapy

CRRT has become the most widely used RST modality for critically ill children with AKI [18, 19]. CRRT can be configured easily to provide convective clearance (continuous venovenous hemofiltration, CVVH), diffusive clearance (continuous venovenous hemodialysis, CVVHD) or combined convective and diffusive clearances (continuous venovenous hemodiafiltration, CVVHDF). Ultrafiltration can be provided with all of these modalities to achieve fluid removal. Isolated ultrafiltration (slow continuous ultrafiltration, SCUF) is rarely employed in pediatric CRRT [20], although it is a mainstay of EMCO support and will be discussed in the ECMO portion of this chapter.

CRRT membranes typically have pore sizes 15–30 KDa, although higher cutoff membranes do exist [21]. Although CRRT provides less efficient clearance per unit time than IHD, its continuous facet can lead to significantly greater daily clearance than IHD, which is of paramount importance in drug dosing, especially for those with small MW, low V_d and protein binding [22]. CRRT clearance is defined as the combination of daily dialysis fluid and replacement fluid

rates normalized to patient size in either L/kg/h [23] or mL/h/1.73 m² (for smaller children) [20].

17.9   Putting It All Together

The dialytic clearance of cardiovascular drugs in the acute care setting has not been studied widely; most studies focus on antimicrobial clearance in acute dialysis or anti-hypertensive medication clearance in patients receiving chronic dialysis. CRRT clearance of inotropic agents, such as dopamine and norepinephrine is minimal [24]. One pediatric study demonstrated CRRT clearance rates approaching fluid delivery rates of vasopressin [25]. Finally, CVVHDF was employed effective in a case of atenolol overdose [26].

These small studies highlight the principles noted above – drugs with low protein binding that are small in size and have a low V_d are likely to be easily cleared with IHD or CRRT. Since there is minimal literature with respect to cardiovascular drugs, a potential empiric approach to assessing the need for dose adjustment would be as follows:

1. Adjust for drugs with $V_d < 1$ L/kg, less than 2 KDa in weight and with less than 50 % protein binding.
2. For IHD, consider giving a bolus dose in the middle or at the end of the dialysis treatment (this is commonly done for anti-convulsant and anti-microbial medications).
3. For a CRRT prescription, provide the medication dose and interval that correlates with the package insert for the same renal function. For instance, if the CRRT dose is 25 mL/kg/h, this corresponds to a clearance of 29 mL/min in a 70 kg adult. Thus, drug dosing should be based on at this clearance added to any residual kidney function.

17.10   Conclusions

ECMO can potentially have a myriad of effects on the clearance of drugs in the pediatric population. Universally, the volume of distribution is increased. The magnitude of this

effect depends on the size of the child, the size of the ECMO prime, and the volume of distribution for the drug in a patient not on ECMO. The most variable effect of ECMO on drug action is the degree to which the circuit and oxygenator bind the agent. This seems to be greatest for drugs with a high partition coefficient (i.e., more lipophilic). These alterations in drug pharmacokinetics are clearly most acute when the circuit is new, and they diminish over time. Therefore, increased drug dosing may be necessary earlier in an ECMO run compared with a later time. Frequent monitoring of drug levels and therapeutic effects are recommended to ensure proper dosing in the child receiving ECMO support.

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Chapter 18
Parenteral Nutrition

Megan Horsley, Lindsey Justice, Ryan Moore, and David S. Cooper

Abstract Growth failure is common in infants born with congenital heart disease and malnutrition among patients with complex heart disease has been estimated to be as high as 53 % [25]. Poor nutrition is associated with worse outcomes in children undergoing surgery and those with critical illness. Any neonate undergoing cardiopulmonary bypass (CPB) experiences a more profound metabolic response to stress than seen in older children and adults. This puts the neonate at a higher risk for

M. Horsley, RD, LD, CSP, CNSC (✉)
Department of Pediatrics, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: megan.horsley@cchmc.org

L. Justice, MSN, CPNP-AP
Department of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

R. Moore, MD
Pediatric Cardiology, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

D.S. Cooper, MD, MPH
Department of Pediatrics, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

morbidity, organ dysfunction and postoperative complications. The care of the neonate after cardiac surgery is heterogeneous and complex. Nutrition plays a vital role in preserving body mass, promoting wound healing, and growth.

This chapter is written to provide general guidelines for delivering safe total parenteral nutrition (TPN) in the cardiac patient. It includes a discussion on how to estimate parenteral nutrition and fluid goals; types of access; initiation and advancement; complications; and safe transition off TPN.

18.1   Introduction

Growth failure is common in infants born with congenital heart disease and poor nutrition is associated with worse outcomes in children undergoing surgery and those with critical illness [1, 3, 12]. Any neonate undergoing cardiopulmonary bypass (CPB) experiences a more profound metabolic response to stress than that seen in older children and adults [14]. This puts the neonate at a higher risk for morbidity, organ dysfunction and postoperative complications. The care of the neonate after cardiac surgery is heterogenous and complex. Nutrition plays a vital role in preserving body mass, promoting wound healing, and growth.

Dudrick and colleagues demonstrated in the late 1960's that total parenteral nutrition (TPN) could be successfully delivered to patients with gastrointestinal failure [22]. It was through their work that a paradigm was set for the application of TPN to many patients even those with non-gastrointestinal failure like malignancies and critical care. Parenteral nutrition is the most aggressive form of providing nutrition support and can be costly. A thorough nutrition assessment should be completed by a Registered Dietitian prior to prescribing TPN for patients.

This chapter is written to provide general guidelines for delivering safe total parenteral nutrition in the cardiac

patient. It includes a discussion on how to estimate parenteral nutrition and fluid goals; types of access; initiation and advancement; complications; and safe transition off TPN.

18.2   Indications and Access

It is well documented that early enteral nutrition (EN) should be the preferred route of nutrition support if feasible in any patient [10]. However, in the pediatric cardiac population there are several factors that can influence the method of nutrition support chosen, many of which are dependent on the specific cardiac lesion that is present at birth. Whether the lesion is classified as acyanotic or cyanotic, or if the lesion requires surgical repair with the use of CPB, the neonate is at risk for increased metabolic requirements and postoperative complications. Neonates born with cyanotic lesions where there is a concern for low cardiac output and/or decreased systemic perfusion to the organs of the body have an increased risk for Necrotizing Entercolitis (NEC); therefore, enteral feeding is not optimal until corrective or palliative surgery occurs [14, 18]. Total parenteral nutrition can be initiated early to support vital organ function, prevent malnutrition and preserve lean body mass.

There are many barriers that may be present when trying to initiate and optimize nutrition support for the patient after cardiac surgery. These include hemodynamic instability, hyperglycemia, hypotension, and fluid limitations due to medication infusions. If fluid is limited to less than 50 % maintenance, intravenous fluid (IVF) can be given at less cost with a more concentrated dextrose solution to provide approximately 15–20 kcal/kg/day until the amount of fluid for nutrition increases.

Duggan and colleagues suggest that malnourished children receive TPN when EN cannot be administered for >3 days; however short TPN courses <5 days are unlikely to yield significant nutrition benefits [6, 18]. It is generally accepted that in low birth weight or preterm infants, nutrition should be initiated within the first 24 hours of life. [10]. If it is anticipated that sub-optimal nutrition will be longer than

7 days then full TPN by central venous access is indicated. There are typically four types of central venous access: peripherally inserted central catheter (PICC), non-tunneled, tunneled, and totally implanted venous access devices called ports [10]. It is important when providing a hypertonic solution like TPN through a central vein that there is radiographic confirmation of the appropriate line-tip location of catheter. This is essential for patient safety. The ideal location for a central line is at the junction of the right atrium and superior vena cava because there is a large diameter vessel where venous flow is maximal. The practitioner should be familiar with hospital-specific procedures for documenting and confirming catheter tip location for the use of TPN.

For less than 7 days, an infusion of a more dilute solution by peripheral vein may be adequate. Providing full energy needs may be difficult given the limitations with osmolarity of PN infused through a peripheral vein. The maximum osmolarity of PN administered peripherally is typically restricted to 900–950 mOsm/L [13] due to the risk of phlebitis and sclerosis. This corresponds approximately to a solution of 10 % dextrose and 2 % amino acid with standard amounts of electrolytes and minerals. Both 10 and 20 % intravenous lipid solutions provide an isotonic source of calories and can be given peripherally or centrally.

18.3   Nutrition Assessment

The first step in ordering PN for the cardiac patient is to determine the nutritional goals. A Registered Dietitian with pediatric experience is critical when establishing the nutritional requirements, goals and factors that may impact ones nutritional intake [18]. It is important that you have accurate anthropometric measurements for your assessment. These measurements are the basis for determining body surface area, body mass index, fluid, and macro and micro nutrient needs. Methods for determining calorie needs like indirect calorimetry can be helpful in developing nutrition goals for the critically ill patient. Predictive equations often over or

TABLE 18.1 Recommended daily fluid requirements [1, 8, 13]

Weight (kg)	Fluid volume required
0–10	100 ml/kg
10–20	1,000 ml for 10 kg + 50 ml/kg for each kg >10
>20	1,500 ml for 20 kg + 20 ml/kg for each kg >20

under estimate needs and do not account for changes in metabolic state. The thermogenic effect of food is negated when receiving PN support; therefore calorie needs are approximately 10 % less than enteral requirements [9].

Fluid requirements are determined first in the cardiac patient due to the many barriers as mentioned above. The Holliday-Segar method is most commonly used when estimating goal fluid requirements. See Table 18.1 above [10, 13]:

Note that fluid requirements may be higher when there are increased insensible losses like fever, tachypnea or sensible losses such as diarrhea, vomiting, ostomy losses or other gastric output. Routine clinical evaluation of the patient's hydration status is essential when receiving PN.

TPN should be withheld until it can provide approximately 30–40 mL/kg/day or more. After cardiac surgery, total fluid is often restricted to avoid fluid retention. The body's inflammatory response to surgery causes capillary leak syndrome which can lead to edema. Provision of PN fluid is impacted by the fluid the patient is receiving from continuous and intermittent medications and flushes. When initiating PN following cardiac surgery fluid intake is typically restricted to 50–80 % of maintenance fluid needs [14]. As the patient recovers, medications are discontinued, and fluid balance is liberalized, the parenteral nutrition fluids should be increased to a maintenance fluid goal in order to meet daily fluid requirements [13].

18.4 Initiation and Advancement

The initiation and advancement of TPN requires careful consideration of the patient's metabolic state, laboratory values and energy requirements. Providing adequate protein is

TABLE 18.2 Calorie guidelines for patients >1 month of age [1, 8, 13]

	1 month– 1 year	1–3 years	4–10 years	>11 years
Initial (kcals/kg/day)	35–45	40–45	35–40	30–40

	1 month–1 year	1–7 years	7–12 years	>12 years
Maximum (kcals/kg/day)	85–105	75–90	50–75	30–50

crucial in the post-operative period due to increased nitrogen losses. Initial prescription is recommended in the range of 55–60 kcal/kg/day during the acute post-operative phase in order to meet basal energy requirements. Advancement of TPN should be daily until goal nutrition is achieved. For infants, goal TPN to promote recovery and healing is often in the range of 90–100 kcal/kg/day and 3–4 gm/kg of Protein [13]. It is important to consider ones change in metabolic response to stress often monitored by C-Reactive Protein (CRP) and other inflammatory markers. Post-operatively, cardiac patients are often mechanically ventilated and on sedatives and/or neuromuscular blocking agents which may affect resting energy needs.

The minimum caloric requirements and calorie goals for patients beyond the newborn period vary depending on their age. Table 18.2 displays the minimum calorie guidelines for patients greater than 1 month of age.

Parenteral nutrition is largely made up of macronutrients which include carbohydrates, protein and fat. Electrolytes and minerals like sodium, potassium, chloride, calcium and phosphorus are also important ingredients in TPN. Often times, trace elements like zinc and copper are added to TPN. Medications like Ranitidine and Insulin might be added to help minimize total fluid intake. If shortages among TPN are identified, follow individual institution guidelines to assure safe practice. See the chart below that provides the macronutrients and their energy density they provide in PN (Table 18.3).

Table 18.3

Macronutrient	Energy density (kcal/g)
Dextrose	3.4
Amino acids	4
Fats	9

Table 18.4 Minimum glucose requirement to prevent hypoglycemia [17, 21]

Age	Glucose consumption (mg/kg/min)
Neonate	6
Newborn	8
1 year	7
5 years	4.7
Adolescent	1.9

Carbohydrate in the form of dextrose monohydrate is the major source of calories for PN. If given in excess, hyperglycemia and overfeeding may occur. Therefore, it is important to pay attention to glucose infusion rates (GIR) and initiate at a lower dose and increase respectively to goal. Often times in infants, GIR does not exceed 15 mg/kg/min. Table 18.4 exceed 12–15 mg/kg/min. Protein in PN is in the form of crystalline amino acids and are ideally used as a substrate for enzyme synthesis and lean body accretion instead of a primary fuel source. Intolerance to parenteral protein may be represented by an elevation in blood urea nitrogen (BUN) or Creatinine. It is often difficult to assess true intolerance to parenteral protein intake in the cardiac patient if the patient is also being aggressively diuresed. Lipids are in the form of soybean and/or safflower emulsions and are necessary for preventing essential fatty acid deficiency. They provide a concentrated, isotonic source of calories. Lipid tolerance is monitored with liver panels that include by serum triglyceride (TG), gamma-glutamyl transpeptidase (GGT) and bilirubin levels. It is recommended to monitor liver profiles twice per week and if hypertriglyceridemia is noted, a reduction in lipid infusions is warranted [17, 21].

TABLE 18.5 Initial glucose, protein, and lipids that should be included in parenteral nutrition, as well as the rate of advancement and final goals for these components

Age	Initial			Advancement			Maximum		
	Glucose mg/kg/min	Protein g/kg/day	Fat g/kg/day	Glucose mg/kg/min	Protein g/kg/day	Fat g/kg/day	Glucose mg/kg/min	Protein g/kg/day	Fat g/kg/day
Preterm <1 year	5–7	1–3	0.5–2	1–2	0.5–1	0.25–1	14	3–4	3–3.5
Term <1 year	6–9	1–3	0.5–2	1–2	0.5–1	0.5–1	14	2.5–3.5	3
1–10 years	7–9	1–2	1–2	2–3	1	0.5–1	11	1–3	2–3
>10 years	3.5–5	0.8–1.5	1	1–3	1	1	7	0.8–2.5	1–2.5

Refer to Table 18.5 for comprehensive recommendations regarding the initial glucose, protein, and lipids that should be included in parenteral nutrition, as well as the rate of advancement and final goals for these components [8, 24].

Initial guidelines for pediatric vitamin and minerals were developed in the 1970s and 1980s by two groups, American Medical Association (AMA), and the Nutrition Advisory Group of the Department of Food and Nutrition. At the time of development there was only one multivitamin preparation available for use in infants and children compared to several formulations for adults. Therefore, the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition (ASCN) met to review all the data available on the use of multivitamin preparations. The results of this subcommittee are formulated in the table 18.6 [7, 10]. It should be noted that the pediatric version (MVI Pediatric) of multivitamins differs significantly from the parenteral multivitamin for adults. It includes Vitamin K, a greater amount of Vitamin D and a lower amount of B vitamins. Vitamin and mineral doses are based on weight so accurate weight measurements are necessary. The current formulations do not account for the requirements of the malnourished, patients with renal or liver disease, premature infants, and/or children with short bowel. It is recommended to tailor the nutrient delivery accordingly.

The American Society for Parenteral and Enteral Nutrition (ASPEN) has approved some electrolyte and trace element dosing guidelines for infants and children. This provides a recommended range for the amount of these substances that should be included in PN (Table 18.7) [13].

Trace elements are commonly added to PN solutions. Below are the recommendations for trace elements in PN (Table 18.8).

For patients that have cholestasis, copper and manganese should be omitted from the PN solution. In renal dysfunction, selenium, chromium and molybdenum should be reduced or discontinued.

TABLE 18.6 Recommended intake levels for intravenous multiple vitamins

Vitamin	Term infants	Preterm infants Current suggestion	Preterm infants Best new estimate
Vitamin A (IU)	2,300 IU	920	1,643
Vitamin E (mg)	7	2.8	2.8
Vitamin K (µg)	200	80	80
Vitamin D (IU)	400	160	160
Vitamin C Ascorbic acid (mg)	80	32	25
Thiamin (mg)	1.2	0.48	0.35
Riboflavin (mg)	1.4	0.56	0.15
Niacin (mg)	17	6.8	6.8
Pantothenate (mg)	5	2	2
Pyridoxine (mg)	1	0.4	0.18
B12 (µg)	1	0.4	0.3
Biotin (µg)	20	8	6
Folate (µg)	140	56	56

Greene et al. [7]

18.5   Monitoring Parenteral Nutrition

The aim of PN is to provide full nutritional support when enteral nutrition is not feasible during critical illness. Daily monitoring of electrolytes is recommended to work towards achieving normal levels of sodium, potassium, chloride, calcium, magnesium, and phosphorous. Adjustments in electrolytes should be made daily per lab values but correction of lab values should not be expected through TPN. A bolus of an electrolyte is more appropriate for correcting any electrolyte disturbances. Glucose levels allow for assessing the appropriateness of the selected GIR. Bicarbonate levels allow the practitioner to assess for acidosis and add acetate as needed.

TABLE 18.7 American Society for Parenteral and Enteral Nutrition (ASPEN) approved electrolyte and trace element dosing guidelines for infants and children. The recommended range for the amount of these substances that should be included in parenteral nutrition

Electrolyte	Preterm neonates	Infants/children	Adolescents and children >50 kg
Sodium	2–5 mEq/kg	2–5 mEq/kg	1–2 mEq/kg
Potassium	2–4 mEq/kg	2–4 mEq/kg	1–2 mEq/kg
Calcium	2–4 mEq/kg	0.5–4 mEq/kg	10–20 mEq/day
Phosphorus	1–2 mmol/kg	0.5–2 mmol/kg	10–40 mmol/day
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	10–30 mEq/day
Acetate	As needed to maintain acid–base balance		
Chloride	As needed to maintain acid–base balance		

Reprinted with permission from Mirtallo et al. [10]
Refer to Chapter 34 of the A.S.P.E.N. Pediatric Nutrition Support Core Curriculum
*Assumes normal organ function and losses

TABLE 18.8 Recommendations for trace elements in PN solutions

Trace element	Preterm neonates <3 kg (mcg/kg/day)	Term neonates 3–10 kg (mcg/kg/day)	Children 10–40 kg (mcg/kg/day)	Adolescents >40 kg (per day)
Zinc	400	50–250	50–125	2–5 mg
Copper	20	20	5–20	200–500 mcg
Manganese	1	1	1	40–100 mcg
Chromium	0.05–0.2	0.2	0.14–0.2	5–15 mcg
Selenium	1.5–2	2	1–2	40–60 mcg

Reprinted with permission from Mirtallo et al. [10]
Refer to Chapter 34 of the A.S.P.E.N. Pediatric Nutrition Support Core Curriculum
*Assumes normal organ function and losses

Once a stable recipe of TPN is achieved, it is reasonable to decrease the monitoring of electrolytes from daily to once or twice weekly.

For patients requiring diuretic therapy, it is not uncommon to check electrolytes more often in conjunction with TPN laboratory monitoring. This is due to the common electrolyte abnormalities that are seen with diuretic usage, especially hypokalemia. Monitoring trends of BUN and creatinine levels also provide insight into the efficacy of the diuretics. There are groups of patients that require more frequent monitoring of electrolytes like those on immunosuppression therapy ventricular assist devices (VAD), or dialysis.

The table below represents some common metabolic conditions in patients receiving PN.

Complication	Potential cause	Clinical presentations	Prevention/ treatment
Hyperglycemia	Diabetes, metabolic stress, excessive dextrose infusion, corticosteroids, peritoneal dialysis	Elevated serum glucose >200 mg/dL	Decrease or limit dextrose infusion Add insulin
Hyper-triglyceridemia	Excessive lipid infusion, liver failure/sepsis, medications	Serum triglycerides >200 mg/dL	Avoid excess or decrease lipid infusion to 0.5–1 g/kg/day
Hypokalemia	Medications(Lasix), increased GI losses, inadequate potassium supplementation	Metabolic alkalosis, arrhythmias, muscle weakness, ileus	Increase K in PN Add supplemental K
Hyperkalemia	Renal insufficiency, medications (Aldactone), excessive K	Arrhythmias, paresthesias	Monitor levels daily Decrease K in PN

Hyponatremia	Fluid overload, SIADH, increased losses	Seizures, confusion, lethargy	Fluid restriction/ avoid excessive fluid administration
			Increase Na/ replace
Hypernatremia	Dehydration, excessive Na, osmotic diuresis	Thirst, muscle tremor, elevated serum levels	Fluid replacement if dehydrated
			Decrease Na in PN
Metabolic acidosis	Increased intestinal or renal losses of bicarb, lactic acidosis, excessive chloride	N/V/D, convulsions	Increase acetate
			Decrease chloride
Metabolic alkalosis	Gastric acid losses, excess base administration, aggressive diuretic therapy	N/V/D, convulsions	Measure/ treat output
			Treat underlying cause

[11]

18.6   Medications and Parenteral Nutrition

Cardiac patients who receive PN are often on multiple medications. Often times questions related to compatibility or coadministration of the medication with the TPN arise. Coadministration of medications should be avoided if possible due to the risk of precipitation, infiltrates and/ or infections. There are medications that are generally considered safe for coadministration with PN and lipids. Some of these common cardiac medications include: Atropine, Clindamycin, Digoxin, Epinephrine, Gentamicin, Heparin, Insulin, Morphine, Ranitidine, Tacrolimus and Vancomycin

[10]. Common medications that are incompatible with PN and are frequently administered in the cardiac patient are: Octreotide, Amphotericin, Ampicillin, Metoclopramide and Nitroprusside [10]. It is always recommended to consult with pharmacy prior to coadministering any medication with PN.

18.7   Limitations and Special Considerations

Acute Renal Failure (ARF) occurs in 1–9 % of pediatric patients after cardiac surgery [14]. This condition greatly impacts the provision of PN to these patients. During ARF, the kidneys are unable to adequately regulate fluid and electrolytes. The management plan must focus on preventing volume overload and hyperkalemia, both which may impact ones PN prescription. If dialysis is necessary for ARF management protein needs are increased due to rapid protein turnover and the loss associated with therapy [14].

In post-operative cardiac surgical patients, fluid restriction is often employed in an attempt to avoid fluid overload and generalized edema. In addition, the fluid available for parenteral nutrition is further restricted by the fluid volume the patient is receiving from medications and flushes. Maximum nutrition should be provided in the volume of fluid allowed using concentrated solutions. Some institutions use peritoneal dialysis (PD) to aide in fluid removal post-operatively. This can allows for more nutritional fluid to be given. The patient will begin to tolerate more fluid as they recover and the amount of fluid available for nutrition within the patient's total fluid volume will increase as medications are weaned and discontinued [14].

Patients on Extracorporeal Membrane Oxygenation (ECMO) should be given PN as soon as possible. These patients have difficulty achieving optimal nutrition due to their baseline illness, fluid limitations, and high protein catabolism. Delayed healing, weight loss or wound breakdown may be a result of poor nutrition. TPN can be ran through the ECMO circuit and lipids are safe to give to a patient on ECMO. Initiation of a PN solution that provides 100–120 kcal/kg/day and protein up to 3 g/kg/day may be necessary [23].

If the cardiac patient has open wounds or delayed sternal closure this presents additional nutritional challenges. The patient is more susceptible to the loss of lean body mass due to higher baseline requirements. Adequate intake of protein is the single most important nutritional intervention in ill or postoperative children. Protein is required to maximize protein synthesis and preserve skeletal muscle protein mass, as well as to facilitate wound healing and the inflammatory response [16]. To date, there are no specific guidelines for neonates or children in regards to nutritional treatment for pressure ulcers. There are laboratory tests that can be obtained at baseline when following a pressure ulcer. These include albumin level, prealbumin, zinc metabolic panel and total blood count. Intrinsic and extrinsic factors may be affecting tissue tolerance and should be assessed. Some intrinsic factors include deficiencies in vitamins A, C, D, Vitamin B2, calcium, zinc and copper [16]. Testing for vitamin absorption is suggested but there is no evidence to support this. A systemic review/meta-analysis, along with a randomized controlled trial, support enteral nutritional enhancement and/or the use of supplemental arginine, vitamin C, and zinc in patients at risk for or presenting with pressure ulcers [17, 18].

18.8   Complications

While PN may be essential during periods of critical illness, it carries risks that should be acknowledged. The most common complication of TPN in the immediate period is infection which is secondary to presence of an intravenous catheter. Catheters are foreign bodies in the blood vessels and are subject to infection and/or clotting. Monitoring for these complications should occur on a daily basis with close attention paid to the patient and line status. Longer term complications from TPN cause hepatobiliary dysfunction. This includes TPN cholestasis and cholecystitis. It is recommended to monitor liver panels that include, triglycerides, bilirubin and liver enzymes on a weekly basis to monitor for these complications.

18.9   Transition Off PN

There are many variables when considering transitioning off PN to EN or oral intake. Age, tolerance to EN or oral advancement, psychologic factors, medical procedures, history of feeding difficulties and length of time off feeds are all factors that can affect how quickly one is weaned off PN. One suggested method for weaning is to decrease the hourly rate of infusion in appropriate conjunction with the advancement of the enteral feed rate. Another method is to cut TPN in half or decrease the total hours of infusion during the day to encourage an increase in oral intake. Despite which method used, monitoring blood glucose, nutrient intake and fluid status is imperative in the weaning process.

18.10   Conclusion

In conclusion, TPN can be life saving for infants and children in the cardiac unit. Early nutrition can prevent malnutrition, preserve lean body mass, and promote growth for those who are unable to meet their nutritional requirements enterally within days after birth or for extended periods of time. Careful attention and routine monitoring is required when administering TPN. Frequent assessment of the patient and the medical nutrition therapy is necessary to provide safe and cost-effective PN.

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Chapter 19
Medication Errors

Robert L. Poole and Phuong-Tan Nguyen-Ha

Abstract   Medication errors in pediatric and neonatal inpatients continue to be reported with an increased frequency during the past two decades. A medication error is defined as an error that originates at any point in the medication use process, from prescribing and transcribing, to dispensing, administering, or monitoring. Errors may occur at any time during a patient's hospital stay and may result from the action or inaction of physicians, pharmacists, nurses, other hospital personnel, or the patient.

Keywords   Medication errors • Pharmacogenomics • ADRs

The Institute of Medicine's report: "To Err Is Human: building a Safer Health System" made the headlines with startling

R.L. Poole, PharmD, FPPAG, FCSHP, FASHP
Department of Pharmacy, Lucile Packard Children's Hospital Stanford,
Clinical Professor of Pharmacy, University of California,
San Francisco, CA, USA
e-mail: rpoole@stanfordchildrens.org

P-T. Nguyen-Ha, PharmD
Department of Pharmacy, Children's Hospital of Pittsburgh of UPMC,
Pittsburgh, PA, USA
e-mail: phuongtan.nguyen@chp.edu

figures on the human costs of medical errors. Highlights o the report included the following findings: 44,000–98,000 annual deaths are a result of medical errors, and medication errors are the leading cause, followed by surgical mistakes and complications; more Americans die from medical errors each year than from breast cancer, AIDS, or car accidents; 2 % of patients admitted to hospitals experience and adverse drug event that results in an increased length of stay and nearly $4,700 increase in cost per event; the total cost of medical errors in the United States is estimated to be between $8.5 billion and 17 billion annually; and Computerized Provider Order Entry (CPOE) can improve the safety of medication use [1].

Medication errors in pediatric and neonatal inpatients continue to be reported with an increased frequency during the past two decades. A medication error is defined as an error that originates at any point in the medication use process, from prescribing and transcribing, to dispensing, administering, or monitoring. Errors may occur at any time during a patient's hospital stay and may result from the action or inaction of physicians, pharmacists, nurses, other hospital personnel, or the patient [2].

Each day, physicians, pharmacists, and nurses in children's hospitals address the special medication needs of pediatric and neonatal patients weighing between 400 g and 200 kg. The dosing of most drugs is weight-based in pediatrics, which results in the potential for a 500-fold dosing error [3]; in contrast, an adult patient may experience a maximum of a two-fold dosing error potential. There are many reasons for this potential disparity including: (1) pharmaceutical manufacturers provide medications in ready-to-administer unit dose packaging for adults. Very few drugs are available from manufacturers in ready-to-administer pediatric or neonatal unit dose or dosage forms. Pediatric pharmacists are routinely required to prepare dilutions, repackage, or compound dosage forms [4, 5]. (2) Most health care institutions are built around the needs of adult patients with very few staff trained in pediatric care. (3) Young children are less likely to withstand a medication error due to immature organ function and (4) children cannot always effectively communicate with providers when something is not correct [9]. Examples of the most common pediatric errors are listed in Table 19.1 [9].

TABLE 19.1 Common types pediatric medication errors

The most common types pediatric medication errors	Pediatric medication errors most often caused by
Improper dose/quantity (37.5 %)	Performance deficit (43 %)
Omission error (19.9 %)	Knowledge deficit (29.9 %)
Unauthorized/wrong drug (13.7 %)	Procedure/protocol not followed (20.7 %)
Prescribing error (9.4 %)	Miscommunication (16.8 %)
Wrong administration technique/wrong time/drug prepared incorrectly/wrong dosage form/wrong route	Calculation error/computer entry error/inadequate or lack of monitoring/improper use of pumps/documentation error

2006–2007 USP's MEDMARX ® database

Most of the more than 10,000 drugs on the market in the United States are not labeled with a pediatric indication, nor have they been studied in pediatric or neonatal populations. These problems put pediatric and neonatal patients at increased risk for medication errors. Studied have shown that the majority of medication errors in pediatrics occur in patients younger than 2 years of age [6]. Additionally, it is noted that based on USP's MEDMARX ® database, nearly 2.5 % of pediatric medication errors can lead to patient harm [9].

Pediatric and neonatal intensive care units are prime sites for medication errors. The therapeutic regimens of intensive care patients are often complex and require numerous calculations. Medications are often needed quickly, which puts added pressure on staff members in a stressful environment, which can additionally result in mistakes. Errors, adverse drug reactions (ADRs), and drug interactions are commonplace. Table 19.2 lists the medications considered high risk or high alerts. These medications require "special attention", because they have been associated with serious morbidity and mortality in pediatric patients. High risk and high alert medications should not be dispensed or administered until the patient has been weighed and each dose has been double checked during

TABLE 19.2 High risk-high alert medications

Potassium chloride
Sodium chloride (concentrate)
Insulin
Narcotic analgesics
Heparin, warfarin
Chemotherapeutic agents
Magnesium
Calcium
Dopamine, vasoactive agents
TPN (total parenteral nutrition)

preparation in the pharmacy and by nurses prior to administration to the patient. The use of "smart" infusion pumps should be utilized when appropriate as a final check [9].

Several excellent reports that provide strategies and guidelines for the prevention of medication errors in pediatrics have been published over the years [6–8]. They provide recommendations for system improvements, unit based pharmacist, education, the use of automation, and the benefits of CPOE systems. System improvement can included standardization of drug concentrations, engaging the staff and remain focus on the patient [10]. The value of unit-based clinical pharmacists has been demonstrated to reduce both potential and actual medication errors. Studies have proven that there is a correlation with a decrease in patient harm when pharmacists are available to prevent, identify and correct patient orders, especially when medications were reviewed prior to administration [12]. CPOE has also been shown to reduce medication errors. The potential benefits of CPOE are numerous and include the following: reduction in duplicate laboratory testing; the ability to recommend less expensive drug therapy; increased adherence to therapy pathways; annual savings in the millions of dollars; decrease turnaround times; pharmacy time saved; nursing time saved; and a 50 %

reduction in prescribing errors [11]. However, hospital computer systems and software applications are usually developed for adult patient populations. The healthcare provided for adult patients represents 95 % of all health care. Although pediatrics makes up the remaining 5 % of healthcare, only 1 % (75) of the 7,000 hospitals in the United States are children's hospitals. The safety of CPOE systems designed for adults is slowly being adapted for use in pediatrics. Computer order entry errors will most likely increase as more systems are automated and CPOE is implemented [13]. The careful implementation of technology to include a robust clinical decision support to avoid alert fatigue and the need to design systems to maximize effective workflow will be important to maximize safety and avoid developing a whole new set of errors [14].

Other CPOE software that has come to the market include Total Parenteral Nutrition (TPN) ordering and compounding process which makes this high-risk therapy much safer as well as bar code technology. Bar code technology has helped improve the safety of medication administration at the bedside with reported decrease in medication administration errors [15, 16].

Workplace factors also contribute to the occurrence of medication errors. Frequent interruptions, working long or double shifts, excessive noise, and inadequate lighting are but a few of the common hospital environmental factors that can contribute to medication errors. A more complete list appears in Table 19.3. Awareness and continued efforts to minimize the impact of these factors, especially when performing calculations, is critical to the prevention of medication errors.

Prevention of medication error should focus on the following basic concepts: (1) enforce standards for prescribing: complete orders; generic names only; no abbreviations for drug names, lists of "do not use" abbreviations; (2) standardization where possible: doses; time of administration; storage, packaging, and labeling; dosing of insulin and potassium; use of protocols and storage of potentially lethal injectable drugs; (3) unit dose system of drug distribution; (4) simplification: limit the number of infusion pump types; (5) pharmacy-based

TABLE 19.3 Environmental factors associated with medication errors

Distractions: telephone, pagers
Excessive workload; fatigue
Staffing: temporary, inexperienced, or insufficient numbers of staff
Shift changes
Patient transfers
Poor communication among provides
Verbal orders
Emergencies: Code Blue, STAT orders
Information not available
Patient names same or similar
Drugs "similar or sound alike" or spelled similarly
Space inadequate
Computer system down

admixture of all intravenous (I.V.) medications and solution; (6) allergy information reliably displayed; (7) eliminate double shift and long shift and long shifts; (8) computerized drug profiles; (9) effective adverse drug event monitoring systems; and (10) adopting list of "sound a-like, look a-like" medications and using tallman lettering to differentiate drug names (example: DOPamine vs. DOBUTamine and niCARdipine vs. NIFEdipine) [6–9].

The Joint Commission of the Accreditation of Healthcare Organizations (JCAHO) has developed National Patient Safety Goals each year since 2003 to improve patient safety and patient care [17]. The goals focus on problems in health care safely and how to solve them. These goals, as they relate to medication safety, are listed in Table 19.4.

Table 19.4 JCAHO patient safety goal 2012

Identify patients correctly

NPSG.01.01.01 Use at least two ways to identify patients. For example, use the patient's name and date of birth. This is done to make sure that each patient gets the correct medicine and treatment

NPSG.01.03.01 Make sure that the correct patient gets the correct blood when they get a blood transfusion.

Improve staff communication

NPSG.02.03.01 Get important test results to the right staff person on time.

Use medicines safely

NPSG.03.04.01 Before a procedure, label medicines that are not labeled. For example, medicines in syringes, cups and basins. Do this in the area where medicines and supplies are set up.

NPSG.03.05.01 Take extra care with patients who take medicines to thin their blood.

NPSG.03.06.01 Record and pass along correct information about a patient's medicines. Find out what medicines the patient is taking. Compare those medicines to new medicines given to the patient. Makes sure the patient knows which medicines to take when they are at home. Tell the patient it is important to bring their up-to-date list of medicines every time they visit a doctor.

Prevent Infection

NPSG.07.01.01 Use the hand cleaning guidelines from the Centers for Disease Control and Prevention or the World Health Organization. Set goals for improving hand cleaning. Use the goals to improve hand cleaning.

NPSG.07.03.01 Use proven guidelines to prevent infections that are difficult to treat.

(continued)

TABLE 19.4 (continued)

NPSG.07.04.01	Use proven guidelines to prevent infection of the blood from central lines.
NPSG.07.05.01	Use proven guidelines to prevent infection after surgery.
NPSG.07.06.01	Use proven guidelines to prevent infections of the urinary tract that are caused by catheters.
Identify patient safety risks	
NPSG.15.01.01	Find out which patients are most likely to try and commit suicide.
Prevent mistakes in surgery	
UP.01.01.01	Make sure that the correct surgery is done on the correct patient and at the correct place on the patient's body.
UP.01.02.01	Mark the correct place on the patient's body where the surgery is to be done.
UP.01.03.01	Pause before the surgery to make sure that a mistake is not being made.

JCAHO has also developed an official "Do Not Use" list for common abbreviations that have led to medication errors (see Table 19.5) [17].

The best approach to reduce mediation errors is to assume that errors occur in your institution. Recognize that medication errors are usually system failures and not human errors. Errors are almost always multifactorial. Encourage the reporting of errors. Know which patient populations are at high risk. Understand which process are error prone and focus improvement projects in these areas. Know which medications are high alert and put patients at a higher risk, and develop procedures that require extra care to ensure safety.

Additional references regarding medication errors in pediatrics and adverse drug event reporting are available in the literature [18–21].

TABLE 19.5 JCAHO official "Do Not Use" list

Do not use	Potential problem	Use instead
U (unit)	Mistaken for "0" (zero), the number "4" (four) or "cc"	Write "unit"
	Potential 10× error	
IU (international unit)	Mistaken for I.V. (intravenous) or the number 10 (ten)	Write "international unit"
Q.D, QD, q.d., qd (daily)	Mistaken for each other	Write "every other day"
Q.O.D., QOD, q.o.d., qod (every other day)	Period after the Q mistaken for "I" and the "0" mistaken for "I"; potential 4× error	
Trailing zero (X.0 mg)	Decimal point is missing	Write X mg
Lack of leading zero (.X mg)	Potential 10× error	Write 0.X mg
MS	Can mean morphine sulfate or magnesium sulfate	Write "morphine sulfate"
MSO_4 and $MgSO_4$	Confused for one another	Write "magnesium sulfate"

19.1   ADRS in Children

ADRs continue to be a major cause of morbidity and mortality in the United States, with a negative economic impact, estimated to be greater than $30 billion annually [22]. It has been estimated that 2–6 % of admissions to the hospitals in the United States are the result of an adverse reaction to a prescribed medication. Somewhere between 5 and 30 % of patients admitted were reported to have experienced an ADR. A fatal reaction to a drug occurs in approximately 0.3 % of hospitalized patients [23]. Toxic effects from marketed drugs rank among the top 10 causes of death in the United States. There are a number of different ADR definitions. The World Health Organization (WHO), the US Food and Drug Administration (FDA), and the American Society of Health System Pharmacists (ASHP) versions are provided in Table 19.6.

ADRs can happen when you do everything right. You administer the right drug, for the right indication, in the right dose, at the right time, and a bad outcome still occurs. Most ADRs are identified during the clinical trial phase of bringing a new drug to market, a time when all ADRs are required to be reported to both the FDA and the drug's manufacturer. Once a drug has been approved for marketing by the FDA, ADR reporting is voluntary. Voluntary reporting relies on the goodwill and good intentions of healthcare professionals, and has resulted in the gross underreporting of ADRs. Because of this, the actual incidence of ADRs is not known. Carleton et al. reported in 2001 that physicians in the United States voluntarily report an ADR to the FDA once every 336 years, whereas pharmacists report at a rate of once every 26 years [22]. These rates were based on the number of physicians and pharmacists in the United States, and the number of ADRs reported to the FDA in 1997–1998. Conservative estimates suggest that 5 % of all hospital admissions in the United States result from ADRs. In 1994, there were 7.2 million hospital patients who had serious ADRs; 106,000 of the ADRs were fatal.

TABLE 19.6 ADR definitions

Organization	Definition
1. WHO	Any injurious, unintended, and undesired response to a drug administered at doses used normally among humans for prophylaxis, diagnosis, or therapy
2. FDA	Any experience associated with the use of a drug, whether or not considered to be drug related, including any side effect, injury, toxicity, or sensitivity reaction, or significant failure of expected pharmacological action
3. ASHP	Any unexpected, unintended, undesired, or excessive response to a drug that: 1. Requires discontinuing the drug 2. Requires changing the drug therapy 3. Requires modifying the dose 4. Requires admission to a hospital 5. Prolongs hospitalization 6. Requires supportive treatment 7. Complicates diagnosis 8. Negatively affects prognosis 9. Results in temporary or permanent harm, disability or death

ADRs in children are not well understood because greater than 75 % of drugs currently on the market have not been studied in children and do not have a labeled pediatric indication for use. This fact has many clinicians referring to children as "therapeutic orphans." Additionally, infants and young children cannot evaluate and express their own response to medications. Information obtained from research in adults cannot be directly applied to infants and children that may have immature organ systems or different metabolic pathways. Information regarding a drug's use in pediatrics is

usually not included in the drug's package insert. Instead, statements similar to the following appear: "not approved for use in children younger than 12 years of age" or "safety and efficacy in children has not been established." Active surveillance systems for monitoring and reporting pediatric ADRs have been proposed. Prospective studies of hospitalized pediatric patients reporting the incidence of ADRs will vary depending on the severity of illness and the number of concurrent drugs being administered. Reported incidences of ADRs ranged between 4.4 and 16.8 % [23]. Gill et al. prospectively studied ADRs in a pediatric intensive care unit and found a 7 % incidence [24]. In another prospective study, Weiss et al. studied ASRs in a pediatric isolation ward. In their study, ADRs occurred in 21.5 % of patients [25]. An active monitoring system for reporting ADRs in children via a network of family pediatricians reported an incidence of 1.5 % in nonhospitalized patients [26]. Clearly, in a controlled environment such as a hospital, active reporting yields better, more complete data. Le et al. conducted a retrospective cohort study that reviewed ADRs in children that were reported over a 10-year period in a community-based, tertiary care, children's teaching hospital. A total of 1,087 ADRs were reported, with an overall incidence of 1.6 % [27]. This incidence was very low compared with the previously reported rates with prospective, active surveillance methods. Active surveillance systems must be put in place to address this serious issue in pediatrics, because the underreporting of ADRs in children continues to be a serious problem.

The drug classes most commonly associated with ADRs reported in pediatric patients are listed in Table 19.7. The types of pediatric ADRs that have been reported in the literature are listed in Table 19.8.

Postmarketing surveillance for pediatric ADRs cannot be overemphasized. Reporting systems must be improved and reporting needs to be mandatory instead of voluntary. All hospitals are required to have an ADR reporting system. Most include the use of FDA's Med Watch program for ADR reporting. The FDA will notify the drug manufacturer of all

TABLE 19.7 "Top 10" drug classes associated with ADRs in pediatrics

Drug classes	Frequency
1. Antibiotics	More common
2. Narcotic analgesics	
3. Anticonvulsants	
4. Sedatives/anxiolyitics/hypnotics	
5. Antineoplastic agents	
6. Antifungal agents	
7. Gastrointestingal agents	
8. Corticosteroids	
9. Cardiovascular drugs	
10. Immunoglobulins	Less common

TABLE 19.8 "Top 10" types of pediatric ADRs reported

Type of ADR	Frequency
1. Rash	More common
2. Flushing	
3. Pruritus; urticaria	
4. Blood pressure changes	
5. Fever, chills, rigor	
6. Neutropenia; thrombocytopenia	
7. Arrhythmias	
8. Respiratory depression	
9. Decreased renal function	
10. Abnormal liver function tests	Less common

reported ADRs and require the manufacturer to follow-up each reported occurrence. Table 19.9 is an example of a reporting chain at Veterans Affair health care system [28].

Table 19.9 Pyramid representation of the chain of allergy and adverse drug reaction (ADR) reporting within the Department of Veterans Affairs (VA) health system [28]

| 5. Pharmacovigilance by VA or FDA |
| 4. Report to FDA |
| 3. Facility Review and Report Submission to VA adverse drug event reporting system |
| 2. ADR report entry into computerized patient record system |
| 1. ADR recognition through patient-clinician interaction |
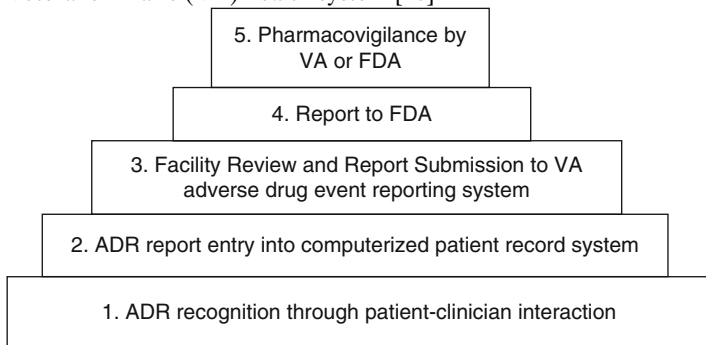
Pharmacogenomics is the study of the role of inheritance in individual variation in drug response. It refers to the general study of all of the many different genes that determine drug behavior. Progress has been made in the field of pharmacogenomics to help identify the genetic basis of severe and fatal ADRs in children and adults. For example, testing for variations in the CYP2C9 and VKORC1 in patients can prevent increased bleeding risks in patients taking warfarin [29]. Rapid advances in the field of pharmacogenomics aim to develop a rational means to improve drug therapy and achieve maximum benefit with minimal adverse effects and toxicity. These approaches promise the advent of 'personalized medicine" where drug therapies will be optimized for each patient's genetic makeup. In recent years, genes responsible for anthracycline cardiotoxicity, cis-platin induced deafness and ultra-rapid metabolizers of codeine have been identified. With the future development of genetic screening tests prior to drug therapy, these known adverse effects and toxicities can be minimized or avoided [30–33]. Until such time, ADR reporting systems must be improved [34].

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