Preventive Pharmacotherapy of Headache Disorders

Edited by

Jes Olesen
Stephen D. Silberstein
and Peer Tfelt-Hansen

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Preventive Pharmacotherapy of Headache Disorders

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Preface

Until 1990 there were long intervals between the appearances of new migraine drugs. For the acute treatment of migraine the only new drugs were the non-steroidal antiflammatory agents (NSAIDs). Like NSAIDs most other drugs were developed for other indications, but also proved to be effective in migraine prophylaxis. Then came sumatripan followed by several other triptans over the next decade. This was a major improvement in therapeutic possibilities as these drugs were more effective than previously used drugs and had considerably fewer side effects than for example ergotamine. However, the success of these acute treatments directed the interest of the pharmaceutical industry away from prophylaxis to such an extent that several possibilities for prophylactic drug development were simply not pursued.

All migraine patients deserve effective treatment for each individual attack with a minimum of side effects. In contrast, only patients with frequent, severe and/or long lasting attacks need a prophylactic drug. It goes without saying that highly efficient acute treatment for each attack reduces the need for prophylactics. For several years it was actually believed that the need for prophylactic drugs was insignificant after the advent of the triptans. However, this proved not to be true, and it has been estimated that approximately 10% of all migraneurs or approximately 1–2% of the population need an effective migraine prophylactic treatment with few side effects. This sounds like a modest figure compared to the 10–20% of the population who are in need of acute treatment, but prophylactic agents have to be taken every day and, therefore, the costs of effective prophylaxis could be much higher than the cost of treating each attack. For this reason, and because the triptan wave seems to have come to an end with no promising new acute drugs on the horizon, focus is now shifting towards prophylactic treatment both in the industry and among doctors. The present book, which derives from the 12th International Headache Research Seminar held in March 2003, is therefore timely. It provides most of the existing evidence in the field of pharmacological-prophylaxis of migraine and other chronic headaches and may, thus, serve as a platform for new initiatives in this field. Hopefully, it will also help the many doctors who now realize that proper treatment of severely affected migraneurs involves a prophylactic medication in addition to a triptan or other acute treatment. Once patients have an attack frequency of 4–5 a month, they should not increase the use of triptans but should have a supplementary prophylactic drug to keep attack frequency down. By doing so one can avoid medication overuse headache and preserve the patient in a much better state than by an injudicious escalation of acute antimigraine agents. Hopefully, this book will contribute to promote these sound therapeutic principles.

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July 2003

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Session I

Methodology of prophylactic trials

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1 Principles of preventive pharmacotherapy in primary headache

P. J. Goadsby

Preventive management for recurrent headache syndromes is one of the key tasks for physicians interested in headache. This review was commissioned to provide a backdrop for the discussions that will follow so it will be general, drawing on specific examples when appropriate, but will not be an exhaustive treatise on preventive therapies. Textbooks have been written[1–3] and much of what follows in this volume will cover the details of preventive therapy. Invariably, principles in medicine have a personal flavour and I am aware that much of what is written is couched in the first person. This chapter is an amalgam of my mentor's views,[2] the views of my colleagues, many of whom I have written with and collaborated with, and balanced by mistakes I have made myself and learnt from. Some principles are so generic that they apply across all primary headaches, applying as effectively in Chronic Migraine as they do in Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT).

The general principles are:

- Clarify the diagnosis and explain what it means to the patient.
- Assess the burden of the headache.
- Establish what the patient expects.
- Be clear about what the physician can offer.
- Counsel on areas in which the patient can intervene: life-style advice.
- Optimize treatment of acute attacks.
- Plan preventive treatment.

Although preventive pharmacotherapy may be required for some patients with Secondary Headaches, as classified by the International Headache Society,[4] Primary Headache syndromes were the task assigned to this section of the volume. Many of the issues raised are so generic they apply equally to Secondary Headaches.

I will deal below with the principles offering some particular examples by way of explanation.

Diagnosis

If one cannot make a diagnosis then all is virtually lost. A physician can be supportive of burden, offer generic counselling and hope, but without a diagnosis there is little concrete that can be done. To make a diagnosis in headache requires a good history. For complex or for difficult headaches this simply takes time. There is no short cut, no algorithm, no simple guide to taking a headache history, except to allow time. Time needs to be booked, allocated, or allowed since there is no substitute. After time comes expertise: it might be a difficult problem, it might be unusual, it might be odd, maybe even never previously described, so the physician should remain patient and open. Just because one has never heard of the description, do not assume it is a psychological problem. It does not matter how many medicines we have, or how many MRIs, or for the foreseeable future, functional imaging or genetic tests, a clear history will remain our most potent tool. Unvalued and unloved, a clear history is the single most valuable part of the whole process of management.

There are many textbooks that give excellent descriptions of history taking; it can be difficult to obtain a good history in medicine in general, in neurology in particular, and quintessentially in headache. It is important to both listen to the patient and to *take the history*, meaning that history taking is active. If you want to know if a patient has photophobia, you have to get an answer. *Not really* is not an answer, rather an invitation to probe further. Patients will often say of a detailed history that they have never been questioned in that way, and I think they appreciate both the thoroughness and the interest. This will be repaid in terms of compliance with what is arduous for anyone, taking medicines regularly.

A diary can be invaluable either to establish the basic pattern,[5] clarify a particular phenomenology,[6] or in the future with electronic diaries more clearly establish relationships between triggers and other aspects of the headache presentation.[7] This author has misdiagnosed patients with various Trigeminal Autonomic Cephalgias (TACs)[8] until a clear diary demonstrated the frequency and length of attacks. A diary can be both a helpful diagnostic tool and an invaluable management tool to document the outcome from preventive treatments.

As part of the diagnostic process, it is useful in primary headache to establish causality in some way. A normal physical examination and a clinical diagnosis of migraine renders brain imaging unnecessary.[9]

Lastly, and by no means least, one uses the diagnosis to explain to the patient what is happening to them. Causality is a very helpful concept that Professor Neil Raskin once pointed out to me (personal communication). If one establishes for migraine patients that they are in a *headachy* family, then they begin to accept what they have, and seek management not tests and cures. Establishing the familial principle is particularly rewarding in childhood headache; certainly adolescents have no difficulty ascribing yet another of their burdens to their parents! For cluster

Table 1.1 Preventive therapies in migraine classified by pharmacology

Potential mechanism	Drugs useful in migraine prevention
Amine modulation	
◆ Serotonin (5-HT_2 receptor) antagonists	◆ Pizotifen, Methysergide
◆ Adrenergic (β-receptor) antagonists	◆ Propranolol
◆ Dopamine receptor antagonists	◆ Flunarizine
◆ Amine reuptake blockers	◆ Amitriptyline
◆ Monoamine oxidase inhibitors	◆ Phenelzine
Channel modulators	
◆ Calcium	◆ Flunarizine ◆ Gabapentin
◆ Potassium	◆ Valproate
Second messenger modulators	
◆ Phosphorylation	◆ Topiramate

headache, explaining that recent research has established a likely brain locus for their disease in a part of the brain involved in body timing, comes as no surprise to them but certainly as a relief, *that something is being done*. Telling patients with migraine that they have dilated vessels and that you will constrict them with some treatment is both unhelpful and inaccurate. The mechanism of action of preventive medications (Table 1.1) does not, as a common theme, involve vasoconstriction, and as a pathophysiological explanation for migraine it does not stand up to scrutiny.[10] Migraine is a disorder of brain processing of sensory information in which the senses, in various combinations *shout* at the patient. Explaining that migraine involves a fluctuating brain physiology that becomes susceptible to various triggers and is marked by a sensitivity to change, will make sense to most patients and facilitates the provision of lifestyle advice.

Establish the burden of the headache

It is important to understand what the headache does to the patient. It is clear that migraine can be an extremely disabling problem.[11] Lipton and Stewart need to be singled out for doing the crucial clinical science behind developing disability tools. The Migraine Disability Assessment Score (MIDAS) is a reliable,[12] easy to use and clinically meaningful way[13] in establishing disability in migraine. We use it for all new patients, and find at a glance the degree of the burden. It is, of course, important in the consultation to allow patients to express the burden or disability of their own headache. I recently saw a cluster headache patient who was perhaps most burdened by the fact that his attacks rendered him crying with pain; he was embarrassed to do this in front of his children. Again a diary will help quantify the burden but primary headache can have intensely personal consequences that as physicians we are privileged to discuss with our patients.

Understand what the patient wants and explain what you can do

It is very useful to understand what the patient wants. I have seen patients with indomethacin-sensitive headaches, who have diagnosed themselves and had their Primary Care Physicians start them on treatment, who just want to talk about their problem; the particular patient just wanted an explanation. On the other hand, one sees patients who want an entire life transplant. Both tasks are difficult in their own way. It is important to explain to patients with Primary Headache syndromes that they have a constitutional problem. I often explain it is too late in life to have new parents or be re-born. If the patient with migraine wants a cure, we cannot do that, we cannot cure any primary headache. It is important that one establishes that we can help patients understand their problem, and we can help them manage it. We can provide advice, which the patient has to act on; we cannot make their life less stressful nor can we control the weather.[14] We can provide medicines but only the patient can use them.

Offer advice on how the patient can control their own problem—lifestyle advice

It is not the sole province of Complementary Medicine to offer advice to patients about how they might avoid provoking headache: the holistic approach. This advice is highly individual to the headache syndrome. For migraine it is perhaps easiest; avoiding chocolate, cheese, and orange juice may be in a popular magazine, but for most patients with troublesome headache is so useless a piece of advice as to be insulting. If one has explained (see above) that migraine is a brain disorder involving a cycling tendency to headache triggered largely by physiological disturbances: changing sleep patterns, stress patterns or physical activity, such as with over-exertion, then the principle of lifestyle advice is simple yet powerful. Regularity of sleep, eating, physical activity, indeed stress, and avoiding excess intake of caffeine, and analgesics, is basic but constructive advice. Some chemicals will trigger migraine, such as wine and nitrates, and this is important to note, although it would be exceptional to find a patient who had not worked this out.

For cluster headache, most patients have long worked out their triggers: alcohol, volatile chemicals, and warm environments, and such information is more confirmatory from a diagnostic point of view than useful advice to the patients. For Tension-Type Headache one is forced to say that avoiding emotional stress is useful, but since I have seen so little pure Tension-Type Headache, I can only rely on what is reported in studies.[15] Some lifestyle advice, which might otherwise be potent seems unhelpful: it is useless to ask patients with Hypnic Headache not to sleep, and unduly restrictive to ask patients with Sex Headache to refrain from the trigger activity.

Use of medicines

To adequately manage any primary headache one must ensure that acute attacks are treated properly. I explain to patients that they cannot make an informed choice about taking a preventive unless it is clear that what they do for acute treatments has been optimized. The fundamental equation for the initiation of a preventive therapy relates how easily an attack can be treated, the level of disability in any attack and how frequently the patient experiences the problem.

$$\text{acute\_attack\_tractability}^{\text{disability}} \times \text{attack\_frequency}$$

One may start a preventive because a very few acute attacks are impossible to manage and severely disabling, or because the attack frequency is so great that acute attack medicine is not practical for every attack. The latter issue, best illustrated by the Primary Chronic Daily Headache syndromes,[16] where frequency is the greatest driver for commencing a preventive. However, one must never exclude prevention if the disability is sufficient. I have initiated preventive management in a patient with migraine with aura who had one to two attacks a year. The problem being that his attacks consisted of a confusional state, and during the attack prior to starting treatment he was found wandering on a Tube platform in London. The consequences could have been disastrous, and thus the exponential importance of the degree of disability of the attack.

In general terms I initiate a discussion about prevention when there are more than four attacks a month, and particularly when the headache diary suggests an increasing trend, or the patient reports that acute attack treatments are becoming less effective. At three to four attacks a month a diary for three to six months will be very helpful in determining the way forward, and at one to two attacks per month issues of tractability and disability are paramount.

Using preventive treatments

The initiation of treatment with preventives is entirely dependent on the primary headache that one must deal with and the degree of disability surrounding the problem. For Chronic Migraine and Chronic Tension-Type Headache it is better to carefully and slowly initiate preventive strategies to minimize tolerability problems and maximize compliance. For TACs, such as Cluster Headache it is important to push treatments quickly to minimize suffering, similarly for Paroxysmal Hemicrania or SUNCT.

In my experience the two commonest reasons for treatment failure are misdiagnosis, and so inappropriate treatments, and under-treatment. Preventive treatments in migraine need to be given for long enough and at reasonable doses. In Cluster Headache, for example, verapamil dosing may be as high as 960 mg daily, and methysergide doses may be as high as 12 mg daily before attacks are controlled.

An issue that sometimes arises in treatment is that almost all preventive therapies have been transplanted from another indication. The two most celebrated examples would be the use of anticonvulsants and the use of antidepressants in migraine. In Table 1.1, I have set out another way of thinking about these treatments. Given that a drug like gabapentin is as effective in neuropathic pain as it is in epilepsy, and perhaps more so, why should it be called an anticonvulsant? Similarly, why call medicines used for bed-wetting simply antidepressants? Perhaps medicines would be better described by their mechanisms than their indications

Conclusion

Preventive therapies have been the poor second cousins in the last decade as acute attack therapies dominated the landscape. This was never true for our patients. While all physicians seeing headache patients applaud the development of acute attack therapies, prevention is the great unmet need, which this meeting in a very timely fashion seeks to address. Current preventive treatments can do much good; hopefully newer preventives will do much more good.

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PJG is a Wellcome Senior Research fellow.

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2 Methodology and implementation of systematic reviews

H. J. McQuay

What constitutes evidence?

Finding and using the best available evidence should be part of our professional lives.

There are several interlinked strands:

- finding the evidence;
- appraising the evidence;
- making the evidence (doing trials or systematic reviews);
- using the evidence.

Systematic reviews and large randomized trials constitute the most reliable sources of evidence we can muster (Table 2.1). Put simply, they are the best chance we have to determine what is true. We discuss how to find trials, and how to appraise their quality. Further on there is advice on how to appraise the quality of systematic reviews themselves.

Where do you get the evidence?

The randomized controlled trial (RCT) is the most reliable way to estimate the effect of an intervention. The simple principle of randomization is that each randomized patient has the same probability of receiving any of the interventions being compared. Randomization abolishes selection bias because it prevents investigators influencing who has which intervention. Randomization also helps to ensure that other factors, such as age or sex distribution, are equivalent for the different treatment groups. Inadequate randomization, or inadequate concealment of randomization, lead to exaggeration of therapeutic effect.[2]

An example of this bias is that in a systematic review of transcutaneous electrical nerve stimulation (TENS) in postoperative pain, 17 reports on 786 patients were

Table 2.1 Type and strength of efficacy evidence[1]

Level	Oxford CEBM levels of evidence (May 2001) Therapy/Prevention, Aetiology/Harm
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow CI)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	'Outcomes' Research; Ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

randomized studies in acute postoperative pain. Fifteen of these 17 RCTs demonstrated no benefit of TENS over placebo. Nineteen reports had pain outcomes but were not RCTs; in 17 of these 19, TENS was said by the authors to be analgesic.[3]

To produce valid reviews of evidence, the reviews need to be systematic, and to be systematic, qualitative or quantitative, they need to include all relevant RCTs. How many eligible RCTs exist? Commonly the total is unknown. Usually only for newer interventions are reviewers likely to be sure that they have found all the RCTs. In practice, constrained by time and cost, reviewers have to compromise, and then hope that what they have found is a representative sample of the unknown total population of trials. The more comprehensive the searching the more trials will be found, and any conclusions will then be stronger.

Retrieval bias is the failure to identify reports which could have affected the results of a systematic review or meta-analysis.[4] This failure may be because trials are still ongoing, or completed but unpublished (publication bias) or because although published the search did not find them. Trying to identify unpublished trials by asking researchers has a very low yield,[5] and is not cheap. Registers of ongoing and completed trials are another way to find unpublished data, but such registers are rare.

The importance of basing systematic reviews on the highest quality evidence (randomized trials) is obvious. The process is laborious, but is easier now because citations of known RCTs have been added to the Cochrane Library, so that others do not have to repeat the hand-searching process. For topics that are not mainstream the hand-searching process will still have to be done.

Although databases can tell us how well the patient or the health care professional thought the intervention worked, any conclusions about treatment efficacy are subject to the selection and observer bias which RCTs are designed to minimize. Estimates of treatment efficacy from database data are therefore likely to be

overestimates, and confounded by other influences, such as the medical condition itself and by other drugs.

Trials: quality and validity issues

Once you have found all the reports of the trials relevant to your question you need to confirm that these reports meet certain **quality standards** and second whether the trial is **valid**.

Imagine a situation where you found 40 reports of trials on your question. You then discover that 20 of the reports say that the intervention is terrific, and 20 conclude that it should never be used. Delving deeper you find that the 20 'negative' reports score highly on your quality standards scale. The twenty 'positive' reports score poorly for quality. What then will you conclude? Without a quality scale you would vote for the intervention. With the quality scale you would vote against.

The quality scale should include measures of bias. Bias is the simplest explanation why poor quality reports give more positive conclusions than high quality reports. The quality standards which you require cannot be absolute, because for some clinical questions there may not be any randomized trials (RCTs). Setting RCTs as a minimum absolute standard would therefore be inappropriate for all the questions we might want to answer. In the pain world, however, there are two reasons for setting this high standard, and requiring trials to be randomized. The first reason is that we do have, particularly for drug interventions, quite a number of RCTs. The second is that we would argue that it is even more important to stress the minimum quality standards of randomization and double-blinding when the outcome measures are subjective.

Developing and validating a quality scale

What makes a trial worthy of the label 'high quality'? In this context quality primarily indicates the likelihood that the study design reduced bias. Only by avoiding bias is it possible to estimate the effect of a given intervention with any confidence. A simple scale was designed to assess this aspect of quality (Table 2.2).

Validity of trials

A study may of course be both randomized and double-blind, and describe withdrawals and dropouts in copious detail (so scoring well on this quality scale) and yet be invalid. One example is the injection of morphine into the knee joint to reduce pain after arthroscopy.[6,7] In some trials this injection was made after the operation without knowledge of whether or not the patients had enough pain for the intervention to make a difference. If they had just mild pain rather than moderate or severe pain it is quite possible that the success ascribed in that trial to the intervention was actually due to the fact that they did not have any pain to begin with. A second example is a review which proclaimed that fewer patients

Table 2.2 Scale (3 point) to measure the likelihood of bias

1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop outs?

Give a score of 1 point for each 'yes' and 0 points for each 'no'. There are no in-between marks

Give 1 additional point if:	On question 1, the method of randomization was described **and** it was **appropriate** (table of random numbers, computer generated, coin tossing, etc.)
and/or:	If on question 2 the method of double-blinding was described **and** it was **appropriate** (identical placebo, active placebo, dummy, etc.)
Deduct 1 point if:	On question 1, the method of randomization was described and it was inappropriate (patients were allocated alternatively, or according to date of birth, hospital number, etc.)
and/or:	On question 2 the study was described as double blind but the method of blinding was **inappropriate** (e.g. comparison of tablet vs injection with no double dummy)

would die after major surgery if they had regional plus general anaesthesia.[8] The statistical significance which led the authors to this potentially important conclusion came from a number of small trials with 30% mortality rates, rates so high as to make one question the validity of the trials. Reviews should not include invalid trials. A subsequent big RCT showed that the review's conclusion was wrong—there was no difference.[9]

Systematic reviews: quality, utility and output

Judging quality of systematic reviews

Systematic reviews of inadequate quality may be worse than none, because faulty decisions may be made with unjustified confidence. Quality control in the systematic review process, from literature searching onwards, is vital. How to judge the quality of a systematic review is encapsulated in the questions:[10]

- Were the question(s) and methods stated clearly?
- Were the search methods used to locate relevant studies comprehensive?

- Were explicit methods used to determine which articles to include in the review?
- Was the methodological quality of the primary studies assessed?
- Were the selection and assessment of the primary studies reproducible and free from bias?
- Were differences in individual study results explained adequately?
- Were the results of the primary studies combined appropriately?
- Were the reviewers' conclusions supported by the data cited?

Outcome measures chosen for data extraction should also be sensible. Usually this is not a problem, but again it is a part of the methods that needs to be read carefully to see if you agree with the outcome measure extracted. The reviewer may have used all that is available, and any problems were due to the original trials, but it is a determinant of the clinical utility of the review.

The questions a systematic review should answer for us are:

- How well does an intervention work (compared with placebo, no treatment or other interventions in current use)?
- Is it safe?
- Will it work and be safe for the patients in our practice?

Not all data can be combined in a meta-analysis: qualitative systematic reviews

It is often not possible or sensible to combine (pool) data, resulting in a qualitative rather than a quantitative systematic review. Combining data is not possible if there is no quantitative information in the component trials of the review. Combining data may not be sensible if trials used different clinical outcomes or followed the patients for different lengths of time. Combining continuous rather than dichotomous data may be difficult. Even if trials measure and present dichotomous data, no matter how many patients did or did not achieve a specified outcome, if the trials are otherwise of poor quality[11] it may not be sensible to combine the data.

Making decisions from qualitative systematic reviews

Making decisions about whether or not a therapy works from such a qualitative systematic review may look easy. In the example above, 15 of the 17 RCTs of TENS in acute pain showed no benefit compared with control. The thinking clinician will realize that TENS in acute pain is not an effective analgesic. The problem with this simple vote counting, counting how many trials showed benefit and how many did not, is that it may mislead. It ignores the sample size of the constituent studies, the magnitude of the effect in the studies and the validity of their design even though they were randomized.[12]

Evaluating efficacy

Combining data: quantitative systematic reviews

There are also two parts to the 'does it work?' question: how does it compare with placebo and how does it compare with other therapies. Whichever comparison is being considered, the three stages of examining a review are a L'Abbé plot, statistical testing (odds ratio or relative risk), and a clinical significance measure such as NNT.

L'Abbé plots[13]

A first stage for evaluating therapies is to look at a simple scatter plot, which can yield a surprisingly comprehensive qualitative view of the data. Even if the review does not show the data in this way it can be done from information on individual trials presented in the review tables. Figure 2.1 contains data from an updated systematic review of single dose paracetamol in acute pain. Each point on the graph is the result of a single trial, the size of each point being proportional to the size of each trial, and what happens with paracetamol (experimental event rate [EER]) is plotted against the event rate with placebo (control event rate [CER]).

Trials in which the experimental treatment proves better than the control (EER > CER) will be in the upper left of the plot, between the *y*-axis and the line of equality. Paracetamol was better than placebo in all the trials; although the plot does not say how much better. If experimental was no better than control then the point would fall on the line of equality (EER = CER), and if control was better than experimental then the point would be in the lower right of the plot, between the x-axis and the line of equality (EER < CER).

Visual inspection gives a quick and easy indication of the level of agreement among trials. Heterogeneity is often assumed to be due to variation in the EER—the effect of the intervention. Figure 2.1 shows that variation in the control event rate can also be a source of heterogeneity, even though the controls were all matched placebos in relatively homogeneous acute pain conditions with single dose treatment.

L'Abbé plots have several benefits and the simple visual presentation is easy to assimilate. They make us think about the reasons why there can be such wide variation in (especially) placebo responses, and about other factors in the overall package of care that can contribute to effectiveness. They explain the need for placebo controls if ethical issues about future trials arise. They keep us sceptical about overly good or bad results for an intervention in a single trial where the major influence may be how good or bad was the response with placebo.

Variation in control (placebo) response rates

The reason for large variations in event rates with placebo, which happens in most therapeutic areas, may have something to do with trial design and population. The overwhelming reason for large variations in placebo rates in pain studies (and probably studies in other clinical conditions) is the relatively small group sizes in

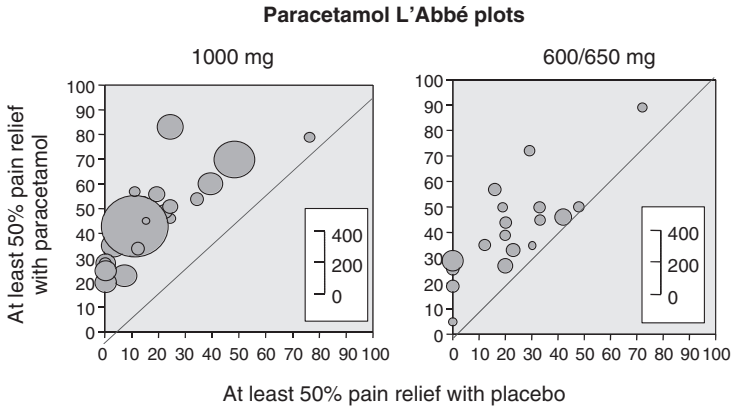

Fig. 2.1 L'Abbé plot of Experimental Event Rate (EER; %> 50% relief on treatment) against Control Event Rate (CER; %> 50% relief on placebo) for RCTs of paracetamol 1000 and 600/650 mg.

trials. Group sizes are chosen to produce statistical significance through power calculations—for pain studies the usual size is 30–40 patients for a 30% difference between placebo and active analgesic. An individual patient can have no pain relief or 100% pain relief. Random selection of patients can therefore produce groups with low placebo response rate or high placebo response rate, or somewhere in between. Mathematical modelling based on individual patient data shows that while group sizes of up to 50 patients are likely to show a statistical difference 80–90% of the time, to generate a close approximation to the 'true' clinical impact of a therapy requires as many as 500 patients per group (or more than 1000 patients in a trial).[14] Credible NNTs for effective analgesics need data from 500 patients.

The lessons are that information from individual trials of small size should be treated with circumspection in pain and probably other therapeutic areas, and that variation in outcomes seen in trials of small size is probably artefactual.

Heterogeneity

Clinicians making decisions based on systematic reviews need to be confident that apples are not being compared with oranges. The L'Abbé plot is a qualitative defence against this problem. While statistical testing ostensibly provides a quantitative way of checking for heterogeneity, the tests lack power,[15] so that while a test positive for heterogeneity suggests mixed fruits are being compared, a negative test does not provide complete reassurance that there is no heterogeneity. Heterogeneity will also appear to occur because of variations in control and experimental event rates due to the random play of chance in trials of small size. Generally trials of fewer than 10 patients per group should be omitted from systematic reviews,[13] but considerable variability will occur in group sizes below 50 patients. The crucial issues are whether the trials are clinically homogeneous and sufficiently large.

Indirect versus direct comparisons

What clinicians really need are the results of direct comparisons of the different interventions, so called head to head comparisons. These are rarely available, and what we have to work with are comparisons of each of the interventions with placebo. Indeed at present we have no method to use the data from the direct comparisons of efficacy. The methods illustrated here tell us how fast each competitor runs against the clock, rather than who crosses the line first in a head to head challenge.

Statistical significance

When it is legitimate and feasible to combine data, the odds ratio and relative risk (or benefit) are the accepted statistical tests to show that the intervention works significantly better than the comparator. As systematic reviews are used more to compare therapies, clinicians need to grip these clinical epidemiological tools, which present the results in an unfamiliar way.

Odds ratios

The odds ratio can give a distorted impression when analyses are conducted on subgroups which differ substantially in baseline risk.[16] Where control event rates are high (certainly when they are above 50%), odds ratios should be interpreted with caution.

Relative risk

The fact that it is the odds ratio rather than relative risk reduction that is used as the test of statistical significance for systematic reviews seems to be due to custom and practice rather than any inherent intellectual advantage. Relative risk may be better than odds ratios because it is more robust in situations where control event rate is high.[17] With event rates above 10%, relative risk produces more conservative figures.[18] There is still considerable uncertainty and disagreement amongst statisticians and reviewers as to whether odds ratios or relative risk should be used. Importantly, odds ratios should be interpreted with caution when events occur commonly—as in treatments—and odds ratio may over estimate the benefits of an effect when event rates are above 50%. They are likely to be superseded by relative risk because it is more robust in situations where event rates are high.[16,19]

How well does the intervention work?: clinical significance

While odds ratios and relative risks can show that an intervention works compared with control they are of limited help in telling clinicians how well the intervention works—the size of the effect or its clinical significance. The product of systematic review and particularly meta-analysis—often some sort of statistical output—is often not interpretable or usable in day-to-day clinical practice. A common currency to help make the best treatment decision for a particular patient is what is

needed. We believe that this common currency is the number-needed-to-treat (NNT). The choice of analgesic for both professional and patient will be made on the balance between efficacy and risk, where the risk may be adverse effect or drug interaction with other drugs which the patient is taking.

Effect size

One method of estimating the amount of benefit, the effect size, is to use the standardized mean difference.[20] The advantages of this approach are that it can be used to compare the efficacy of different interventions measured on continuous rather than dichotomous scales, and even using different outcome measures. The *z*-score output is in standard deviation units, and therefore is scale-free. The (major) disadvantage of effect size is that it is not intuitive for clinicians.

Number-needed-to-treat (NNT)

The NNT is the number of people who have to be treated for one to achieve the specified level of benefit. This concept is proving to be a very effective alternative as the measure of clinical significance from quantitative systematic reviews. It has the crucial advantage of applicability to clinical practice, and shows the effort required to achieve a particular therapeutic target.

Technically the NNT is the reciprocal of the absolute risk reduction, and is given by the equation

$$\mathrm{NNT} = \frac{1}{\left(\mathrm{IMP}_{\mathrm{act}}/\mathrm{TOT}_{\mathrm{act}}\right) - \left(\mathrm{IMP}_{\mathrm{con}}/\mathrm{TOT}_{\mathrm{con}}\right)}$$

where: $\mathrm{IMP}_{\mathrm{act}}$ is the number of patients given active treatment achieving the target; $\mathrm{TOT}_{\mathrm{act}}$ is the total number of patients given the active treatment; $\mathrm{IMP}_{\mathrm{con}}$ is the number of patients given a control treatment achieving the target; $\mathrm{TOT}_{\mathrm{con}}$ is the total number of patients given the control treatment.

Advantage

The advantage of the NNT is that it is clinically intuitive, showing how many patients need to be treated for one to benefit. It is treatment specific. It describes the difference between active treatment and control. The level of benefit or threshold used to calculate NNT can be varied, but the NNT is likely to be relatively unchanged because changing threshold changes results for both active and control. The threshold used for the single dose analgesic data (Fig. 2.2) was 50% pain relief. This is a difficult target for analgesics, and, in cancer pain, patients feel a treatment is beneficial if it produces 30% relief.[21] What is judged worthwhile relief may vary with the clinical context, but in terms of the NNT calculation the choice of threshold makes little impact on the relative efficacy of the different treatments, because the results for the control will improve if the threshold is lowered, and deteriorate at a higher threshold. Some patients will of course benefit from the treatment but at a lower level than the threshold.

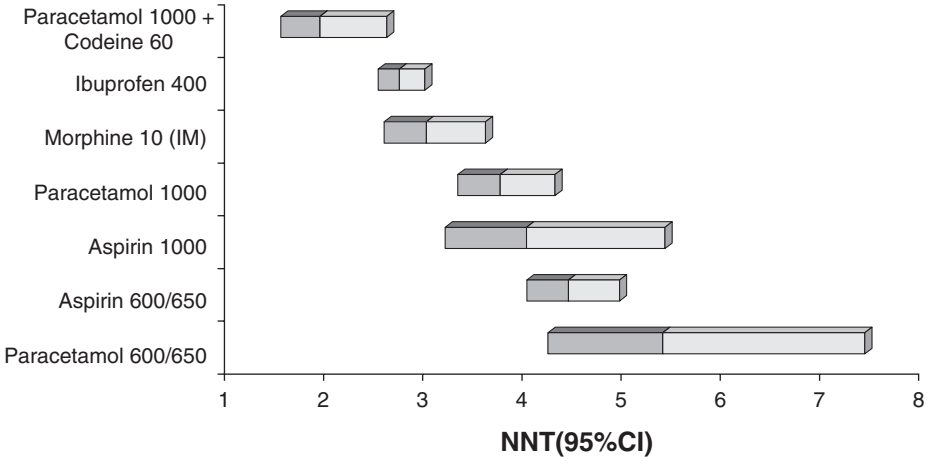

Fig. 2.2 Numbers-needed-to-treat (NNT) for 50% pain relief in postoperative pain (single dose). NNT point estimate is at the junction of the grey and white bar segments. Grey bar segement is the lower 95% confidence interval, white is the upper).

An NNT of 1 describes an event that occurs in every patient given the treatment but in no patient in a comparator group. This could be described as the 'perfect' result in, say, a therapeutic trial of an antibiotic compared with placebo. For therapeutic benefit the NNT should be as close as possible to 1; there are few circumstances in which a treatment is close to 100% effective and the control or placebo completely ineffective, so NNTs of 2 or 3 often indicate an effective intervention. For unwanted effects, NNT becomes the number-needed-to-harm (NNH), which should be as large as possible.

It is important to remember that the NNT is always relative to the comparator and applies to a particular clinical outcome. The duration of treatment necessary to achieve the target should be specified. The NNT for cure of head-lice at two weeks with permethrin 1% compared with control vehicle was 1.1 (95%CI 1.0–1.2).[22,23]

Confidence intervals

The confidence intervals of the NNT are an indication that 19 times out of 20 the 'true' value will be in the specified range. If there is inadequate or conflicting data then the NNT may not have finite confidence intervals, and the statistical tests (odds ratio or relative risk) will not be statistically significant. An NNT with an infinite confidence interval may still have clinical value as a benchmark, but should be treated cautiously until further data permits finite confidence intervals.

Disadvantages

The disadvantage of the NNT approach—apparent from the formula—is that it needs dichotomous data. Continuous data can be converted to dichotomous for acute pain studies so that NNTs may be calculated, by deriving a relationship between the two from individual patient data.[24] Because of the way it is calculated,

NNT will also be sensitive to trials with high control event rates (CER). As CER rises, the potential for treatment specific improvement decreases: higher (and apparently less effective) NNTs result. So, as with any summary measure from a quantitative systematic review, NNT needs to be treated with caution, and comparisons can only be made confidently if the pooled trials do not show major variation in their CERs.

Evaluating safety

Estimating the risk of harm is a critical part of clinical decisions. Systematic reviews should report adverse events as well as efficacy, and consider the issue of rare but important adverse events. Large RCTs apart, most trials study limited patient numbers. New medicines may be launched after trials on 1500 patients,[25] missing these rare but important adverse events. The rule of three is important here. If a particular serious event does not occur in 1500 patients given the treatment, we can be 95% confident that the chance of it occurring is at most 3/1500.[26]

Much the same rules apply to harm as to efficacy, but with some important differences; the rules of admissible evidence and the NNH (number-needed-to-harm) rather than NNT. The absence of information on adverse effects in systematic reviews reduces their usefulness.

Rules of evidence

The gold standard of evidence for harm—as for efficacy—is the RCT. The problem is that in the relatively small number of patients studied in RCTs rare serious harm may not be spotted. Therefore, study architectures of lower intrinsic quality may be admissible for an adverse effect systematic review. An extreme example is that observer blinding is superfluous if the outcome is death. Such rare and serious harm cannot and should not be dismissed just because it is reported in a case report rather than in an RCT. The 'process rules' in this area have yet to be determined.

Number-needed-to-harm (NNH)

For adverse effects reported in RCTs, NNH may be calculated in the same way as NNT. When there is low incidence it is likely that point estimates alone will emerge (infinite confidence intervals). Major harm may be defined in a set of RCTs as intervention-related study withdrawal, and be calculated from those numbers. Precise estimates of major harm will require much wider literature searches to trawl for case reports or series. Minor harm may similarly be defined in a set of RCTs as reported adverse effects. The utility of these reports is because they are reported simply as present or absent, with no indication of severity or importance to the patient.

Conclusion: using NNT and NNH to evaluate analgesics

In the ideal world you will have three numbers for each intervention, an NNT for benefit and NNHs for minor and major harm. The thrust of this chapter is that

these methods can be used to show the effectiveness or otherwise of a range of interventions, and if effective, to use the NNT as a benchmark of just how effective a particular intervention is. This then becomes the yardstick against which alternative interventions, each with its NNT for benefit, NNH for minor harm and NNH for major harm should be judged, and is the pivot for the clinical decision on whether or not to use the intervention for an individual patient. Figure 2.2 ranks the analgesics by their efficacy estimate; clinical choice might be to prescribe or take a safer although marginally less effective drug.

To provide robust recommendations on choice of analgesic, prescription, or over-the-counter, requires evidence of the highest quality. These methods can deliver high quality efficacy estimates if there are randomized trials of adequate size and quality, but not if the trials are deficient in number, size, or quality. Safety estimates are more difficult, not least because the data from which they are derived come commonly from study designs which are not randomized and hence more subject to bias.

Conclusion

We know how to provide robust evidence about the efficacy of interventions. To provide that evidence we need high quality trials. We should not shy away from doing high quality trials just because they are difficult. At the same time we need to acknowledge that the methodology is not yet adequate to design adequate studies of the ways in which we deliver care, either packages of care or the context in which they are delivered.

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3 Adverse events, equally important as efficacy as an outcome parameter?*

D. I. Stenver

Abstract

This chapter reflects on the diverting attitudes throughout history towards efficacy and safety parameters.

For several decades drug development was focused on providing effective mediactions indicated for life-threatening diseases. The randomized clinical trial was designed with the purpose of demonstrating efficacy and provides only scarce information on safety. This is exemplified by migraine prophylaxis trials.

In recent years documentation has emerged that adverse drug reactions represent a major cause of mortality and morbidity. Therefore, the various stakeholders pay increasing attention to safety. A need for developing scientific methods appropriate for a high-quality evaluation of safety signals is recognized.

A short introduction to drug safety surveillance—pharmacovigilance—is provided, with focus on current trends and new tools. The need for adjusting the design of clinical trials in order to get valuable and useful information on safety parameters is stressed.

Introduction

Are adverse events equally important as efficacy as an outcome parameter in clinical trials? This important and relevant question will obviously depend on the disease, on whether the drug is for treatment or prevention and on the kind and nature of the adverse event. It will also depend on to whom you put this question: the patient, the

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health care professional, the drug manufacturer, the researcher, the regulator? The aim of this short paper is to present some views of the regulatory authority.

Efficacy versus safety in a historical perspective

In a historical perspective it is evident that efficacy parameters have been subject to much more attention than safety parameters. For several decades drug development was focused on providing effective medications indicated for potential life-threatening diseases, e.g. malignant diseases, infectious diseases and diseases, which in other ways affect vital organ functions. The need for effective medications for a variety of serious diseases was substantial and indisputable. In this setting safety could still in the 20th century be considered as a luxury problem.

In the 21st-century documentation has emerged that adverse drug reactions represent a major cause of mortality and morbidity.[1] Based on this and other current trends in pharmacovigilance it is also evident that there is a need for strengthening drug safety surveillance, and the various stakeholders in the pharmacovigilance field do pay increasing attention to safety—patients, health care professionals, governments, and companies being the key stakeholders.

Differences between efficacy and safety parameters in relation to clinical trials

In relation to research there are major differences between efficacy and safety parameters. The randomized controlled clinical trial is designed primarily to demonstrate efficacy. When researchers consider a study design and the appropriate statistical methods, efficacy is expected to occur in the majority of the patients, and efficacy parameters are well-defined. On the contrary, adverse drug reactions are expected to occur in a minority of the patients, may be entirely unexpected, and as such are not well-defined. The short duration and the highly selective enrolment of patients in clinical trials further underlines that clinical studies have a limited capacity for providing safety information.

Historically we have had scientific methods for demonstrating *efficacy* for several decades; however, when it comes to *safety* there is considerable room for improvement. As an inherent feature of the study design, clinical trials provide far more information on efficacy than on safety.

This is also true in, for example, migraine prophylactic trials, regardless of the drugs trialled; beta-blockers, amin-antagonists, calcium-antagonists, or NSAIDs.[2]

Experiences with migraine prophylaxis trials

A small number of highly selected patients are enrolled and treated for a short period of time. This does not leave much time to elucidate and characterize the safety profile of a pharmaco-therapeutic principle. For both parameters—efficacy

and safety—trials are difficult to compare due to different designs and different ways of reporting, e.g. the use of complex headache indices.

Furthermore comparability is seldom substantiated by narrow confidence intervals. Even in small trials with grossly inadequate power lack of significance is often confused with lack of difference.

Similar ADR-profiles and frequencies can be observed between the active drug and placebo, reflecting a methodological problem rather than the true condition.

Finally, publication bias, with preference for publishing significant and positive differences, and with highly variable scientific documentation for different drugs, makes it difficult to extrapolate the results to the clinical setting, where the risk/benefit evaluation has to be done. In particular, in *preventive* pharmacotherapy administered for *long* periods of time this evaluation is evidently very important.

CPMP draft note for guidance on clinical investigation of medicinal products for treatment/prophylaxis of migraine[3]

The Committee of Proprietary Medicinal Products (CPMP) has taken the initiative to provide a guideline on clinical investigation of medicinal products for treatment/prophylaxis of migraine. The guideline has recommendations concerning the strategy and design of therapeutic and prophylactic confirmatory studies as well as recommendations specifically addressing clinical safety evaluation, e.g. specific adverse events to be monitored, the extent of patient exposure and long term safety. The final guideline will be published at the Website of the European Medicines Evaluation Agency (EMEA) (www.emea.eu.int).

Pharmacovigilance—drug safety surveillance

Bearing in mind that clinical trials do not provide detailed information on safety parameters it is important to identify the alternative sources of information. It is also essential to understand the basic principles for drug safety surveillance—pharmacovigilance.

Per tradition pharmacovigilance is defined as the process of drug safety surveillance including improvement of drug safety in the post-marketing phase.[4] It is generally agreed that the safety profile of particular drugs is only partly known at the time of marketing. In recent times initiatives have been taken internationally, e.g. by the EMEA and the Heads of Agencies, aiming at strengthening the pharmacovigilance in the pre-marketing phase.[5]

The primary *objectives* in pharmacovigilance are risk detection, risk assessment, risk minimization, and risk communication. Risk detection or signal generation is extensively supported by current technology and data-processing networks. Risk assessment aims at judging if the observed events are casual or causally related to the drug and classifies the events as serious or non-serious. Risk minimization and prevention of ADRs requires intensive monitoring in the pre- and post-authorization phases and

should be based on rational pharmacotherapy. Risk communication aims at providing useful and appropriate information to relevant parties at the right time.

The *focus* in pharmacovigilance is on the degree of seriousness, whether an observed adverse event is expected or maybe a new signal, on the patient exposure, and on whether or not the ADR is specific for a particular drug or is a class-effect.

Currently and partly based on clinical trials we are primarily capable of demonstrating frequently occurring ADRs after short term use, but ideally we should be able to demonstrate infrequently occurring ADRs and ADRs after long term treatment in patients suffering from chronic conditions like migraine. This is one of many challenges in pharmacovigilance.

Trends in pharmacovigilance in 2003

In relation to drug approval, the globalization and international harmonization of the 21st century has made it possible to bring new drugs to markets of considerable dimensions, e.g. through the centralized drug approval procedure in the EU. A large number of patients are therefore exposed within a short time, and as such may be at risk if serious, but infrequently occurring ADRs were not identified in the pre-authorization phase. Today products are withdrawn from the market due to identified serious safety issues. Severe hepatoxicity (e.g. tolcapone) and prolonged QT-syndrome (e.g. sertindole) are examples of adverse drug reactions with significant impact on the risk/benefit ratio of drugs, in certain cases leading to withdrawals. On the other hand old drugs tend to stay on the market, although their positions are challenged by newer alternatives. But as recent examples have shown—e.g. centrally acting anorectics—the pharmaceutical legislation does not provide the basis for revoking marketing authorizations unless new data document lack of efficacy or demonstrate harmful effects while used under normal circumstances.

The health burden and socio-economic burden of adverse drug reactions are documented e.g. by investigations showing that 3–6 % of hospitals admissions are caused by ADRs, out of which many are preventable.[6] Underreporting is prevailing.[7]

Polyfarmaci is now more the rule than the exception, and new drug interactions are demonstrated almost every day so there is a very good chance of medication errors.

Sources of safety information post-marketing

Clinical trials provide only a part of the safety information and evidence. Other sources of information are the spontaneously submitted ADR reports from HCPs, pharmacists and patients, company-derived data in the form of single-case ADR reports, mandatory periodic safety update reports, post-authorization safety studies and risk management programmes, registries in different countries and databases, and finally literature publications.

The thalidomide catastrophe in the 1960s[8], where thousands of children were born with malformations due to the use of thalidomide for treatment of

pregnancy-related nausea, elicited the establishment of adverse drug reaction registries throughout the western part of the world. While the spontaneous reporting system has been a cornerstone for decades, it is evident that spontaneous reports have their limitations. Most importantly, spontaneous reports are signals, which may give rise to safety concerns and theories, but the spontaneous reports almost never provide the solid documentation of a causal link. The exception is anaphylactic shock occurring instantaneously after administration of the drug. The spontaneous reporting system does not either provide information on the frequency of the particular adverse event, as the true patient exposure is not known. Underreporting is prevailing.

On this basis increasing attention has been paid to the need for developing and improving the methods applied in pharmacovigilance; sources of information, exchange of information, and scientific and statistical approaches in general.

Periodic safety update reports (PSUR)

From the mid-nineties a new document was introduced in drug safety surveillance and laid down in pharmaceutical legislation: the periodic safety update report (PSUR).[9,10] This document is a valuable new tool, which systematically provides collected safety information in the post-marketing phase. Every holder of a marketing authorization is obliged to submit safety update reports to the regulatory authorities at intervals; half-yearly in the first 2 years after marketing, then yearly until the renewal-procedure at 5 years and thereafter at each renewal, or at the request from the authorities.

The PSUR provides an overview of the current safety profile of the drug on the basis of all safety data collected from all sources and from all markets. The PSUR provides a basis for re-evaluating the risk profile. The conclusion can be that the presented data reflects current knowledge of the identification of new safety issues that raise concern. As a minimum the product information is revised. Eventually a repeated risk/benefit analysis has to be done and even suspension or withdrawal has to be considered.

Exchange of safety information

An extensive exchange of safety information between involved parties takes place due to internationally agreed procedures among stakeholders. An example is the development of the electronic network—Eudranet—in the European Union. Through this network safety data originating e.g. from health care professionals, are circulated between companies and regulatory authorities, and via the EMEA to other countries and the WHO. The observations done by health care professionals are thus brought to the attention of a large community, which is important to bear in mind.

How can the researchers contribute to improved safety of medicinal products?

It is crucial that researchers and scientists adjust the design of studies and focus on safety, and it is deemed necessary that short term efficacy studies are supplemented by long term safety-studies. This enables the researchers to make a far better contribution to the development and improvement of pharmacovigilance which requires a multi-disciplinary approach.

Model for excellence in pharmacovigilance

Recently a scientific model for the future conduct of pharmacovigilance was proposed by Waller *et al.*[11] This model for excellence in pharmacovigilance includes the following major areas:

First, the evidence base for pharmacovigilance needs to be improved by moving up the evidential hierarchy, from spontaneous reporting to e.g. pharmacoepidemiological studies. Second, high-quality evidence will form the basis for robust assessment and decision making. Third, outcome measures must be defined and audit performed, and cultural and scientific developments must be stimulated and utilized. Then the community meets the need for measuring the performance of the surveillance in terms of public health benefit.

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4 The methodology of prophylactic trials: discussion summary

P. Tfelt-Hansen

The question about the CONSORT statement (Begg *et al*. 1996) for reporting clinical trials was raised. It was commented that these rules make common sense; and *Cephalalgia*, the official journal of the International Headache Society, has introduced a policy of requiring that papers submitted on randomized clinical trials conform with the CONSORT statement.

In some headache centres patients may be included multiple times in clinical trials over the years. This may lead to a selection of failures, as has been observed for example in patients with non-opiate sensitive pain. In addition, patients in these centres are not representative for the general migraine population. In highly specialized headache centres one should not use the group of too severe affected patients for clinical trials.

The question of the choice of an active comparator drug in prophylactic migraine trials was raised. It could vary from country to country but most physicians involved in prophylactic migraine trials will probably agree that propranolol is currently the most established drug for migraine prophylaxis (Tfelt-Hansen and Shanks 2000).

Prophylactic treatment of migraine in young females and the potential for inducing fetal malformations during pregnancy is a problem, especially for antiepileptics. In Europe there is a register where physicians can report on use of antiepileptic drugs during pregnancy (Tomson *et al*. 2000). More safety data on most prophylactic migraine drug use during pregnancy are needed; and for the moment the policy as recommended by the panel should be: 'stop prophylactic migraine treatment before pregnancy, and tell the patients that after the first trimester the migraine normally gets better'. If prophylactic treatment of migraine is needed the beta-blockers propranolol and metoprolol can be used (Pfaffenrath and Rehm 1998, Aube 1999).

In the registration of adverse events after drugs used for migraine prophylaxis, tolerability and safety are not directly separated, but a distinction is made between serious and non-serious adverse events. Lack of tolerability, most often due to non-serious adverse events, is a major clinical problem in migraine prophylaxis and the current way of reporting adverse events in prophylactic migraine trials is unsatisfactory because it does not reflect this clinical experience.

Adverse events should be reported extensively in migraine prophylactic trials, especially withdrawal due to intolerance to treatment should be reported, and probably some ways of reporting disability connected with adverse events should be found.

The current European recommendations for reporting adverse events can cause problems and there is a big, complicated medical dictionary on how to report adverse events. The neuropathic pain trials with gabapentin (Backonja *et al*. 1998, Rowbototham *et al*. 1998) were recommended as an example of good reporting of adverse events.

The reporting of adverse events in acute treatment trials was criticized. Any unusual events occurring up to 7 days after intake were reported as adverse events. This is most likely done for regulatory purposes but it is not clinically relevant.

The adverse events reporting in prophylactic trials can vary from open questions about adverse events every 4 weeks to daily questions about typical adverse events in a diary.

It was suggested that the International Headache Society Clinical Trial Subcommittee should work on improving the future reporting of adverse events, especially in prophylactic migraine trials.

It was finally commented that chronic cluster headache patients often have a benefit/tolerability ratio different from that of migraine patients. Thus if very high doses of, for example, verapamil are used with good efficacy, cluster patients are normally willing to cope with moderate or even severe adverse events.

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Session II

Prophylactic drugs I

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5 Key issues in the methodology of prophylactic migraine trials

P. Tfelt-Hansen

Introduction

When designing a randomized clinical trial (RCT) the possible results can be regarded to be 'dependent' on the following theoretical equation:

$$\frac{\text{Pharmacological effect}}{\text{Variability ('noise')}}$$

This equation looks like a *t*-test. To get the biological signal through, one should, when planning the RCT, estimate the pharmacological effect and the variability.

A 'large' pharmacological in prophylactic migraine trials could be efficacy of active drug A versus placebo. Examples of 'small' pharmacological effects could be: I, dose-response curve for drug A; II, minimum effective dose for drug A versus placebo; III, comparability among drug A and drug B; IV, adverse events after drug A versus adverse events after placebo.

Examples of variability ('noise') in prophylactic migraine trials are, among others: I, migraine *per se* is a variable among patients; II, the individual patient's migraine may vary over time; III, variability of efficacy measures, definitions of migraine attacks, migraine days, migraine periods, severity, duration, etc.; IV, difficulties in distinguishing between effectively treated migraine attacks and attacks of tension-type headache; V, placebo effect, and variable placebo effect, for efficacy; VI, placebo effect for adverse events; VII, time-effect; VIII, variable baseline; IX, non-responders; X, dropouts, due to either lack of efficacy or due to intolerance; XI, major psychosocial events occurring during the trial.

How do we then get the pharmacological signal through in a prophylactic migraine RCT? The unknown theoretical pharmacological effect in a certain RCT is fixed but should be estimated in the planning phase of a prophylactic RCT. We thereafter mainly have to work on the denominator of the equation: variability ('noise').

In the following, some aspects of selection of patients, trial design, evaluation of results, and statistics will be mentioned with the main emphasis on their influence on variability. For more extensive recommendations on prophylactic migraine drug trials, see (IHS 2000).

Selection of patients

Variability can be decreased by increasing the number of patients in the RCT but, of course, increasing numbers does not help if the wrong patients are selected. Selecting the right patients is therefore of major importance both for the clinical relevance of the results and in order to decrease variability.

The first point, of course, is the migraine definition and here the diagnostic criteria of the IHS (Headache Classification Committee of the International Headache Society 1988) should be adhered to strictly. There are people with attacks that do not meet IHS criteria but, nevertheless, in clinical practice are diagnosed with migraine and respond to prophylactic migraine therapy (International Headache Society Clinical Trial Subcommittee 2000). For prophylactic migraine RCTs, however, requirements should be more rigid than in clinical practice. It is my experience that relatively few people will be excluded by requiring IHS criteria.

Attacks of migraine in patients included in migraine prophylactic RCTs should occur 2 to 6 times per month (International Headache Society Clinical Trial Subcommittee 2000). It is important that prophylaxis is clinically indicated in patients who enter prophylactic trials. An upper limit of attacks per months is important for excluding patients with drug overuse, see below.

Other headaches (so-called interval headaches) can be permitted if the patient can clearly differentiate them from migraine by the quality of pain and/or by the profile of associated symptoms. The frequency of other headaches should be no more than 6 days per month (International Headache Society Clinical Trial Subcommittee 2000).

Patients who make themselves available for multiple trials may not fairly represent the target population. The use of migraine patients for several prophylactic RCTs may lead to selection of non-responders.

Patients with overuse of analgesics and specific drugs for migraine should not be included in prophylactic migraine RCTs both because they suffer from drug overuse headache and because they tend to be non-responders to prophylactic treatment.

Trial design

The placebo effect in migraine prophylaxis varies considerably and can be high. A drug must therefore be demonstrated to be superior to placebo. It has recently been suggested, based on an analysis of the placebo-response in migraine prophylaxis (van der Kuy and Lohman 2002), that if the percentage of responders (>50% reduction in attack frequency) in an open-labeled prophylactic drug trial is above 35–40%, or if a reduction in migraine attack frequency is found of 40% or more, further studies are indicated to determine the prophylactic activity of the drug.

However, based on migraine days a placebo response of 75% was found in one trial (Migraine-Nimodipine European study Group (MINES) 1989), and recently a 51% responder rate for frequency of attacks was reported for placebo (Pradalier *et al.*, poster presented at IHRS 2003). Thus even if a considerable prophylactic effect is observed in an open study this could still be a placebo effect; and in my view there is no case for evaluating possible prophylactic drugs in migraine first in small open-labeled trial and then possibly in RCTs if an effect is indicated in the open study. In addition, the 95%CI, for example a 35% response in 20 patients, will be 15% to 59%. The only reasonable way to investigate a drug for migraine prophylaxis is therefore a randomized, placebo-controlled, double-blind, clinical trial.

In parallel-groups trials, patients could be stratified for frequency of migraine attacks (e.g. ≤3 or >3 attacks per 4 weeks) occurring during baseline. In some studies (e.g. Jensen *et al.* 1994), the extent of the prophylactic effect of drugs has varied depending on baseline frequency. It is therefore reasonable to use frequency of attacks as a basis for stratification in order to decrease variability, especially because this is the principal outcome measure and baseline equality for this is necessary.

In most prophylactic RCTs, a 4 weeks baseline (run-in) period is used (International Headache Society Clinical Trial Subcommittee 2000). It should be noted that the use of 4 weeks run-in can increase the inherent variability when the RCT are analysed for changes in migraine frequency from run-in to treatment periods, normally a mean of at least 12 weeks, because the frequency in the run-in is determined with less precision than in the treatment period.

It has been recommended that treatment periods of at least 3 months should be used (International Headache Society Clinical Trial Subcommittee 2000).

Relatively long treatment periods increase the power of the trial by providing more stable estimates of attack frequency, see Fig. 5.1. So instead of a range of 2 to 6 attacks per month, by meaning, for 3 months the range is decreased to 3.4 to

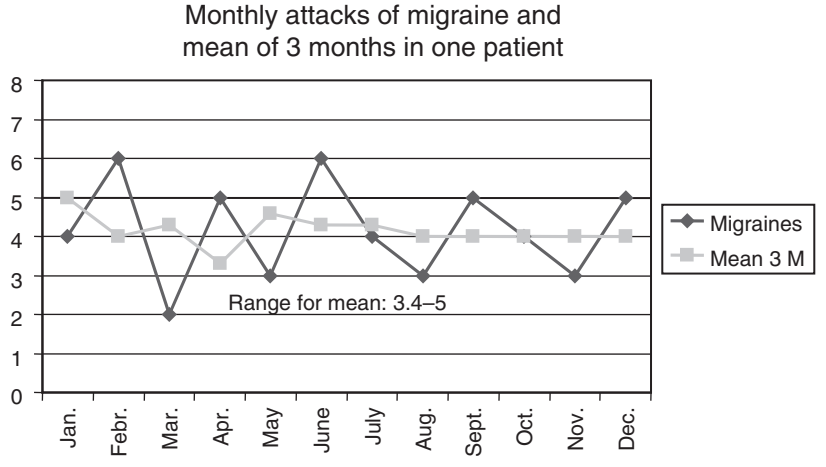

Fig. 5.1 Simulated variability of frequency of migraine attacks per months during one year in one patient ◆ . For each month the mean of this month, the previous and the next month is given by ■ .

5 attacks per month. In addition, longer treatment periods provide more events for measuring the possible pharmacological effect. The efficacy of some drugs accrues gradually (i.e. needs some weeks or months before becoming fully established) and need longer treatment periods. Furthermore, only effects of sufficient duration are clinically relevant.

Either crossover, e.g. Tronvik *et al.* (2003), or parallel-groups, e.g. Freitag *et al.* (2002), designs can be used, depending upon the research objectives and drugs under study. The advantage of the crossover design is that it is approximately 8 times more powerful than the parallel-groups design in prophylactic migraine trials (Tfelt-Hansen and Nielsen 1987). For certain parallel-groups designs, however, the number of patients required is no more than 2 to 4 times the number required in a crossover design (Lewis 1987). Thus the intra-patient variability is in most cases less than the inter-individual variability. The major drawbacks of the crossover design are: (i) the possibility of a carryover effect; (ii) the need for a long total period of treatment (extended by washout periods) with concomitant increases in dropouts and loss of statistical power; and (iii) side effects which can more easily unmask blinding when a patient is exposed to both treatments. A time-effect is not a problem in the crossover design, because suitable statistical techniques can deal with it (Olesen *et al.* 1981).

Evaluation of results

Frequency of migraine attacks per 4 weeks should be the primary efficacy measure.

The number of migraine attacks should be recorded irrespective of their duration, and the following rules should be used for distinguishing an attack of long duration from 2 attacks, or for distinguishing between attacks and recurrences (International Headache Society Clinical Trial Subcommittee 2000):

(a) A migraine attack which is interrupted by sleep, or temporarily remits, and then recurs within 48 hours should be recorded as one attack, and not two.
(b) An attack treated successfully with medication but with relapse within 48 hours counts as one attack.
(c) A practical solution to differentiating these using diary entries over the previous month is to count as distinct attacks only those that are separated by an entire day headache-free.

Most migraine prophylactic RCTs permit the inclusion of patients with so-called interval headaches, but only if patients are able to differentiate them well from migraine attacks, see above. The headache diary should differentiate between migraine and other headache by simply asking the patient: 'Is this a true migraine attack or another headache?' When identified, other headaches may simply be recorded by the number of days per 4 weeks affected. In some RCTs (e.g. Tfelt-Hansen *et al.* 1984), interval headaches seem to respond to migraine prophylactic treatment.

Number of days with migraine per 4 weeks can be used as an outcome measure. Because of the difficulties with defining the duration of a migraine attack

the use of migraine days has been proposed as a simpler alternative (Tfelt-Hansen and Olesen 1985). This measure, which allows the use of a more simple headache diary, where the patient for each day can indicate whether or not a migraine headache was present, will probably be most useful in large-scale long-term pragmatic trials. In the same diary the patients can also indicate other headaches.

Responder rate is defined as the percentage of subjects in a treatment group with 50% or greater reduction in attack frequency during treatment compared with the baseline period. In some RCTs the responder rate (50%) is defined as the percentage of subjects in a treatment group with 50% or greater reduction in attack frequency during the last 4 weeks of treatment compared with the baseline period.

The choice of 50% or greater reduction is traditional and arbitrary, and e.g. presenting the results for both 50%, 75%, and >90% reduction may be more meaningful. This dichotomous measure is relatively insensitive to treatment effects; and results of this sort are particularly vulnerable to selection bias, limiting the generalisability of the study results.

Responder rates can be used in meta-analyses of placebo-controlled RCTs. In some RCTs the patients with the highest attack frequency seem to have a higher response rate than patients with lower frequency of attacks, e.g. Jensen *et al.* (1994).

Response rate calculated as difference from baseline to the last 4 weeks of the treatment period can be influenced by the fact that both are heavily dependent on the inherent variability in time of the migraine *per se* in the individual patients. The deal would be e.g. the mean of 3 months baseline versus the mean of 3 months treatments.

The current system for reporting adverse events (AEs) and design of prophylactic RCTs to pick up AEs in prophylactic RCTs is not satisfactory and tends not to reflect current clinical experience. In many papers on prophylactic RCTs in migraine, it is stated that the drug was well tolerated and caused no more AEs than placebo. In clinical practice AEs are a major problem in prophylactic migraine treatment, often leading to discontinuation of treatment. Incidence of adverse events, especially adverse events leading to discontinuation of treatment, should therefore be regarded as one of the major measures for judging a prophylactic migraine drug.

One of the main arguments for including placebo in prophylactic RCTs in migraine is that that is the only way to get a valid estimate of the tolerability profile of a drug. RCTs in migraine prophylaxis should be powered to detect more AEs after active drugs than after placebo. One of the major advantages of the crossover design may be its ability to detect more AEs after active drugs than after placebo, e.g. Tfelt-Hansen *et al.* (1984).

With the current reporting system it happens that up to 80% AEs are reported for placebo (Klapper *et al.* (1997) and in such a case it will of course be impossible to detect statistically significant more AEs for the active drug, in this case divalproex.

In conclusion, there is a need for the International Headache society to work on an optimal way of reporting AEs in prophylactic RCTs in migraine.

For a more extensive discussion of AEs in migraine prophylactic RCTs, see Stevner (this volume)

Statistics

In the parallel-groups design comparisons between groups can be made either as direct comparisons during the treatment periods or as comparisons of changes from baseline. The latter is conceivably more powerful, but analyses have so far shown only that this is marginally so (Tfelt-Hansen, personal observation). In parallel-groups trials the use of the baseline value as a covariate can also be examined but results of this analysis should be judged with caution (Assmann *et al.* 2000).

Suitable statistical methods (Olesen *et al.* 1981) can be used in the crossover design for correction for a period effect ('time effect'), if present.

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6 Migraine prophylaxis: a pharmacoepidemiological study of practices used by general practitioners and neurologists in France

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Introduction—objective

One aspect of a comprehensive migraine treatment plan is long-term preventive therapy. In France, the Framig I study has demonstrated that only 7% of all migraine subjects use a preventive therapy. In order to understand such an undertreatment, we conducted a pharmacoepidemiological survey to describe the pattern of utilization of migraine prophylactic drugs by French physicians.

Methods

A telephone survey using a computer assisted telephone interview (CATI) system was carried out in September 1998 and French physicians completed a phone-mail-phone questionnaire which inquired about migraine prophylactic treatment.

The 202 general practitioners (GPs) and 161 neurologists (Ns) included in the survey were representative of the French medical population.

The phone-mail-phone questionnaire was focused on several aspects of the migraine prophylactic treatment:

- main criteria used to institute migraine prophylactic treatment;
- agents most commonly prescribed for migraine prophylaxis among: dihydroergotamine, beta-blockers, tricyclics, pizotifen, flunarizine, indoramine (an alpha-blocker used in France), oxetorone (a serotonin antagonist used in France), methysergide, verapamil, and valproic acid;
- time interval between treatment onset and evaluation of the prophylactic efficacy;
- main criteria used to evaluate the prophylactic efficacy;
- overall duration of prescription of migraine prophylactic treatment.

A chi-2 test was used for statistical analysis between GPs and Ns.

Results

Main criteria used to institute migraine prophylactic treatment are indicated in Table 6.1. The attacks frequency was reported by 81% of general practitioners and 81% of neurologists (ns). Decrease of quality of life was reported by 11% of neurologists and 4% of general practitioners ($p<0.05$). Drug overuse was only reported by 2% of general practitioners and 2% of neurologists (ns).

Agents most commonly prescribed for migraine prophylaxis are indicated in Table 6.2. Dihydroergotamine was commonly prescribed by 72% of general practitioners and 39% of neurologists ($p<0.05$) and beta-blockers by 37% of general practitioners and 71% of neurologists ($p<0.05$). Neurologists also commonly prescribed tricyclics (33% vs 3% of general practitioners, $p<0.05$) or pizotifen (27% vs 6% of general practitioners, $p<0.06$) and to a lesser degree indoramine (18% vs 8% of general practitioners, $p<0.05$), flunarizine (14% vs 8% of general practitioners, $p<0.05$) and oxetorone (11% vs 3% of general practitioners, $p<0.05$). Few general practitioners and neurologists declared to prescribe commonly

Table 6.1 Main criteria used to institute migraine prophylaxis. Responses from general practitioners (GPs) and neurologists (Ns)

	GPs (%)	Ns (%)	
Attacks frequency	81	81	ns
Quality of life alteration	4	11	s ($p<0.05$)
Attacks severity	10	3	s ($p<0.05$)
Abortive treatment failure	2	1	ns
Abortive treatment overuse	2	2	ns
Attacks duration	1	2	ns

Table 6.2 Agents most commonly prescribed for migraine prophylaxis (several responses possible). Responses from general practitioners (GPs) and neurologists (Ns)

	GPs (%)	Ns (%)	
Beta-blockers	37	71	s ($p<0.05$)
Dihydroergotamine	72	39	s ($p<0.05$)
Tricyclics	3	33	s ($p<0.05$)
Pizotifen	6	27	s ($p<0.05$)
Flunarizine	8	14	s ($p<0.05$)
Indoramine (alpha-blocker)	8	18	s ($p<0.05$)
Oxetorone (serotonin antagonist)	3	11	s ($p<0.05$)
Methysergide	3	3	ns
Verapamil	1	2	ns
Valproic acid	0	0	ns

Table 6.3 Time interval between treatment onset and efficacy evaluation. Responses from general practitioners (GPs) and neurologists (Ns)

	GPs (%)	Ns (%)	
1 month	17	13	ns
2 months	29	33	ns
3 months	45	47	ns
4 months	3	4	ns
5 months	1	0	ns
6 months	3	2	ns
>6 months	2	1	ns

methysergide or verapamil and neither general practitioners nor neurologists declared prescribing commonly valproic acid.

Time interval between treatment onset and efficacy evaluation is indicated in Table 6.3. The time interval was from 2 to 3 months for 74% of general practitioners and 80 % of neurologists.

Main criteria used to evaluate the efficacy of migraine prophylaxis are indicated in Table 6.4. Reduction of attacks frequency was reported by 47% of general practitioners and 57% of neurologists (ns). Improvement of quality of life was reported by 44% of general practitioners and 36% of neurologists (ns).

Overall duration of prescription of migraine prophylactic treatment is indicated in Table 6.5. The duration was from 6 months to 1 year for 57% of general practitioners and 65% of neurologists.

Table 6.4 Main criteria used to evaluate the efficacy of migraine prophylaxis. Responses from general practitioners (GPs) and neurologists (Ns)

	GPs (%)	Ns (%)	
Reduction of attacks frequency	47	57	ns
Improvement of quality of life	44	36	ns
Reduction of attacks severity	5	5	ns
Increase of abortive treatment efficacy	3	2	ns
Decrease of attacks duration	1	0	ns

Table 6.5 Overall duration of prescription of migraine prophylactic treatment. Responses from general practitioners (GPs) and neurologists (Ns)

	GPs (%)	Ns (%)	
3 months	11	15	ns
6 months	35	38	ns
1 year	21	27	ns
>1 year	28	18	s ($p<0.05$)
Life-time	5	2	ns

Discussion

Three results of this pharmacoepidemiological survey are important to consider. These results concern the criteria used to institute migraine prophylactic treatment, the choice of prophylactics drugs, and the evaluation of their efficacy.

For a large majority of French neurologists and general practitioners, the introduction of migraine prophylactic treatment is supported by attacks frequency, whereas few French physicians declared using mainly disability or acute medications overuse as criteria to institute it. Such an attitude is not in accordance with current French recommendations for migraine management (ANAES), that focus on the number of attacks that occur each month but also on both global functional impairment and abortive drugs abuse.

Dihydroergotamine and beta-blockers are the main prophylactic agents used by French physicians. Large use of beta-blockers is in accordance with all current recommandations for migraine management considering beta-blockers as drugs with documented high efficacy and mild to moderate adverse events. Large use of dihydroergotamine in migraine prophylaxis is particular to French physicians concerning general practitioners (first choice) but also neurologists (second choice). Even if the dihydroergotamine is a drug with a lower documented efficacy and contraindicated with triptans, an oral programmed-release form of it is available in France and it is associated with a very low incidence of adverse events.

Considering time interval between treatment onset and prophylactic efficacy evaluation, there is no difference between French general practitioners and French neurologists, and around 80% of French physicians make the efficacy evaluation from 2 to 3 months after prophylactic treatment onset. Evaluation is mainly based on attack frequency reduction but more than 40% of general practitioners and nearly 40% of neurologists consider the quality of life improvement as an important criterion. In practice, such use of disability changes seems difficult to apply considering the few French physicians who declared using quality of life alteration as the main criterion to prescribe a migraine prophylactic treatment.

Acknowledgement

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Further reading

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7 Preventive treatment of migraine headache with rofecoxib

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Introduction

The current choices for the prophylactic treatment of migraine include 6 major medication groups: β-adrenergic blockers, antidepressants, calcium channel blockers, selective serotonin receptor antagonists, anticonvulsants, and NSAIDs. The mode of action of most of these classes of drugs in migraine prophylaxis is not fully understood.[1,2] Due to a lack of scientific rigor in many of the reported trials, it is not clear which agents are the most effective in preventing migraine.[3] All of these agents carry the risk of side effects, which can be significant in some cases.[1,2] For example, non-selective NSAIDs are associated with an increased risk of gastrointestinal side effects, such as ulcers, which are thought to be due to inhibition of the COX-1 enzyme. The recent development of agents which are selective inhibitors of COX-2, such as rofecoxib, raises the possibility that these new agents may be effective for migraine prophylaxis with an improved gastrointestinal tolerability profile compared with non-selective NSAIDs. We therefore performed a clinical trial to investigate the efficacy and tolerability of rofecoxib for migraine prophylaxis.

Methods

Inclusion and exclusion criteria

Male and female patients who were at least 18 years of age and met International Headache Society criteria for migraine, with or without aura, for at least one year[4] were included. Patients had on average, by history, ≥3 and ≤8 migraine attacks per month for the past 6 months. Patients were excluded if they had (1) a preponderance of mild attacks; (2) basilar or hemiplegic migraine; (3) taken prophylactic migraine treatment in the 4 weeks prior to study start; (4) a history of non-response to ≥2 classes of prophylactic migraine treatment; or (5) difficulty in

distinguishing their migraine attacks from tension or interval headaches, or a history of tension or interval headaches for ≥15 days per month.

Study design and treatment schedule

This multicentre study consisted of 2 phases: a 2-month, single-blind, placebo run-in phase followed by a 3-month, randomized, double-blind, placebo-controlled treatment phase. Patients who experienced at least 3 migraine attacks in the second month of the placebo run-in phase were randomly assigned to receive either rofecoxib 25 mg (2 × 12.5-mg tablets), montelukast 20 mg (2×10-mg tablets), or placebo once daily for 3 months. Breakthrough attacks were treated with rizatriptan 10-mg tablets; additional analgesics and/or antiemetics were allowed at 2 hours after rizatriptan dosing, if needed.

Results for montelukast have been previously reported (montelukast was not significantly more effective than placebo[5]), and only the comparison between rofecoxib and placebo will be discussed here.

Assessment of clinical efficacy, safety, and tolerability

For all migraine and non-migraine headaches, patients recorded the following information on a diary card: the start date and time of the headache, the presence of associated symptoms (aura; headache got worse with physical activity; headache was pulsing; headache was on one side of the head; sensitive to light; sensitive to sound; loss of appetite; nausea/queasy; vomiting), whether they thought the headache was a migraine, the medication taken to treat the headache, the date and time of headache resolution, and the maximum severity (mild, moderate, or severe). Safety and tolerability were assessed by physical examination, vital signs, 12-lead electrocardiography, laboratory evaluations, and adverse experiences (AEs) recorded in a diary and reported verbally to the investigator.

Statistical analysis

The efficacy analyses were based on the modified intention-to-treat approach including all patients who took at least one dose of double-blind treatment and had a baseline value and at least one set of post-randomization diary information. Migraine attacks were defined as headaches that were classified as migraine attacks by the patient or were treated with rizatriptan or another triptan. The primary variable for efficacy evaluation was the percentage of patients reporting at least a 50% decrease in migraine attack frequency per month (adjusted to 28 days) during the 3-month double-blind treatment period (Months 3 to 5) compared to baseline (placebo run-in Month 2). Secondary efficacy endpoints were also evaluated during Months 3 to 5 and are listed in Table 7.2.

All patients who took at least one dose of double-blind treatment were included in the safety analyses. Formal treatment comparisons were performed for the percentage of patients (1) with at least one AE, (2) with a drug-related AE (defined

as possibly, probably, or definitely drug related by the investigator), (3) with a serious AE, (4) who discontinued treatment due to an AE, (5) with NSAID-type gastrointestinal AEs, and (6) with hypertension-related AEs.

Results

Of the 478 patients who entered the placebo run-in phase, 268 were randomized to the double-blind treatment phase. The main reasons for discontinuation from the placebo phase were as follows: ineligible for double-blind phase ($n=74$), withdrew consent ($n=55$), and lost to follow-up ($n=38$). The double-blind phase was completed by 75 (82%) of the 91 patients randomized to rofecoxib and by 72 (86%) of the 84 patients randomized to placebo. The main reasons for discontinuation from the rofecoxib and placebo groups, respectively, were clinical AE ($n=0.2$), lack of efficacy ($n=1.2$), lost to follow-up ($n=5.3$), patient moved ($n=3.0$), and withdrew consent ($n=5.3$). The rofecoxib group was 91.2% white and 81.3% female; the placebo group was 92.9% white and 88.1% female. The mean age was 39.7 years (range 18 to 63) in both groups. Baseline values for outcome measures were similar between the groups (Table 7.1).

Efficacy results are summarized in Table 7.2. The percentage of responders (patients reporting at least a 50% decrease from baseline in migraine attack frequency per month) during the double-blind treatment period was significantly larger ($p=0.028$) in the rofecoxib group (23.8%) than in the placebo group (10.3%). Figure 7.1 shows the percentage of responders by month of double-blind treatment. The effect of rofecoxib tended to be consistent across months, while the effect of placebo increased steadily from Month 3 to Month 5.

Table 7.1 Baseline values for outcome measures by treatment group

	Rofecoxib 25 mg ($N=88$) Mean (SD)	Placebo ($N=83$) Mean (SD)
Number of migraine attacks per month*	5.22 (2.58)	4.85 (2.00)
Number of migraine and non-migraine headache attacks per month*	6.05 (2.80)	5.70 (2.38)
Average migraine severity†	2.17 (0.50)	2.22 (0.46)
Number of days with migraine per month*	6.35 (3.26)	6.48 (3.36)
Number of days with migraine and non-migraine headache per month*	7.23 (3.56)	7.45 (3.63)
Mean number of rizatriptan tablets used per migraine	1.62 (0.71)	1.67 (0.67)

* Adjusted to 28 days.
† A score of 2 indicates 'moderate' pain intensity, and a score of 3 indicates 'severe' pain intensity.

Table 7.2 Summary of efficacy results during double-blind treatment: Months 3 to 5

	Rofecoxib (*N* = 84)	Placebo (*N* = 78)	*p*-value
Percentage of patients reporting ≥ 50% decrease from baseline in migraine attack frequency per month*	23.8%	10.3%	0.028
Mean change from baseline in number of migraine headache days per month*	–1.1	–0.5	0.211
Mean change from baseline in average migraine severity	–0.0	–0.1	0.377
Mean change from baseline in number of rizatriptan tablets used per breakthrough migraine	–0.0	0.1	0.449
Mean change from baseline in migraine attack frequency per month *	–1.0	–0.4	0.062
Mean change from baseline in migraine and non-migraine attack frequency per month*	–1.2	–0.5	0.079
Median percent change from baseline in migraine attack frequency per month *	–22.8%	–8.0%	0.191
Mean change from baseline in number of migraine and non-migraine headache days per month*	–1.2	–0.7	0.293

* Adjusted to 28 days.

Clinical AEs were reported by 42.7% of the rofecoxib patients and by 41.0% of the placebo patients. These AEs were considered drug-related in 6.7% of the rofecoxib group and in 4.8% of the placebo group. There were no drug-related serious AEs, and none of the rofecoxib patients discontinued due to an AE. The most common AEs (incidence >3%) in the rofecoxib and placebo groups, respectively, were sinusitis (n=5.3), influenza (n=4.4), upper respiratory infection (n=4.7), nausea (n=4.2), pharyngitis (n=3.3), and back pain (n=2.3). The incidence of NSAID-type gastrointestinal AEs (acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, or vomiting) was 6.7% in the rofecoxib group and 2.4% in the placebo group. There were no significant differences between rofecoxib and placebo with regard to clinical AEs, drug-related AEs, serious AEs, NSAID-type gastrointestinal AEs, or hypertension-related AEs, although the study was not powered to detect any differences in AEs.

Discussion

In this study, rofecoxib 25 mg once daily was an effective and generally well tolerated prophylactic treatment for migraine. The percentage of patients reporting at

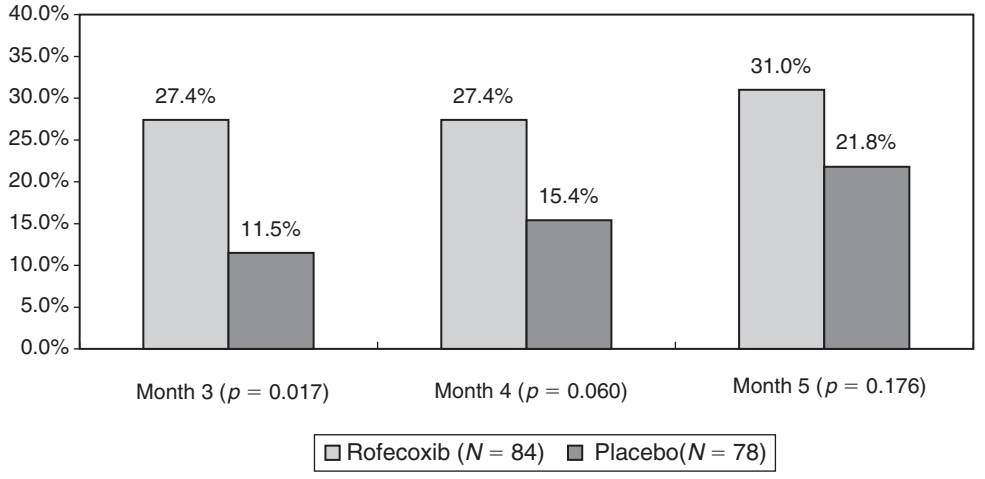

Fig. 7.1 Percentage of patients reporting at least a 50% decrease in monthly migraine attack frequently, by month of treatment.

least a 50% decrease from baseline in migraine attack frequency per month in the rofecoxib group was more than double the percentage of responders in the placebo group. Patients treated with rofecoxib also experienced numerical, but not statistically significant, reductions in migraine attack frequency per month, in migraine plus non-migraine attack frequency per month, and in the median percent change in migraine attack frequency per month, compared with placebo.

The absolute response rate observed with rofecoxib in this study (23.8%) was less than that typically reported for other agents such as timolol (44%), propranolol (48%),[6] and divalproex (44% to 45%).[7] However, the placebo response rate was also lower, so that the therapeutic ratio (active response rate/placebo response rate) for rofecoxib in this study (2.3) was similar to the size of benefit that has been reported for timolol and propranolol[6] and for divalproex.[7] The reduction in the monthly migraine frequency rate observed with rofecoxib (−1.0) was somewhat lower than that reported for divalproex (−1.7), and topiramate (−1.2 to −1.8),[8] while the median percent reduction in migraine attack frequency (22.8%) was at the low end of the range observed with other NSAIDs (22% to 60%; mean 36%).[9] However, it is difficult to compare results across studies due to differences in study design, procedures, and types of patients studied.

Rofecoxib was generally well tolerated during 3 months of treatment in patients with migraine. The safety profile was generally similar to placebo with a very low incidence of NSAID-type gastrointestinal AEs. In conclusion, rofecoxib 25 mg once daily was effective in preventing migraine attacks; additional studies may be desirable to further define its utility.

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8 Prophylactic treatment and course of the disease in headache associated with sexual activity

A. Frese, K. Frese, S. Schwaag, A. Rahmann, I.-W. Husstedt, and S. Evers

Introduction

Since the 1970s, attention has been drawn to a benign form of headache appearing during sexual activity. In their landmark papers, Paulson and Klawans[1] and Lance[2] distinguished three different types of headache associated with sexual activity (HSA), which are regarded as idiopathic. The International Headache Society (IHS) classifies HSA under 'miscellaneous headaches unassociated with structural lesions' (diagnosis 4.6.1–4.6.3) and differentiates three subtypes.[3] Type 1 is a dull ache in the head and neck that intensifies as sexual excitement inscreases. Type 2, also called the explosive subtype, is the most frequent type accounting for 69% of the first 70 published cases of HSA.[4] Its intensity and sudden onset makes the exclusion of a subarachnoid hemorrhage necessary. Type 3 is a postural headache resembling the one caused by low cerebrospinal fluid pressure. This headache develops after coitus.

HSA can be a frightening, distressing, and disabling disease. Since the first systematic descriptions of HSA, several case series or case reports have been published. Patients with one single attack as well as with ongoing repeated attacks have been reported. However, only little is known about treatment options and the prognosis of the disease.

Methods

A clinical survey was performed at the Department of Neurology of the University of Münster, Germany, which runs a supraregional headache outpatient clinic. Between 1996 and 2001, all patients with the diagnosis of HSA according to the IHS classification[3] were subjected to a structured interview. HSA was diagnosed after taking the neurological and medical history and after a clinical examination by physicians experienced in headache diagnosis. In all patients with the first HSA attack or the first bout of attacks, symptomatic headache was excluded by a CT or MRI scan of the brain and by a lumbar puncture. Optionally, an additional CT- or MRI-angiography of the brain were performed. To define the subtype of HSA, the patients had to choose one of the following items. When the patient quoted that the pain intensified slowly and gradually with increasing sexual excitement, HSA type 1 was diagnosed. For HSA type 2, a severe headache occurring 'all of a sudden' had to be indicated. For HSA type 3, a postural headache starting after sexual activity was demanded. To achieve a clear diagnosis, the patient had to select one of the given items depending on the predominant clinical feature. The patients were contacted by phone at the end of 2001 (33.2 ± 19.1 months later). They were interviewed about the course of the disease and their contentedness with therapy.

Results

Out of the 37 patients diagnosed with HSA between 1996 and 2001, 28 could be contacted by phone at the end of 2001 (33.2 ± 19.1 months later). Eight were female, 20 were male. Seven suffered from HSA type 1, 21 from HSA type 2, none from HSA type 3.

Seventeen patients never suffered from HSA again. Four patients suffered from a second phase of the disease but were actually free from HSA. Seven patients reported continued attacks of HSA without longer remissions. Out of those seven, only one had frequent attacks occurring with approximately every second sexual activity, the others had rare attacks (Fig. 8.1).

The total number of attacks from the very onset of HSA until follow-up varied widely (Table 8.1). Out of 25 patients with more than one single attack, 18 had experianced HSA in clusters (one cluster: $n = 14$, two clusters: $n = 4$). The duration of cluster periods was between two days and five years (median duration 4 months). Regarding the prognosis, no significant difference between HSA type 1 and 2 was found.

Nonsteroidal anti-inflammatory agents (ibuprofen, acetylsalicylic acid, diclofenac, paracetamol) for acute therapy were of limited or of no value in 16 out of 17 patients. Thirteen patients with HSA were treated prophylactically with betablockers (propranolol = 10, metoprolol = 3, mean treatment duration 5.0 ± 7.4 months). The dose was 120–240 mg per day for propranolol and 100–200 mg per day for metoprolol. The patients contentedness with the betablocker therapy is shown in Table 8.2. Out of the 13 patients treated with betablockers, two suffered from HSA type 1, the

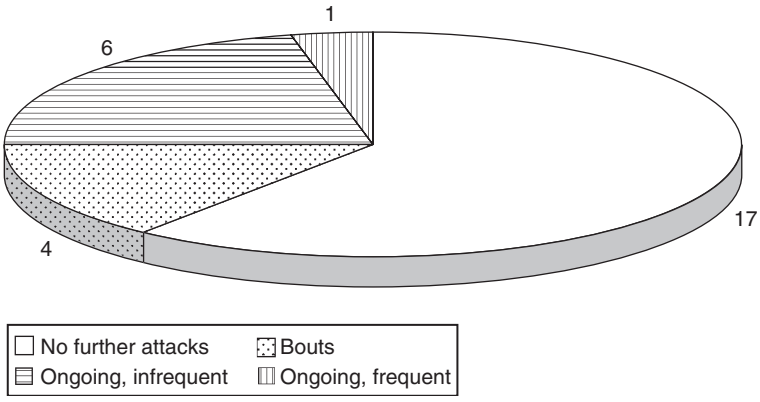

Fig. 8.1 Course of the disease beween first examination and follow-up interview (number of patients).

Table 8.1 Total number of attacks from the onset of the disease until follow-up

1 attack	$n=3$
2–5 attacks	$n=7$
6–15 attacks	$n=7$
16–50 attacks	$n=10$
> 50 attacks	$n=1$

Table 8.2 Patients satisfaction with betablockers for prophylaxis.

Betablocker	Good success	Limited success	No success
Propranolol ($n=10$)	$n=8$	$n=1$	$n=1$
Metoprolol ($n=3$)	$n=3$		

others from HSA type 2. One patient with HSA type 1 reported good results with metoprolol, the other limited success with propranolol. Three patients, all suffering from HSA type 2, had received indomethacin for short-term prophylaxis (50 mg, intake 30–60 min prior to sexual activity). All three reported good results. One patient had received ibuprofen for short-term prophylaxis with limited success, another patient diclofenac without success.

Discussion

We are aware of two other studies focusing on the prognosis of HSA. Silbert *et al.*[5] and Ostergaard and Kraft[6] followed up 30 patients and 26 patients, respectively. After a follow-up period of approximately 6 years, they found recurrence rates of 33%[5] and 50%[6] that are very similar to the recurrence rate in our study. In the vast majority of patients, HSA appears in clusters. In concordance with our data, the results suggest that HSA has a favourable outcome, and that continued, frequent complaints are rare. Regarding the prognosis, no significant differences between HSA type 1 and 2 could be observed.

For those patients with longer lasting clusters or with repeated attacks, prophylactic treatment can be indicated. The previously largest case series dealing with prophylactic treatment has reported eight patients with HSA type 2 completely relieved with propranolol.[7] Another small case series supported the use of propranolol in HSA.[8] On the other hand, there are also reports on treatment failure with propranolol.[1,5,9] Successful treatments of HSA with the betablockers metoprolol and atenolol, and with the calcium channel blocker diltiazem have also been presented.[5,10]

We believe that the absence of controlled studies legitimizes our empirical approach to the treatment of HSA. From our experience, betablockers (propranolol or metoprolol) for prophylaxis or indomethacin for short-term prophylaxis should be used. The optimal dose for betablockers seems to be similar to the application rate usually used in migraine. Data in HSA type 1 is too limited to define possible differences to HSA type 2 regarding medical treatment. For prophylaxis, a short course (2 to 6 months) seems adequate because spontaneous remissions of HSA are frequent.

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9 Prophylactic drugs I: discussion summary

S. D. Silberstein

Key issues in the methodology of prophylactic headache trials were discussed by Peer Tfelt-Hansen. The chosen drug needs to be proven effective in comparison with placebo, even in comparative trials. The minimal effective dose should be determined. Adverse events (AEs) should be quantitated. Onset should be comparable to standard treatment. The benefit/tolerability ratio needs to be estimated. Noise and variability are important issues. Migraine attack frequency fluctuates. Variability can be reduced with a longer period of evaluation. Regression to the mean often accounts for spurious results. Non-responders could be decreased by limiting the number of attacks/month. Dropouts are due to causes other than AEs and lack of efficacy; causes include psychosocial and medical events including pregnancy, death of a near relative, moving, or loss of a job.

The relative merits of cross-over versus parallel design were discussed. Cross-over trials have 4–8 times less variability, narrower confidence intervals, and greater power. They suffer from a potential carry-over effect and longer duration, which can lead to more dropouts. Dr Tfelt-Hansen believes that the carry-over effect can be compensated for.

Pharmacokinetics and dosing of preventive pharmacotherapies was discussed by Carl Dahlof. Less than 10% of patients use preventive drugs in primary care. In Dr Dahlof's clinic, less than 20% of patients use preventive drugs. Drugs are metabolized in two phases. Phase one, which occurs in the liver, is usually by cytochrome P450. Phase two is the addition of a polar group to the product of phase one metabolism to help with excretion.

Many drugs show significant variations in plasma levels. Amitriptyline shows a 10- to 100-fold difference in plasma concentrations. This accounts for individual differences in tolerability and efficacy. Gabapentin bioavailability decreases as the dose increases. Thus, a fixed dose strategy for preventive drugs is not ideal. It is best to start with a low dose and slowly increase it until efficacy occurs or AEs develop. Dr Dahlof usually accomplishes this over a 2 to 3 week period. With amitriptyline, sedation often disappears with time.

NSAIDs and selective COX 2 inhibitors: efficacy and mechanisms were discussed by Peter Isakson. NSAIDs inhibit both COX 1 and COX 2. The selective COX inhibitors are not, therefore, more effective than the NSAIDs, but they have fewer

AEs. Dr Isakson believes that the recently described COX 3 enzyme is a splice variant of COX 1. Selective COX 2 inhibitors rapidly reverse the hyperalgesia and inflammation in the formalin rat paw model. This suggests that prostaglandins are rapidly turning over and their production can be blocked by COX 2 inhibitors. Valdecoxib is comparable in efficacy to Tylox and ibuprofen in dental and post-hysterectomy pain. An interesting observation is the very low placebo rates in dental pain.

Valdecoxib has been compared with placebo in the acute treatment of migraine. In the 001 study placebo valdecoxib (20 mg and 40 mg) was compared to sumatriptan (50 mg) and placebo. Two hour response rates were 45%, 48%, 42%, and 30%, respectively. In another study valdecoxib 40 mg was compared with placebo. Two hour responses rates were 46% and 32%, respectively; pain-free rates at 2 hours were 16% and 8%.

It is rare for NSAIDs, alone, to produce drug induced headache. Many felt that the shorter acting NSAIDs, such as ibuprofen, were most likely to have this problem.

There are no controlled trials of add-on therapy for migraine. This is often the basic practice used for patients with epilepsy and many experts often use add-on treatment. (Do you mean: 'Many experts use add-on therapy for patients with epilepsy.'? If so, I would leave out the first part of the sentence ['this is often the basic practice used for patients with epilepsy…' and just say 'Many experts use add-on therapy…' as above.)

Visser *et al*. presented the results of the rofecoxib trial for migraine prevention. Patients with IHS migraine were treated with rofecoxib 25 mg, montelukast 20 mg, or placebo for 3 months after a 2 month single-blind run-in. The 50% response rate was 23.8% for rofecoxib and10.3% for placebo. The montelukast data was not presented.

Frese *et al*. provided data about the demography, clinical features, and comorbidity of headache associated with sexual activity (HSA) in 51 patients who were questioned via a structured interview. The mean age at onset of the disease was 39.2 years, with a clear male preponderance (2.9:1). Eleven patients suffered from HSA type 1 (dull subtype) which gradually increased with increasing sexual excitement. The remaining (n=40) suffered from HSA type 2 (explosive subtype). The pain was predominantly bilateral (67%), and diffuse or occipital (76%). HSA was not dependent on special sexual habits and most often ocurred during sexual activity with the usual partner (94%) and during masturbation (35%). There was a high comorbidity with migraine (25%), benign excertional headache (29%), and tension-type headache (45%). They found no evidence proving subtypes 1 and 2 to be distinct disorders.

Session III

Prophylactic drugs II

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10 Prevention of migraine: beta-blockers and amine agonists: efficacy

H.-C. Diener and V. Limmroth

Summary

Migraine is one of the most frequent neurological disorders, affecting up to 15% of the general population. Patients with frequent migraine attacks require not only management of individual episodes, but also prophylactic treatment. Beta-blockers, flunarizine, and valporic acid have been established as first-line agents for the prophylaxis of migraine attacks. Among the beta-blockers propranolol and metoprolol are best documented and hence deserve preferential use. On the other hand, it appears that other beta-blockers, perhaps with the exception of those with intrinsic sympathomimetic activity, can be equally effective. Uncertainties regarding the relative merits of various treatment modalities are largely caused by lack of adherence to specific requirements for clinical trials on migraine prophylaxis. Therefore, this article reviews the available literature on the benefit of beta-blockers in migraine prophylaxis.

Introduction

The International Headache Society (IHS) defines migraine as a disorder characterized by intermittent attacks of headache combined with nausea, photophobia and/or phonophobia.[1] Despite the effective therapy of the acute attack made possible by the triptans[2,3] some patients, however, require some form of prophylactic treatment. Although the need for prophylactic treatment in certain patients is undisputed, there is considerable discussion about optimal prophylactic treatment modalities. This is partly due to the fact that no reliable animal models exist to study prophylactic treatment. Therefore, identification of adequate prophylactic treatment relies entirely on clinical studies. The nature of migraine, however,

mandates specific considerations in the design of clinical studies. Many trials in the past were flawed by inadequate trial design which makes an evaluation of some drugs or even a meta-analysis impossible.

Beta-blockers in the prophylactic treatment of migraine

The efficacy of beta-blockers for the prophylaxis of migraine was discovered by chance when patients with migraine, who received beta-blockers for cardiac disorders or hypertension, observed a significant reduction of migraine frequency.[4] Among all agents for prophylactic migraine treatment, beta-blockers have been studied most intensively and are being used the most frequently. Among the beta-blockers, propranolol and metoprolol have been characterized extensively in the prophylaxis of migraine, and are generally recognized to be effective.[5] While different doses of these two agents have been used in the various trials, their meta-analysis suggests that 160 mg/day of propranolol and 200 mg/day of metoprolol can be considered as effective prophylactic doses. These doses have also been used most frequently in comparative studies with other agents (see below), but clinical experience suggests that lower doses may also be effective in many cases. On the other hand, it remains controversial whether prophylactic efficacy in migraine is a property of all beta-blockers or limited to individual members of this drug class with specific properties. beta-blockers are typically classified according to factors such as selectivity for the β_1-adrenoceptor subtype, lipophilicity (and hence penetration into the central nervous system), membrane-stabilizing effects, and intrinsic sympathomimetic activity; moreover, some beta-blockers have high affinity for certain 5-HT receptor subtypes.[6]

β_1-adrenoceptor selectivity does not appear to play a major role in determining prophylactic efficacy since non-selective agents such as propranolol, moderately β_1-selective agents such as metoprolol, and highly β_1-selective drugs such as bisoprolol[7,8] are all effective prophylactics. Thus, concomitant blockade of β_2-adrenoceptors does not appear to be required for effective migraine prophylaxis.

Due to the lack of validated animal models, the site of action for prophylactic beta-blocker effects has not been defined. While propranolol, metoprolol, oxprenolol, and alprenolol are very lipophilic and hence penetrate well into the central nervous system, atenolol, nadolol, and practolol are only slightly or not at all lipophilic.[6] Since several members of the latter group including atenolol[9–11] and nadolol[12–16] have demonstrated their efficacy in the prophylaxis of migraine attacks, high lipophilicity and hence penetration into the central nervous system does not appear required for prophylactic efficacy. The prophylactic efficacy of atenolol, nadolol, and timolol[17–19] demonstrates that membrane-stabilizing effects are also not required to reduce the frequency of migraine attacks.

Four beta-blockers with intrinsic sympathomimetic activity, i.e. acebutolol,[20] alprenolol,[21] oxprenolol,[22] and pindolol,[23,24] have been studied for prophylactic efficacy but did not demonstrate superiority relative to placebo. However, the absence of proof should not be mistaken as proof of absence for a prophylactic

effect for several reasons: firstly, only two studies were performed with pindolol and only one each for the other agents. Second, all of these studies have apparently been underpowered since they included only 26–33 patients, i.e. less than 20 per treatment arm. Third, the headache type was not clearly defined in some studies. Finally, the evaluation time was very short in most of these trials and sometimes lasted only 4 weeks. Given the fact that even clearly effective agents such as propranolol or metoprolol failed to demonstrate superiority in small isolated trials,[10,25,26] the present data are insufficient to define a role for intrinsic sympathomimetic activity in the prophylaxis of migraine due to poor trial design.

Several beta-blockers including propranolol and pindolol exhibit a high affinity for 5-HT receptors including 5-HT_{1A} as well as 5-$HT_{1B/D}$ and 5-HT_2 receptors that are either targets for acute migraine therapy or other prophylactic acting agents, respectively. While propranolol is clearly effective in migraine prophylaxis, pindolol is of questionable efficacy (see above). Therefore, the role of 5-HT receptor affinities still needs to be determined.

Taken together, these data demonstrate that the hypothesis that only certain beta-blockers are effective prophylactic agents is not supported by the available evidence. While the role of intrinsic sympathomimetic activity cannot be determined at present, it is evident that concomitant blockade of β_2-adrenoceptors, lipophilicity or membrane-stabilizing effects are not required. Hence, with the possible exception of drugs with intrinsic sympathomimetic activity, prophylactic efficacy seems to be a class effect of all beta-blockers. From a practical point of view, these data suggest that beta-blockers with intrinsic sympathomimetic activity should not be used for the prophylaxis of migraine attacks, whereas propranolol and metoprolol appear to deserve preferential use. However, this preference is not based on superior efficacy or tolerability relative to other beta-blockers but merely reflects the fact that these two have been investigated more extensively than the other drugs.

Clinical trials on beta-blockers in the prophylaxis of migraine

Among all beta-blockers propranolol—and to a lesser extent metoprolol—underwent the most extensive clinical testing and served in many clinical trials as reference drugs when beta-blockers were compared with non-adrenergic drugs. Propranolol[5,27] and metoprolol[26,28,29] have both been convincingly shown to have migraine prophylactic activity. Holroyd *et al.*[5] performed a meta-analysis for propranolol in the prophylaxis of migraine. The 53 studies included in the meta-analysis involved 2403 patients who were treated with either propranolol (modal treatment 160 mg), a reference substance and/or placebo. On average, propranolol yielded a 44% reduction in migraine activity when daily headache recordings were used to assess treatment outcome, and a 65% reduction of migraine activity when clinical ratings of improvement and global patient reports were used. The drop-out rate due to side effects was 5.3%. If efficacy is shown, the overall performance among the group of beta-blockers is very similar with regard to the reduction of

migraine attacks. Atenolol,[10,30] timolol,[17,18,31] nadolol,[12] and bisoprolol[7,32] are beta-blockers with a possible prophylactic action. Again, following a run-in phase an evaluation time of at least 3 months is necessary to receive reliable data on the potential efficacy in migraine prophylaxis.

Other prophylactic anti-migraine drugs in comparison with beta-blockers

Various drugs have been compared to beta-blockers in the prophylaxis of migraine. Meanwhile, several clinical trials[33–41] compared the calcium channel blocker flunarizine with beta-blockers (six trials with propranolol, two with metoprolol). In all trials flunarizine was equally effective as the beta-blockers, but had a qualitatively different adverse event profile.

In two small clinical trials valproic acid (up to 2000 mg/d) has been compared to propranolol (up to 240 mg/d).[42,43] In both trials the efficacy (reduction of attack frequency) of both drugs was identical, which is in line with the documented efficacy of valproic acid relative to placebo.[44–46] Although the profiles of adverse effects were different, a comparable low rate of adverse events was reported in both trials.

Based on the proven efficacy of NSAID and possibly of acetylsalicylic acid against acute migraine attacks, their prophylactic values have also been tested relative to placebo sodium valproate versus propranolol in the prophylactic treatment of migraine,[47,48] and relative to beta-blockers. As early as 1983 Baldretti *et al.*[49] compared in a small trial including 18 patients the efficacy of propranolol (1.8 mg/kg) with acetylsalicylic acid (13.5 mg/kg). In this trial, both drugs were equally effective and reduced frequency, duration, and intensity of the attacks to the same extent. Other studies, however, were not able to confirm these results. In a small double-blind cross-over trial, 200 mg/d metoprolol were significantly more effective than 500 mg/d acetylsalicylic acid.[50] In a double blind multicentre trial including 243 patients Diener *et al*. compared low dose acetylsalicylic acid (300 mg/d) versus metoprolol (200 mg/d) and placebo.[51] Both drugs were superior to placebo, but metoprolol reduced frequency of migraine attacks significantly better than acetylsalicylic acid (reduction of monthly attacks from 3.55 to 1.82 vs 3.38 to 2.27). Acetylsalicylic acid, however, caused significantly less adverse events and showed a lower rate of drop outs. Rasmussen *et al.*[52] compared propranolol (40 mg t.i.d.) with tolfenamic acid (100 mg t.i.d.) in 76 patients and found both drugs to be equally effective in the reduction of headache time (migraine days and hours) as well as in pain intensity; moreover, tolfenamic acid caused less adverse events and less drop outs. Taken together with the data from the placebo-controlled NSAID trials, these controversial reports have resulted in the classification of NSAID as second line prophylactic agents in migraine treatment.

Calcium entry blockers such as nimodipine or nifidipine have not demonstrated superiority relative to placebo[53–55] and accordingly were also found to be less effective than propranolol.[56] On the other hand, verapamil is frequently used as a migraine prophylactic in the US. While two studies dating from the early 1980s

have reported verapamil to be superior to placebo,[57,58] both do not adhere to the above-mentioned criteria for valid studies and have included too few patients to allow reliable conclusions. Moreover, verapamil has never been tested in comparison to established prophylaxis drugs. Therefore, the scientific basis of its frequent use in the US remains weak, and calcium entry blockers other than flunarizine cannot be considered suitable for migraine prophylaxis.

Conclusions and treatment recommendations

Within the last 30 years more than 100 clinical trials have been conducted to investigate beta-blockers in migraine prophylaxis. While the beneficial effect of propranolol and metoprolol is clearly established, the value of other beta-blockers remains to be determined, since only a minority of trials were carried out with a suitable trial design and enough patients to run reliable statistics. Nevertheless the available data suggest that β_1-selectivity, penetration into the central nervous system, membrane-stabilizing effects, and 5-HT receptor affinity do not play a major role for prophylactic efficacy; in contrast, consistently negative results with beta-blockers with intrinsic sympathomimetic activity suggest that this property may be undesirable for migraine patients. While agents such as flunarizine or valproic acid are now also considered as drugs of first choice for prophylactic migraine treatment, they remain less well established than the beta-blockers. Apart from aspects of regulatory approval, the differential use of beta-blockers relative to other first line agents should largely be determined by the differential adverse event profiles of the various agents relative to concomitant conditions of an individual patient to maximize compliance.

In general, prophylactic treatment will be successful when certain aspects are considered: prior to the start of migraine prophylaxis the patient should note frequency, duration, and severity of migraine attacks in a diary. This diary may help to verify effects of therapy. The initial drug dosage should be low (e.g. propranolol 20 mg/d) and must be slowly increased since adverse effects can occur prior to the prophylactic effects and impair patient compliance. The prophylaxis should be maintained for a minimum of 3 months to allow efficacy evaluation in a specific patient, whereas successful prophylactic treatment should be continued for 12 months. Thereafter, discontinuation can be attempted but drug doses should be decreased slowly, particularly with beta-blockers in order to avoid tachycardia or hypertension. The natural history of migraine should then be assessed for 2–3 months.

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11 AEDs in migraine prevention

S. D. Silberstein

Effective migraine treatment begins with making an accurate diagnosis, ruling out alternate causes, ordering appropriate studies, and addressing the headache's impact. Pharmacotherapy may be acute (abortive) or preventive (prophylactic),[1] and patients who experience frequent, severe headaches often require both approaches.

The Technical Reports of the Agency for Healthcare Policy and Research (AHCPR)[2–5] identified and summarized controlled trial evidence on the efficacy and tolerability of preventive migraine drug treatments. They are the basis of the US Headache Consortium guidelines.[6,7] The US Headache Consortium recommended that circumstances that might warrant chronic preventive treatment include: (1) recurring migraine that significantly interferes with the patient's daily routine despite acute treatment (e.g. two or more attacks a month that produce disability and last three or more days or headache attacks that are infrequent but produce profound disability); (2) failure of, contraindication to, or troublesome side effects from acute medications; (3) overuse of acute medications; (4) special circumstances, such as hemiplegic migraine or attacks with a risk of permanent neurologic injury; (5) very frequent headaches (more than two a week) with the risk of rebound headache development; or (6) patient preference, that is, the desire to have as few acute attacks as possible.[8]

Antiepileptic drugs

Anticonvulsant medication is recommended for migraine prevention because placebo-controlled, double-blind trials prove them effective.[9–13] With the exception of valproic acid and topiramate, anticonvulsants interfere with the efficacy of oral contraceptives.[14,15]

Carbamazepine

The only placebo-controlled trial of carbamazepine suggested a significant benefit, but this trial was inadequately described in several important respects.[12] Another trial, comparing carbamazepine with clonidine and pindolol, suggested that carbamazepine

had a weaker effect on headache frequency than either comparator treatment, although differences from clonidine were not statistically significant.[16] Carbamazepine (Tegretol), 600–1200 mg a day may be effective in preventive migraine treatment.

Valproic acid

Valproic acid is a simple 8 carbon, 2 chain fatty acid with 80% bioavailability after oral administration. Five studies provided strong and consistent support for the efficacy of divalproex sodium[10,17,18] and sodium valproate.[19,20] Two placebo-controlled trials of each of these agents showed them to be significantly better than placebo at reducing headache frequency.[11,18–20] An extended release form of divalproex sodium demonstrated comparable efficacy to the tablet formulation.[21] The adverse event (AE) profile in the clinical trial, however, showed almost identical AE rates for the placebo and active treatment arms.

Clinical trials (Table 11.1)

In 1988, prompted by his clinical observations of valproate's benefits, Sorenson[22] performed a prospective open trial of valproate. Twenty-two patients with severe migraine resistant to previous prophylactic treatment were studied. Follow-up in 3–12 months revealed that eleven patients were migraine-free, six had had a significant reduction in frequency, one had had no change, and four had dropped out.

In 1992, Hering and Kuritzky[19] evaluated sodium valproate's efficacy in migraine treatment in a double-blind, randomized, crossover study. Thirty-two patients were divided into two groups and given either 400 mg of sodium valproate twice a day or placebo for 8 weeks. Sodium valproate was effective in preventing migraine or reducing the frequency, severity, and duration of attacks in 86.2% of 29 patients, whose attacks were reduced from 15.6 to 8.8 a month.

Jensen *et al.* in 1994,[9] studied 43 patients with migraine without aura in a triple-blind, placebo- and dose-controlled, crossover study of slow-release sodium valproate. After a four-week medication-free run-in period, the patients were randomized to sodium valproate ($n=22$) or placebo ($n=21$). Thirty-four patients completed the trial. Fifty percent of the patients had a reduction in migraine frequency to 50% or less for the valproate group compared with 18% for placebo. During the last four weeks of valproate treatment, 65% responded. The most common AEs (33% valproate, 16% placebo) were intensified nausea and dyspepsia, tiredness, increased appetite, and weight gain and were usually mild or moderate. Fifty-eight percent of the patients had no AEs.

In 1995, in a multicenter, double-blind, randomized, placebo-controlled investigation, Mathew *et al.*[11] compared the effectiveness and safety of divalproex sodium and placebo in migraine prophylaxis. A four-week, single-blind, placebo-baseline phase was followed by a 12-week treatment phase (four-week dose adjustment, eight-week maintenance). One hundred and seven patients were randomized to divalproex sodium or placebo (2:1 ratio), with 70 receiving divalproex

Table 11.1 Clinical trials

Study	Patient Population (Diagnostic Criteria)	No	Design	Dosage (mg/d)/ Other Medication	Plasma Levels	Duration	Results
Hering and Kuritzky (1992)	Migraine	29	Double-blind/ placebo-controlled crossover	800 mg (400 mg bid)	31.1 to 91.9 µg/ml	8 weeks each; total of 16 weeks	86.2% of patients responded better to valproate
Jensen *et al.* (1994)	Migraine without aura	43	Double-blind/ placebo-controlled crossover	1000 to 15000 mg/ Sodium valproate	Mean 73.4 µg/ml	32 weeks	50% valproate 18% placebo
Mathew *et al.* (1995)	Migraine with or without aura	107	Double-blind/ placebo-controlled	500 to 1500 mg/ Divalproex	70 to 120 µg/ml	16 weeks	48% divalproex 14% placebo
Klapper (1995)	Migraine with or without aura	176	Double-blind/ placebo-controlled	500 to 1600 or 1500 mg/ Divalproex	??	10 weeks	43% divalproex 21% placebo
Freitag *et al.* (2002)	Migraine with or without aura	234	Double-blind/ placebo-controlled	500 to 1000 mg/ Divalproex		12 weeks	30% divalproex 24% placebo

sodium and 37 receiving placebo. Forty-eight percent of the divalproex sodium-treated patients and 14% of the placebo-treated patients showed a 50% or greater reduction in migraine headache frequency from baseline ($p < .001$). No significant treatment-group differences were observed in average peak severity or duration of individual migraine headaches. Treatment was stopped in 13% of the divalproex sodium-treated patients and 5% of the placebo-treated patients because of intolerance (p, not significant).

Klapper[18] evaluated the efficacy and safety of divalproex sodium as prophylactic monotherapy in a multicenter, double-blind, randomized, placebo-controlled study. Patients with two or more migraine attacks during the baseline phase were randomized to a daily divalproex sodium dose of 500 mg, 1000 mg, 1500 mg, or placebo. The primary efficacy variable was four-week headache frequency during the experimental phase. During the experimental phase, the mean reduction in the combined daily divalproex sodium groups was 1.8 migraines per four weeks compared with a mean reduction of 0.5 attacks per four weeks in the placebo group. Overall, 43% of divalproex sodium-treated patients achieved ≥50% reduction in their migraine attack rates, compared with 21% of placebo-treated patients. A statistically significant ($p \leq 0.05$) dose–response effect across the dose range placebo, 500mg, 1000mg, 1500mg, was observed for both overall reduction in attack frequency and a ≥50% reduction in attack frequency. With the exception of nausea, AEs were similar in all groups (divalproex sodium 24%, placebo 7%, $p = 0.015$) and most AEs were mild or moderate in severity.

In an open-label study, Silberstein *et al.*[23] evaluated the long-term safety of divalproex sodium in patients who had completed one of two previous double-blind, placebo-controlled studies. The results, including data from the double-blind study, represented 198 patient-years of divalproex exposure. The average dose was 974 mg/day. Reasons for premature discontinuation (67%) included administrative problems (31%), drug intolerance (21%), and treatment ineffectiveness (15%). The most frequently reported AEs were nausea (42%), infection (39%), alopecia (31%), tremor (28%), asthenia (25%), dyspepsia (25%), and somnolence (25%).

Freitag *et al.*[21] evaluated the efficacy and safety of extended-release divalproex sodium compared with placebo in prophylactic monotherapy treatment. Subjects initiated treatment on 500 mg once daily for 1 week, and the dose was then increased to 1000 mg once daily with an option, if intolerance occurred, to permanently decrease the dose to 500 mg during the second week. The mean reductions in 4-week migraine headache rate were 1.2 (from a baseline mean of 4.4) in the extended-release divalproex sodium group and 0.6 (from a baseline mean of 4.2) in the placebo group ($p = 0.006$); reductions with extended-release divalproex sodium were significantly greater than with placebo in all three 4-week segments of the treatment period. The proportion of subjects achieving at least 50% reduction in experimental phase migraine headache rate was higher in the extended-release divalproex sodium group (36/119; 30%) than in the placebo group (28/115; 24%), but the difference was not significant ($p = 0.251$).

Nausea, vomiting, and gastrointestinal distress are the most common AEs of valproate therapy. These are generally self-limited and are slightly less common

with divalproex sodium than with sodium valproate. When therapy is continued, the incidence of gastrointestinal symptoms decreases, particularly after six months. In three of four placebo-controlled trials, the overall percentage of patients reporting AEs with divalproex sodium or sodium valproate was not higher than with placebo. The fourth trial found significantly higher rates of nausea, asthenia, somnolence, vomiting, tremor, and alopecia with divalproex sodium.

On rare occasions, valproate administration is associated with severe AEs, such as hepatitis or pancreatitis. The frequency varies with the number of concomitant medications used, the patient's age and general state of health, and the presence of genetic and metabolic disorders.

Valproate is potentially teratogenic and should not be used by pregnant women or women considering pregnancy.[24] Valproic acid is available as 250 mg capsules and as a syrup (250 mg/5 ml). Divalproex sodium is a stable coordination complex comprised of sodium valproate and valproic acid in a 1:1 molar ratio. Depakote® is an enteric-coated form of divalproex sodium that is available as 125, 250, and 500 mg capsules and a sprinkle formulation. The starting dose is 250–500mg a day in divided doses; this can be slowly increased, monitoring serum levels if there is a question of toxicity or compliance. (The usual therapeutic level is from 50 to 100 mg/ml.) The maximum recommended dose is 60 mg/kg/day.

Gabapentin

Gabapentin was not effective in one placebo-controlled, double-blind study.[25] In a more recent randomized, placebo-controlled, double-blind trial,[26] gabapentin 1800 to 2400 mg was superior to placebo in reducing the frequency of migraine attacks. The responder rate was 36% for gabapentin and 14% for placebo ($p=0.02$). The two treatment groups were comparable with respect to treatment-limiting AEs. Limited data were reported on AEs: the most common were dizziness or giddiness and drowsiness. Relatively high patient withdrawal rates due to AEs were reported in some trials.[4]

Topiramate

Topiramate is a structurally unique anticonvulsant that was discovered by serendipity. It is a derivative of the naturally occurring monosaccharide D-fructose and contains a sulfamate functionality. Topiramate is rapidly and almost completely absorbed. The average elimination half-life is approximately 21 hours.[27] Topiramate readily enters the CNS parenchyma.

Topiramate can influence the activity of some types of voltage-activated Na^+ and Ca^{2+} channels, $GABA_A$ receptors, and the α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate subtype of glutamate receptors. One common characteristic is that they are all regulated by protein phosphorylation.[28–31] One or more subunit of each complex is phosphorylated by protein kinase A, protein kinase C, and possibly Ca^{2+}/CAM-activated kinases. The consensus peptide sequence at the protein kinase A-mediated phosphorylation site exhibits homology;

e.g. the GluR6 subunit of the AMPA/kainate receptor contains RRQS, the β subunit of the $GABA_A$ receptor contains RRAS, and some subtypes of the primary subunit of Na^+ and Ca^{2+} channels contain RRNS and RRPT, respectively. Immediately upon binding, topiramate could exert either a positive or negative allosteric modulatory effect; secondarily, topiramate would prevent protein kinase A from accessing the serine hydroxyl site, thereby preventing phosphorylation, which eventually would shift a population of channels toward the dephosphorylated state. Topiramate also inhibits some isozymes of carbonic anhydrase (CA) and exhibits selectivity for CA II and CA IV.[32,33]

Storer and Goadsby[34] studied the effect of topiramate on trigeminocervical activation in the anesthetized cat. Activation of neurons within the trigeminocervical complex is likely to be the biological substrate for pain in migraine and cluster headache. The superior sagittal sinus (SSS) was isolated and electrically stimulated. Units linked to SSS stimulation were recorded in the most caudal part of the trigeminal nucleus. Topiramate reduced SSS-evoked firing of neurons in the trigeminocervical complex in a dose-dependent fashion. Its inhibition is a plausible mechanism of the action of migraine or cluster headache preventive medicines.

Topiramate has been associated with weight loss, not weight gain (a common reason to discontinue preventive medication) with chronic use.

In a pivotal placebo-controlled clinical trial of 487 patients, the effect of topiramate on migraine was evaluated.[35] Dosages were 50 mg/day, 100 mg/day, and 200 mg/day. In the group treated with topiramate 100 mg/day, there was a mean reduction of 2.1 monthly migraine episodes (5.4 to 3.3), compared with 0.8 for placebo. The responder rate (patients with ≥50% reduction in monthly migraine frequency) was 54% with topiramate 100 mg, compared with 23% with placebo. Topiramate treatment was also associated with reduced consumption of acute-treatment medications. The onset of efficacy was observed by the end of the first month of treatment. The 200 mg dose was not significantly more effective than the 100 mg dose. The most common AEs were paresthesias, fatigue, nausea, anorexia, and abnormal taste. Cognitive AEs occurred in 19% of patients in the 100 mg group, but led to withdrawal in only 4%. Body weight was reduced by an average of 3.8% in the 100 mg and 200 mg groups. In a recent case series study of 74 patients (24 with episodic migraine and 50 with chronic migraine), topiramate, at a mean daily dose of 208 mg, was shown to be effective and well tolerated in migraine prophylaxis.[36] The mean number of headache days was reduced from 20.6 to 13.6 after treatment. Responder rate was 44.6% (58.3% for episodic migraine and 38% for chronic migraine). Mean headache severity was also reduced after treatment. AEs were common; however, only 8.1% of patients discontinued topiramate. Psychiatric comorbidity and the number of preventive drugs used prior to the study did not affect the treatment outcome. Another retrospective study showed that patients with chronic migraine ($n=96$) had a reduction of migraine frequency from 6.3 to 3.7 per 28 days and patients with episodic migraine ($n=70$) had a corresponding decrease of 5.8 to 1.9.[24] Headache severity was also significantly decreased in both patient groups. Topiramate was well tolerated in this study, which also included cluster headache patients, with only 8/178 patients

discontinuing topiramate. The mean daily dose of topiramate was 87.5 mg and the mean duration of treatment was 8.4 months.

Brandes *et al.*[37] assessed the efficacy and safety of topiramate (50, 100, and 200 mg/day) in the prevention of migraine headaches in a 26-week, multicenter, randomized, double-blind, placebo-controlled study (MIGR-002). The primary efficacy measure was the change in mean monthly migraine frequency between baseline and the double-blind phase. Secondary efficacy measures included the percentage of patients who experienced at least a 50% reduction in monthly migraines (responder rate) and mean change in number of monthly migraine days. Four hundred eighty-three patients were randomized to the four treatment groups (placebo=120; topiramate 50 mg/day=120; topiramate 100 mg/day=122; topiramate 200 mg/day=121). There were 468 patients in the intent-to-treat population. Topiramate at a dose of 100 or 200 mg/day was associated with significant improvements in each efficacy measure assessed. The mean monthly number of migraine periods decreased significantly for those patients on 100 mg/day of topiramate (from 5.8 to 3.5, $p=0.008$) or 200 mg/day of topiramate (from 5.1 to 2.9, $p=0.001$) versus placebo (from 5.6 to 4.5). Significant reductions were evident as early as the first month of treatment. A significantly greater proportion of patients exhibited at least a 50% reduction in mean monthly migraines in the groups treated with 50 mg/day of topiramate (39%, $p=0.009$), 100 mg/day of topiramate (49%, $p<0.001$), and 200 mg/day of topiramate ($p<0.001$). There was a greater reduction in mean monthly migraine days for patients treated with 100 mg/day of topiramate ($p=0.003$) and 200 mg/day of topiramate ($p<0.001$) than placebo. Patients treated with 200 mg/day of topiramate lost an average of 4.8% of body weight from baseline through the double-blind phase. In the topiramate groups, the most common AEs (resulting in discontinuation) included paresthesias, fatigue, nausea, and abdominal pain. In this second pivotal study, topiramate was associated with significant improvement in migraine at doses of 100 or 200 mg/day in each efficacy measure assessed. The onset of efficacy was observed as early as the first month of treatment.

These results show that topiramate is effective for migraine prophylaxis. The 100 mg dose seems to have the best efficacy/tolerability ratio. Cognitive side effects are of less concern with doses of 100 mg or less.

Lamotrigine

Lamotrigine blocks voltage-sensitive sodium channels, leading to inhibition of neuronal release of glutamate. Glutamate release may be essential in the propagation of spreading cortical depression, which some believe is central to the genesis of migraine attacks. Lamotrigine has been studied as combination therapy for headache prevention in one relatively large, prospective, open-label trial of 65 patients, most of whom had chronic migraine.[38] Only 35 patients were sufficiently compliant with treatment to warrant inclusion in the analysis, with 12 dropping out because of AEs. The primary end point was reduction in frequency of severe headaches. By this measure, there were 17 (48.6%) responders, at a mean dose of 55 mg/day.

It was noted that those who had migraine with aura had a better response rate (12/18 or 67%), including 4 out of 8 whose headaches were chronic. This finding was supported by another open label study that assessed the impact of lamotrigine on aura itself, and found that the drug significantly reduced both the frequency and duration of aura.[38]

Chen *et al.*[39] reported two patients with migraine with persistent aura-like visual phenomena for months to years. All laboratory investigations were normal except for occipital hypoperfusion on the brain single photon emission computed tomography. After lamotrigine treatment for two weeks, both had resolution of the visual symptoms. Persistent migrainous visual phenomena are benign and probably a status of spontaneous aura.

Steiner *et al*.[40] compared the safety and efficacy of lamotrigine and placebo in migraine prophylaxis in a double-blind, randomized, parallel-groups trial. A total of 110 patients entered; after a 1-month placebo run-in period, placebo-responders and noncompliers were excluded, leaving 77 to be treated with lamotrigine (n=37) or placebo (n=40) for up to 3 months. Initially, lamotrigine therapy was begun at the full dose of 200 mg/day, but, following a high incidence of skin rashes, a slow dose-escalation was introduced: 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, then 200 mg/day. Attack rates were reduced from baseline means of 3.6 per month on lamotrigine and 4.4 on placebo to 3.2 and 3.0, respectively, during the last month of treatment. Improvements were greater on placebo, and these changes, not statistically significant, indicate that lamotrigine was ineffective for migraine prophylaxis. There were more AEs on lamotrigine than on placebo, most commonly rash. With slow dose-escalation, their frequency was reduced and the rate of withdrawal for AEs was similar in both treatment groups.

Zonisamide

Two retrospective, open-label studies of zonisamide in the preventive treatment of episodic migraine have been reported.[41,42] In the study conducted by Drake *et al.*,[41] 34 patients with refractory migraine with or without aura were treated adjunctively with zonisamide at doses as high as 400 mg/d.[41] Headache data were obtained from patient headache diaries and telephone reports. A 40% reduction in headache severity, a 50% reduction in headache duration, and a 25% decrease in headache frequency were found at 3 months compared to baseline values. Four patients discontinued the drug because of AEs (12%), and 9 stopped the medicine because they believed it was not working. Krusz reported improvement in 14/33 (42%) of patients, with 4 dropouts due to AEs.[42] Zonisamide was also examined as monotherapy in a small, prospective, open-label study of 9 patients with episodic migraine with or without aura.[43] The drug was titrated to a mean dose of 244 mg/day, and investigator efficacy ratings were made for all patients who remained on a stable dose of drug for 6 weeks. It was effective or very effective in 6/9 (67%) patients.

Conclusion

The goals of treatment are to relieve or prevent the pain and associated symptoms of migraine and optimize the patient's ability to function normally. The AEDs used to treat migraine can be divided into four major categories (Table 11.3): (1) drugs with documented high efficacy and mild to moderate AEs (topiramate and divalproex; (2) drugs with lower documented efficacy and mild to moderate AEs (gabapentin); (3) drugs with unproved efficacy (zonisamide, levetiracetam); and (4) drugs with proven limited or no efficacy (lamotrigine, carbamazepine). Choice should be based on the drug's proven efficacy, its AEs, the patient's preferences and headache profile, and the presence or absence of coexisting or comorbid disease (Tables 11.2 and 11.3).

Comorbid and coexistent diseases have important implications for treatment. The presence of a second illness provides therapeutic opportunities but also imposes certain therapeutic limitations. For the patient with migraine and epilepsy[19,44] or migraine and bipolar illness,[24,45] divalproex sodium, topiramate and the other AEDs are useful choices.

Table 11.2 Migraine comorbid disease

Cardiovascular
Hyper- or Hypotension
Raynaud's
Mitral Valve Prolapse
Angina/Myocardial Infarction
Stroke
Psychiatric
Depression
Mania
Panic Disorder
Anxiety Disorder
Neurologic
Epilepsy
Positional Vertigo
GI
Functional Bowel Disorders
Other
Asthma
Allergies

Table 11.3 Preventive drugs: antiepileptics

High efficacy:
Divalproex, topiramate
Low efficacy:
Gabapentin, tiagabine
Unproven efficacy:
Zonisamide, levetiracetam, phenytoin
Not effective or Low efficacy
Carbamazepine, lamotrigine, phenytoin

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12 Mechanism(s) of action of the antiepileptic drugs valproic acid, gabapentin, and topiramate: implications for the prophylactic management of migraine

H. S. White

Introduction

Migraine is believed to represent a paroxysmal and unique neurovascular disorder. However, the precise underlying pathophysiology processes that lead to an acute migraine attack are not completely understood. In the susceptible individual, migraine can be triggered by a multitude of factors including, but not limited to, alterations in ion and glucose metabolism, an increase in nitric oxide synthesis, altered neurotransmitter function, and abnormal peptide release and metabolism (Fig. 12.1). These and other factors contribute to an increase in neuronal and network hyperexcitability and are thought to contribute to the initiation and propagation of a migraine attack. Increasing evidence also suggests that there is a strong genetic component that contributes to the heightened brain excitability of some susceptible individuals.[1] For example, familial hemiplegic migraine has been linked to missense mutations in the Ca^{2+} channel gene CACNAIA which encodes the pore-forming protein for the P/Q Ca^{2+} channel.

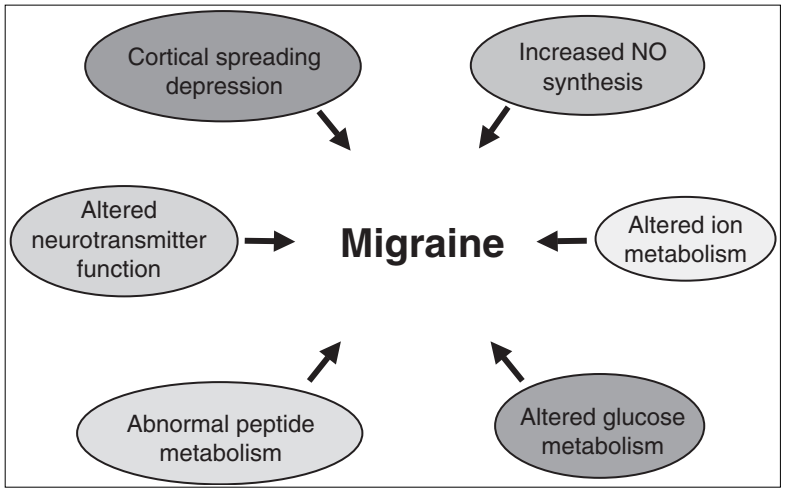

Fig. 12.1 Pathophysiological factors contributing to abnormal neurotransmission associated with migraine initiaion and transmission.

Two theories that have influenced our current understanding of migraine pathogenesis are: (1) the vasogenic theory; and, (2) the neurogenic theory. The central postulate of the vasogenic theory is that transient vasoconstriction contributes to migraine aura and that rebound vasodilation results in the activation of perivascular nociceptive neurones. The neurogenic theory postulates that migraine pain can occur in the absence of significant vascular changes and is determined by a neurophysiological process that leads to the release of nociceptive substances.

The pathophysiological phases of migraine include: initiation; activation and transmission in the primary afferent neurones; and, activation and sensitization of the central nervous system. Pain associated with migraine is presumed to be first detected by repeated and inappropriate activation of nociceptive neurones within the trigeminal and cranial (C1 and C2) nerves. In this regard, migraine-like epilepsy can be considered as an episodic disorder that results in the synchronous discharge of neurones that comprise an organized neuronal network.

Migraine can occur with or without aura. Typically, migraine with aura originates in the occipital cortex; whereas, migraine without aura may initiate centrally or at the level of vessels. The typical aura associated with migraine is visual in nature, spreads slowly over the visual field, and may be triggered by the phenomenon of spreading depression. Spreading depression is associated with a brief wave of excitation that is followed by prolonged neuronal depression. Spreading depression may also be accompanied by regional reductions in blood flow. In animal models, the wave of neuronal depression has been observed to spread at a rate of 3–5 mm/min. Interestingly, this finding is consistent with the rate at which the visual aura of migraine expands.

Initiation of the pain process is followed by activation of primary afferent neurones and subsequent integration within the trigeminal nuclear complex.

The trigeminal nucleus transmits the pain signal through second-order axons to the central pain-processing areas of the brain including the thalamus, limbic system, and neocortex.[2] Because the pain associated with migraine lasts for a period that long out lasts the initiating stimuli, it is believed that there are peripheral or central processes that lead to sensitization of the pain-transmission pathways and reinforcement of the nociceptive signal.

Preventive therapy

The pharmacological management of migraine is divided into acute and preventive approaches. Acute treatment is employed in an effort to reduce the impact of an attack; whereas, preventive treatments are employed prophylactically in an effort to prevent or reduce the frequency of migraines. In addition, preventive therapy is aimed at reducing the severity and duration of a migraine attack; improving the responsiveness to acute medication; improving function; and, reducing disability associated with an attack.[3] Several classes of pharmacological agents have been shown to be useful in the prophylactic treatment of migraine. For example, over the years β-blockers, Ca^{2+} channel antagonists, antidepressants, non-steroidal anti-inflammatory drugs, serotonin antagonists, and antiepileptic drugs (AEDs) have all been found to possess varying degrees of efficacy as migraine preventives. In recent years, three of the currently available AEDs have emerged as effective alternatives to the β-blockers, Ca^{2+} channel antagonists, antidepressants, and other classes of drugs employed in the management of migraine. Of the currently marketed AEDs, valproic acid (VPA), topiramate (TPM), and gabapentin (GBP) have demonstrated efficacy in several double-blind, placebo-controlled trials; whereas zonisamide, levetiracetam, lamotrigine, and carbamazepine have demonstrated limited or no efficacy (lamotrigine and carbamazepine) or have unproven efficacy (zonisamide and levetiracetam) in a limited number of clinical trials (see Silberstein[4] this issue). Although they share some similarities in their proposed mechanisms of action, they each possess certain unique properties that differentiate them from each other. The remainder of this chapter will focus primarily on the proposed molecular mechanisms of action of valproate, gabapentin, and topiramate and the presumed relationship between molecular activity and efficacy.

Antiepileptic drugs

The mechanisms of action of valproate, gabapentin, topiramate, and the other currently marketed AEDs are not fully understood. Although numerous molecular targets exist wherein AEDs may exert an effect, the final common pathway appears to be through modulation of voltage-gated and/or neurotransmitter-gated ion channels.[5–8] Presently, most of the AEDs are thought to exert their primary action by (1) reducing sustained, high-frequency repetitive firing of action potentials by modulating voltage-dependent sodium (Na^+) channels; (2) enhancing GABA-mediated

inhibitory neurotransmission; or (3) modulating neurotransmitter release and neuronal bursting through an effect on voltage-gated and receptor-gated calcium (Ca^{2+}) channels. For the most part, the common link among the various proposed mechanisms involves the ability of an anticonvulsant to modulate ion channel function.

Valproic acid (VPA)

Valproic acid is a broad-spectrum AED that has found utility in the management of partial and generalized seizures, migraine prevention, and certain psychiatric disorders. The studies conducted to date suggest that VPA possesses multiple mechanisms of action including inhibition of Na^+ and Ca^{2+} currents, potentiation of GABA-mediated inhibition, and indirect modulation of PKC activity (see ref.9, Table 12.1).

Valproic acid has been demonstrated to block sustained repetitive firing of mouse central neurons in culture[10] and rat hippocampal slices.[11] Results from considerable *in vitro* investigations support an effect of VPA on voltage-sensitive Na^+ channels. For example, VPA has been found, in isolated *Xenopus leavis* myelinated nerves, to inhibit Na^+ currents.[12] Furthermore, a reduction in Na^+ current was observed with VPA in neocortical neurons *in vitro*.[13] In rat hippocampal neurons, VPA decreased peak Na^+ currents in a voltage-dependent manner and produced a 10 mV leftward shift in the Na^+ inactivation curve.[14] Taken together, these results support an action for VPA at the voltage-sensitive Na^+ channel. However, this effect alone is not sufficient to explain the broad preclinical and clinical profile of VPA. VPA has been observed to produce a modest reduction of T-type Ca^{2+} currents in primary afferent neurons,[15] to elevate whole brain GABA levels, and to potentiate GABA responses at high concentrations (see ref. 7 for reference). In addition, VPA has been found to decrease the activity of protein kinase C which has been found to influence glutamate-mediated excitation.[16,17] In a model of trigeminal pain, the effects of VPA on GABA metabolism and synthesis appear to be particularly relevant to its antinociceptive effect. For example, VPA displayed a dose-dependent inhibition of c-fos expression within the nucleus caudalis following activation of afferent meningeal nociceptive neurons by capsaicin. The finding that this effect of VPA is blocked by the GABA antagonist bicuculline suggests that VPA mediates its action in large part by enhancing GABA-mediated neurotransmission.

In summary, the proposed actions of VPA may contribute, either singly or in concert with each other, to its efficacy in epilepsy, bipolar, and migraine.

Table 12.1 Proposed mechanisms of action of valproate

Enhances GABA-mediated neurotransmission
Attenuates low-threshold T-type Ca^{2+} channels in nodose nucleus
Blocks voltage-dependent Na^+ channels
Attenuates plasma extravasation
Decreases PKC activity

Gabapentin (GBP)

Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, was originally designed and synthesized as a drug to enhance GABA-mediated inhibition by mimicking the steric conformation of the endogenous neurotransmitter GABA.[18]

Despite demonstrated efficacy in both animal and human studies and numerous *in vitro* studies that have described several potential mechanisms of action, the precise mode of action of GBP remains unknown (Table 12.2). Although originally designed to function as a GABA-mimetic, results from a number of studies have essentially excluded this as a possible mechanism of action. Unlike those AEDs that directly modulate voltage- and receptor-gated ion channels, there is a substantial time lag between the appearance of peak plasma and brain concentrations and GBP's time to peak anticonvulsant effect following i.v. administration.[19] This delay in anticonvulsant effect suggests that prolonged synaptic and/or cytosolic exposure to GBP is important and supports an indirect mechanism of action for GBP. This hypothesis is supported by both *in vivo* and *in vitro* studies. For example, only after prolonged application of GBP was a reduction in sustained repetitive action potential firing observed.[20] GBP's ability to limit sodium-dependent sustained action potential firing in cultured mouse spinal cord neurones was observed at clinically relevant concentrations and was voltage- and frequency-dependent but developed slowly with prolonged exposure. The precise mechanism of this effect is not known; however, it is unlikely that GBP inhibits Na^+ currents in a manner similar to that of established Na^+ channel blockers PHT and CBZ.

GBP has also been reported to increase GABA concentrations in discrete brain regions; this effect parallels its anticonvulsant time-course.[21] Similarly, GBP has been reported to increase the cytosolic concentration of GABA in isolated rat optic nerves from neonatal rats.[22] Since this preparation contains mostly axons from retinal ganglion cells and glial cells and lacks neuronal cell bodies and synapses, the majority of GABA is presumed to be localized in the glial compartment. The significance of this finding is that GABA can be released from glial cells in a calcium-independent manner by the GABA uptake inhibitor nipecotic acid.[23] For example, by acting as a substrate for the GABA transporter nipecotic acid can release GABA by reversing the GABA transporter. Once released, GABA produces a $GABA_A$-dependent depolarization that is blocked by bicuculline. GBP pretreatment enhances nipecotic acid-induced depolarization presumably by increasing the amount of GABA that is released by reversal of the GABA transporter.[22] GBP has also been demonstrated to enhance nipecotic acid-induced inward currents in isolated CA1 hippocampal pyramidal neurons in culture.[24] Thus, it would appear

Table 12.2 Proposed mechanisms of action of gabapentin

Increases brain GABA levels
Binds to $\alpha_2\delta$ subunit of Ca^{2+} channel
Inhibits monoamine neurotransmitter release
Decreases sustained-repetitive firing

that GBP possesses a unique ability to increase the concentration of releasable GABA in both the glial and neuronal compartment. GBP has also been reported to increase *in vivo* occipital lobe GABA levels in epilepsy patients.[25] This effect, determined using ^{1}H nuclear magnetic resonance spectroscopy, was significantly higher in control than in those patients receiving 40 mg/kg/day GBP.

GBP may increase brain GABA turnover by interacting with a number of different metabolic processes. It has been demonstrated to enhance glutamate dehydrogenase and glutamic acid decarboxylase and inhibit branched-chain amino acid aminotransferase and GABA aminotransferase. Although any one of these effects could singly, or in concert with each other, contribute to the anticonvulsant action of GBP, it is not clear at this point which effects are important.[26]

Finally, GBP has been reported to bind to a novel site in rat brain.[27] Specific [^{3}H]-GBP binding is not affected by any of the standard AEDs including PHT, CBZ, VPA, PB, diazepam, or ESM. Furthermore, GBP binding is not displaced to any significant extent by NMDA or AMPA receptor ligands. On the contrary, [^{3}H]-GBP binding is displaced by unlabelled GBP and several structural GBP analogues including 3-isobutyl GABA. GBP is transported across several membrane barriers via a system L-amino acid transporter. Transport is stereospecifically blocked by L-amino acids including L-leucine, L-isoleucine, L-methionine, and L-phenylalanine, thereby suggesting an association between the [^{3}H]-GBP binding site and the system L transporter of neuronal cell membranes.[28] However, the precise relationship between the GBP binding site and system L transporter remains unclear. Subsequent studies have demonstrated that GBP binds with high affinity to the $\alpha_2\delta$ auxiliary subunit of a high-voltage activated Ca^{2+} channel.[29] Although the precise function of this auxiliary subunit is not known, it has been suggested that gabapentin may somehow modify neurotransmitter release through its interaction with Ca^{2+}. Indeed, GBP has been reported to decrease release of several monoamine neurotransmitters.[26]

In summary, results from a number of *in vitro* and *in vivo* studies would also suggest that the mechanism of action of GBP is unique among the existing AEDs. Among the many possible hypotheses being tested, the two that appear most closely associated with its anti-migraine action are related to GBP's ability (1) to enhance GABA turnover and release, and (2) to decrease neurotransmitter release by binding to the $\alpha_2\delta$ subunit of a voltage-gated Ca^{2+} channel.

Topiramate (TPM)

TPM [2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate] is a chemically novel AED. A number of different mechanisms of action have been identified which may account for TPM's broad clinical profile.[30,31] At therapeutic concentrations (3–30 μM), TPM blocks voltage-sensitive Na^{+} and Ca^{2+} channels, attenuates kainate-evoked currents, enhances GABA-evoked chloride currents, and inhibits carbonic anhydrase (Table 12.3). Collectively, these actions of TPM contribute to its unique ability to decrease excitation and enhance inhibition.

TPM has been found to inhibit sustained repetitive firing in cultured hippocampal neurons in a use- and concentration-dependent manner.[32,33] Qualitatively similar results have been observed in mouse spinal cord neurones.[34] In addition, McLean

and colleagues have demonstrated that TPM's ability to inhibit sustained repetitive firing is voltage-dependent. The ability of TPM to limit sustained repetitive firing is suggestive of an interaction between TPM and the voltage-sensitive Na^+ channel. Results obtained from cultured cerebellar granule cells[35] and altered neocortical neurons are consistent with this conclusion. In these studies, TPM was demonstrated to reduce voltage-activated Na^+ currents.[36] In additional electrophysiological studies conducted on cultured hippocampal neurons, TPM, at a therapeutic concentration of 10 μM, was reported to reduce the duration and frequency of action potentials within spontaneous epileptiform bursts.[32] These effects on sustained repetitive firing, Na^+ currents, and spontaneous burst firing are consistent with its apparent ability to reduce seizure spread in rodent and human studies.

TPM has also been reported to reduce kainate-evoked whole-cell currents in hippocampal neurons.[32,37,38] This effect was evident at 10 μM and was concentration-dependent between 10 μM and 100 μM. At 100 μM, TPM had no effect on NMDA-evoked inward currents. When compared to other AEDs this effect of TPM on kainate-evoked currents is unique to TPM and is consistent with a decrease in neuronal excitability.

TPM has also been reported to enhance GABA-evoked chloride single-channel currents in cultured neocortical neurones.[39,40] Kinetic analysis of single-channel recordings from excised outside-out patches demonstrated that TPM increased the frequency of channel opening and the burst frequency but was without effect on open channel duration or burst duration. In this respect, the effect of TPM on $GABA_A$ channel activity was similar to that observed with BZDs. However, in contrast to the BZDs, the ability of TPM to enhance $GABA_A$-evoked current was not reversed by the BZD antagonist flumazenil. This effect would not be predicted from previous *in vitro* studies wherein TPM did not displace radiolabelled ligand binding to known binding sites on $GABA_A$ receptors.[41] Interestingly, TPM's ability to modulate GABA currents appears to be dependent on the conformation of the $GABA_A$ receptor. For example, TPM displays a preferential affinity for those $GABA_A$ receptors expressing α4 and β3 subunits.[42] This is of particular interest because these subunits are upregulated by seizure activity.[43]

Activation of neurons in the trigeminocervical complex by superior sagittal sinus (SSS) stimulation is thought to model the pain pathway in migraine and cluster headache. In the anesthetized cat, topiramate was found to dose-dependently reduce SSS-evoked firing of neurons in the trigeminocervical complex.[44] Inhibition of SSS-evoked firing by TPM may represent one mechanism by which TPM prevents migraine or cluster headaches.[44]

Table 12.3 Proposed mechanisms of action of topiramate

Decreases non-NMDA (AMPA and KA) mediated excitatory neurotransmission
Inhibits voltage-activated Na^+ channels
Potentiates $GABA_A$ receptor-mediated neurotransmission
Attenuates high-threshold activated Ca^{2+} channels
Inhibits Type II and IV isoforms of carbonic anhydrase

Table 12.4 Comparative mechanistic profile of valproate, gabapentin, and topiramate

AED	Sodium channel blockade	Calcium channel blockade	Glutamate antagonism	GABA potentiation	Carbonic anhydrase inhibition
Valproate	X	X		X	
Gabapentin		X		X	
Topiramate	X	X	X	X	X

See Loscher, 2002 [9]; Taylor, 2002 [26]; and White, 2002 [31], for references and discussion.

Through multiple and complementary mechanisms of action, topiramate may disrupt the pathophysiological cycle of migraine by modulation of cortical hyperexcitability that leads to cortical spreading depression; by inhibition of glutamatergic signalling by trigeminal afferent nerves; and by modulation of nociceptive signalling through $GABA_A$ receptors in the TNC or descending brain stem pathways.

Summary

It is fair to say that the mechanisms underlying the efficacy of antiepileptic drugs utilized for the preventive management of migraine are not completely understood. Furthermore, it is likely that the AEDs valproic acid, gabapentin, and topiramate possess more than one mechanism of action that may act additively or synergistically to modify the abnormal neuronal activity that contributes to the initiation of migraine attack (Table 12.4). Collectively, all three of these AEDs modify voltage- and receptor-gated ion channels that contribute to the synchronous firing of neurones.

At the molecular level, valproic acid, gabapentin, and topiramate share the ability to enhance GABA-mediated inhibitory neurotransmission and to modify voltage-gated Ca^{2+} channels. Furthermore, all three AEDs limit sustained high-frequency repetitive firing of neurons, albeit through different mechanisms. TPM is unique in that it is the only AED that possesses the ability to modify excitatory neurotransmission through the non-NMDA AMPA receptor. In addition to preventing the synchronous firing of neurons, these activities would be expected to decrease or prevent the release of neurotransmitters and vasoactive peptides that contribute to the activation and sensitization of primary afferent and central neurons. Hypothetically, the ability of TPM to modulate AMPA-mediated excitatory neurotransmission would be expected to reduce or prevent spreading depression and thereby eliminate one of the proposed triggers of a migraine attack.

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13 Experience with topiramate in patients with refractory migraine

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Migraine is a frequent condition affecting 18% of women and 6% of men in the United States. The American Migraine Study reported that 24% of migraine sufferers experience four or more migraine attacks every month. However, only 3–5% of migraine sufferers receive preventive therapy.[1] Classes of agents used as preventives for migraine include beta-blockers, calcium-channel blockers, serotonin antagonists, antidepressants, non-steroidal anti-inflammatory drugs, and antiepileptics. Many patients with migraine find the currently available preventives unsatisfactory, due to their limited efficacy and not infrequent adverse effects. Consequently, there is a need for better prophylactic options.[2]

Several recent open-label or small placebo-controlled studies suggest that topiramate may be efficacious for prophylaxis of migraine and cluster headache.[3–11] Topiramate has a variety of mechanisms of action that could potentially contribute to migraine prophylaxis, including state-dependent inhibition of voltage-gated Na^+ and Ca^{2+} channels, inhibition of glutamate-mediated neurotransmission at the AMPA/kainate receptor subtypes, and enhancement of $GABA_A$ receptor-mediated chloride flux.[12]

We report here our experience with topiramate in the prophylaxis of patients with frequent migraine previously refractory to usual preventives.

Methods

We offered treatment with topiramate to patients with the diagnosis of frequent IHS migraine[13] who had not tolerated (33%) or responded (67%) to beta-blockers, amitriptyline, flunarizine and/or valproate. Even though each investigator was free

to use his own treatment protocol in a particular patient, topiramate was usually initiated at 25 mg/day and was increased by 25 mg weekly up to a target dose of 100 mg/day. Two obligatory follow-up visits were scheduled. The first one took place at the end of the initial treatment month. This visit was planned mainly to check for tolerability and to increase topiramate dose if no response had occurred. Maintenance dose could be even lower if tolerability problems appeared, or else increased up to a maximum of 400 mg daily, if migraine frequency did not improve. The final obligatory visit took place at the end of the third treatment month. In this visit, headache frequency in the last month was rated upon a calendar review when available, or based on patient recall when a calendar was not available. The parameters analysed in this visit were 'response' (reduction in migraine frequency >50%), excellent response (>75%), and tolerability.

Results

Patients

This series includes a total of 100 patients (76 women), aged between 16 and 81 years (mean 42 years). Eighty-six met migraine without aura criteria, while the remainder had a history of both migraine with aura and migraine without aura episodes. All the patients had frequent (>1 migraine days per week) migraine episodes. In fact, 69 met Silberstein *et al.*'s criteria for transformed migraine.[14] After 3 months, daily maintenance doses of topiramate varied between 25 mg and 400 mg (mean 98.7 mg/day; mode and median 100 mg/day). The distribution of topiramate doses in this study is illustrated in Fig. 13.1.

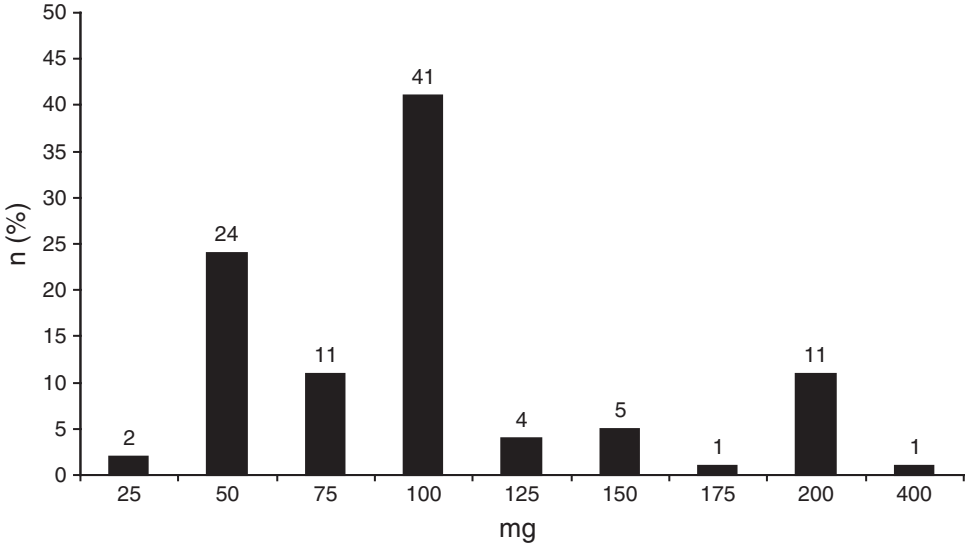

Fig. 13.1 Distribution of topiramate doses among the patients included in this study.

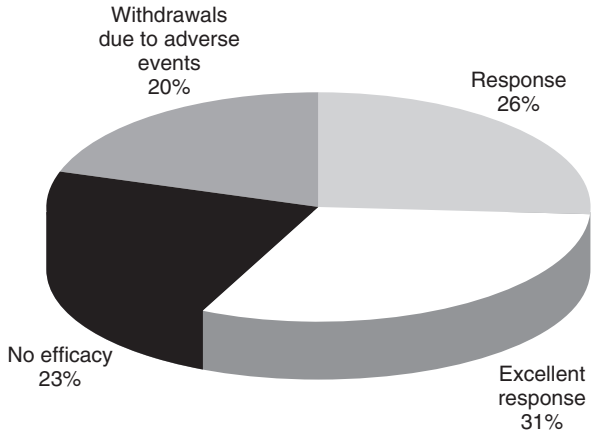

Fig. 13.2 Summary of study results.

Efficacy

A total of 23 patients found topiramate inefficacious. Conversely, 57 patients showed response to topiramate therapy. Response was excellent in 31 cases (Fig. 13.2).

Tolerability

Twenty patients withdrew due to adverse events, already at doses as low as 25–50 mg and most of them during the first month of therapy. One of these withdrawals was due to excessive weight loss (13 kg), one due to digestive intolerance and the remaining 18 due to cognitive difficulties (expressed as decreased concentration or memory problems) sometimes associated with drowsiness sensation. The remaining 80 patients frequently reported other adverse events (being the most frequent distal paresthesias in at least 28 cases), but they were mild, well tolerated, and improved on decreasing the dose of topiramate. No serious adverse events were seen. Fourteen patients referred to significant weight lost (3–13 kg in 3 months).

Discussion

The results of this observational study indicate that topiramate is a good therapeutic option to try in migraine patients refractory to other preventives and/or frequent attacks. In a specialist's clinical setting, topiramate seems to be effective in about half of these patients. The response was usually excellent in these patients, which, together with the previous failure to other preventives also administered by us, make a relevant placebo effect very unlikely. Our findings concur with those reported in placebo-controlled trials and observational studies.[3–11] Edwards *et al.*, in a placebo-controlled trial of episodic migraine, found a 50% or greater reduction in

headache frequency in 47% of patients. Storey *et al.*, in a placebo-controlled trial of episodic migraine patients, reported a median percent reduction in monthly headaches of 33%. Several authors have recently studied the effect of topiramate in both episodic and transformed migraine in observational trials. Response in transformed migraine patients in these studies has ranged from 30% to 58% of patients. The rather high-efficacy rates in our observational study may be due to the ability to optimize the dose and individualize treatment, and could be representative of the outcomes which might be expected in a real clinical setting.

The data of our study might help to clarify two debatable points: what the best dose of topiramate should be and what the adverse event profile of topiramate is in migraine patients. In our experience, and concurring with that of Mathew *et al.*,[10] the optimal dose of this drug for migraine prevention in most patients is around 100 mg/day. Higher doses lead to an increase in efficacy in few patients and clearly impair tolerability.[12] Poor tolerability was the reason for discontinuing topiramate in exactly 20% of our patients. Adverse events were mostly subjective cognitive impairment and, very importantly, usually appeared already on doses as low as 25–50 mg daily. It should, therefore, be clearly explained to the patients when prescribing this drug.

Similarly to other trials in headache and non-headache patients, weight loss was a quite frequent adverse event.[11,15] The reported range of weight loss is consistent with that of previous studies. With only one exception, it was not considered by our patients as a negative adverse event. In fact, most considered weight loss as a beneficial adverse event. In summary this observational study provides further experience with topiramate in migraine prophylaxis, in a large series of ambulatory patients. The results of the large controlled trials of topiramate in this setting are awaited for a confirmation of its efficacy.

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14 Topiramate in a selective group of therapy refractory headache patients

R. M. Agosti and S. Eugster

Introduction

Topiramate (Topamax®) was developed and introduced as a broad spectrum antiepileptic drug. It is shown to be effective in migraine prophylaxis in several open-label and controlled trials including three double-blind placebo-controlled studies.[1–7] The mechanism of action in migraine is not known[8] but several of the mechanisms discussed for epilepsy could be effective in migraine including inhibition of voltage-gated sodium and calcium channels, limitation of glutamate-mediated neurotransmission at the AMPA-kainate receptor subtype, and enhancement of $GABA_A$ receptor-mediated chloride flux. Further an inhibition of the carbo-anhydrase is known which seems to be responsible for one of the side effects, i.e. tingling in hands and feet. Topiramate also bears a surprising but likewise unexplained effect on body weight in the sense that many patients report a weight loss.

At the Zurich University Hospital, and since December 2002 at the Headache Center Zurich Hirslanden, high therapy refractory headache patients are treated in a specialized headache unit. Topamax® is registered in Switzerland only for epilepsy and may be registered for migraine soon. Therefore the use of topiramate for migraineurs and other headache patients was justified only as 'last choice' after many prophylactic agents had not been effective or were not tolerated. The success rate for any additional prophylactic treatment in such a refractory situation is expected to be low. Nevertheless, almost any new substance tried under these circumstances can still have some unexpected benefits and is thus worth a trial. In addition, therapy refractory patients express very clearly that they continue to suffer and that they are eager to try new approaches. We treated a group of refractory patients suffering from migraine and other chronic headaches with topiramate successfully, and encourage the use of topiramate in resistant migraine and other difficult-to-treat headaches.

Patients

Under the above-described circumstances our patient population consisted of severely refractory headache patients. They often presented with more than one headache diagnosis that resulted often in chronic daily headaches. The average duration of headaches before treatment with topiramate was several years to several decades. Almost all patients received at least four prophylactic agents. In many patients concomitant treatment could not be avoided when treatment with topiramate was started.

Methods

In a retrospective analysis a selective group of patients with various types of resistant primary (MO 2, MA1, TT 3, comb 3, according to IHS 1988 criteria) and chronic secondary headaches were treated open-label with topiramate at various dosages. Initial doses were 25 mg in the evening and titration increments were usually 25 mg per week to a recommended final dose of 100–200 mg per day divided in two doses. Diagnostic, demographic and outcome data, and body weight were collected and analyzed. Body weights were measured at each visit.

Results

Twenty nine headache patients were treated with topiramate. Ten patients were lost for follow-up (LF) or have not yet returned for follow-up. Of the remaining 19 patients, 12 patients (63%) responded in a favourable way (PO: positive outcome group) to topiramate with at least 50% reduction of headache intensity and/or frequency. Most impressive was elongation of intervals between migraine attacks. Seven patients did not respond (NO: negative outcome group). This group was remarkable for a low tolerability of topiramate. Mean maximal dose was 57 mg (25–100 mg) in the NO group.

Headache diagnoses were mixed in both groups and included migraine, tension-type, and other headaches. Distribution of diagnoses (multiple diagnoses possible) in the PO group was MA 6, MO 3, CTTH 7, TMJ 1, HA after lightening 1, HA after cerebellar infarcts and mild TBI 1. Diagnoses in the NO group were: MA 1, MO 3, CDHA 4, medication-induced headache 1. Most were chronic. The mean age of the three groups (PO, NO, and LF) was comparable (46 vs 48 vs 44). Mean maximal daily dosage of the PO group was 293 mg (25–700 mg) and in the NO group 57 mg (25–100 mg). Patients were encouraged to find their individual optimal dosage level. One patient found a surprisingly low effective dose at 25 mg daily. This patient took also a beta-blocker for chronic tachycardia.

Most side effects in the PO group were mild tiredness and tingling, and in the NO group tiredness, tingling, feeling drunk, and 'feeling awkward'. One person

in the PO group described visual perceptual changes that are familiar to him from MTV video clips, i.e. like being sucked into a funnel. Many patients observed a substantial *weight loss* and in none of the patients was weight gain observed. Patients responded in a very positive way to the weight loss. In the PO group mean weight loss was 4 kg in a period of around four months, ranging from 0 to 13 kg. The observed weight loss seemed to improve compliance in our patients. In the NO group data were not obtained because of the early discontinuation of the medication.

All patients had tried at least five other prophylactic treatments without success, most of the patients even more. A wide variety of concomitant migraine medications were also observed. One patient received pericranial intramuscular injections of botulinum toxin (BoTox®).

Discussion

Topiramate is a valuable alternative to established prophylactic migraine treatments. Superiority to placebo in the treatment of migraine was already shown in three double-blind placebo-controlled trials, with up to 500 patients each, and in open-label trials as well. In our small population, diagnoses showed a high variability with the diagnosis of migraine included in most of the patients. Chronic tension-type headache and a few other secondary diagnoses were mixed with migraines. This was also the case in Mathew's series of patients. Our group was also characterized by patients that were resistant to most of the common prophylactic agents so that topiramate (which is not registered for migraine in Switzerland) was used as a last rescue measure. Such a group of patients is normally not considered for medication studies because of several confounding factors such as the chronification of headaches, presence of multiple concomitant medications, or use of more that just a few prophylactic medications in the past. Nevertheless our results show a positive outcome in a surprisingly high number of patients. For several of the patients topiramate was the one and only prophylactic medication that finally helped.

The well-known tendency of topiramate to cause weight loss was confirmed in our cohort. The average weight did drop and none of the patients reported weight gain. The expectancy of weight loss was a very strong motivation to try a new prophylactic treatment when so many had been tried without success. This was of particular interest for patients who were sceptical about new medications, particularly towards those medications that they often considered as 'chemistry'. This is of particular interest since the majority of established migraine prophylactic drugs stimulate appetite and cause weight gain. Many of the severely affected migraineurs have already experienced weight gain from prophylactic medications in the past.

Tolerability seems to be the key to success: the average dose of topiramate in responders was almost five times higher in comparison to the non-responder group. In other words: if topiramate was tolerated a very high success rate in headache reduction could be expected. By developing better means to tolerate side effects of topiramate, its high efficacy could even be increased.

These promising results are motivating and we will continue prescribing topiramate in the prophylaxis of various resistant types of headaches and migraines. Prospective data on the application of topiramate in this more severely affected group of patients should be collected.

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15 Prophylactic drugs II: discussion summary

J. Schoenen

The presentations, posters, and discussion during this session devoted to beta-blockers, amine antagonists, and antiepileptic drugs confirmed well-known concepts and provided some novel insights in migraine prophylaxis.

Regarding trial methodology, it was pointed out that the outcome measure 'migraine periods' which covers the total duration of a migraine attack does not add much to 'migraine attacks' and 'migraine days' proposed in the IHS guidelines for clinical trials. Referring to valproate studies, attention was drawn to the fact that some cross-over studies, such as the Danish one, were superior in statistical power than certain large trials on parallel patient groups.

Although numerous studies confirm the efficacy of beta-blockers devoid of partial agonist properties (and thus of intrinsic sympathicomimetic activity) in migraine prophylaxis with clear statistical differences between the various compounds, their precise mode of action is still unknown. A case was made against a serotonergic mechanism and in favour of an activity on vascular tone, but a L-tryptophan PET study has shown increased serotonin availability in the brain of migarineurs after beta-blockade. It is not known if beta-blockers have activity on 5-HT_7 or on subtypes of 5-HT_2 receptors. The question whether most prophylactic anti-migraine drugs, including beta-blockers and antiepileptices, might act by reducing anxiety in migraineurs has not been investigated. However, the effect of tricyclics on migraine is not correlated with an effect on anxiety or depression.

Among the antiepileptic drugs, valproate or the combination of valproate and valproic acid remain a standard in migraine prophylaxis. The risk of inducing a polycystic ovarian syndrome in female migraineurs with valproate seems to be small, whereas weight gain and alopecia are adverse effects of concern to female patients. While gabapentin is less efficacious, topiramate has a comparable activity, but it is endowed with a higher rate of adverse events often leading to interruption of treatment. This was the case in 20% of patients in one large open Spanish study (Pascual *et al.*, poster) and most withdrawals were due to cognitive adverse effects such as thought, language, or calculation problems. This seems to be an 'all or none' effect, as several patients tolerate perfectly topiramate, even at high doses. It was confirmed that topiramate, contrary to valproate, seems to be particularly effective in migraine with aura, which is of interest for the discussion on its mode of action

and might indicate that carbonic anhydrase blocking activity could be relevant. Topiramate could be of benefit in certain chronic cluster headache patients, but this needs to be addressed in formal controlled studies.

Finally, a Japanese study has shown that lomerizine, a derivative of flunarizine, but devoid of its side effects, is an efficient and well-tolerated drug in migraine prophylaxis, suggesting that larger controlled trials are worthwhile.

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Session IV

Prophylactic drugs III

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16 Efficacy of antidepressants in headache prophylaxis

L. Bendtsen

Introduction

Antidepressants have been used for headache prophylaxis for more than four decades. As early as in 1964, Lance and Curran[1] reported that the tricyclic antidepressant amitriptyline was effective in tension-type headache independent of the antidepressant effect and a positive effect in migraine was reported in 1973.[2] Antidepressants are widely used for the prophylactic treatment of primary headaches. After beta-blockers, amitriptyline is the most used drug for migraine prophylaxis in the US for both neurologists and primary care physicians.[3] Amitriptyline is the first drug of choice for the prophylaxis of tension-type headache.[4] The newer antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs), are also used in headache, because of their favourable side effect profile.[5] With such an extensive use one would expect a substantial number of studies supporting the effectiveness of antidepressants in headache. But is this the case? The aim of the present paper is to review the scientific evidence for an effect of antidepressants in the prophylactic treatment of primary headaches.

Methods

Trials were identified through a Medline search, from reference lists of publications extracted from the search, and from major headache books. The placebo effect must be taken into account in any study of treatment for headache, and only placebo-controlled trials allow definitive statements about degree of efficacy. In the present review, efficacy of antidepressants was therefore evaluated on the basis of randomized, double-blind, placebo-controlled studies. However, many of the trials on antidepressants in headache prophylaxis were performed during a time when placebo-controlled studies were not frequently used, and few of the studies follow the guidelines for drug trials proposed by the International Headache Society.[6,7]

Because of the limited number of placebo-controlled trials, I will also briefly describe controlled double-blind trials comparing antidepressants and trials comparing antidepressants with other treatments. It should, though, be kept in mind that the predictable result of such studies, i.e. that both treatments are effective and that no difference between the treatments can be detected, is difficult to interpret.

Migraine

Placebo-controlled trials. In 1973, Gomersall and Stuart[2] treated 20 migraine patients with the tricyclic antidepressant amitriptyline 10–60 mg daily in a crossover trial (Table 16.1). The average daily dose was 30–40 mg. Amitriptyline reduced the number of migraine attacks by 42% compared with placebo, which was highly significant. It was not described whether efficacy was related to presence or absence of depression.

Couch and Hassanein[8] tested amitriptyline 50–100 mg daily (Table 16.1). Forty-seven patients were treated with amitriptyline and 53 with placebo. The primary efficacy parameter was a weighted migraine score reflecting frequency, severity, and duration of attacks. Data on migraine frequency were not presented. The migraine score was reduced by more than 50% in 55% of amitriptyline-treated patients compared with 34% of placebo-treated patients. Amitriptyline was significantly more effective than placebo. Efficacy was independent of depression.

In a three-way crossover study, Ziegler *et al.*[9] compared amitriptyline 50–150 mg daily, propranolol 80–240 mg daily, and placebo in 30 patients (Table 16.1). The primary efficacy parameter was the headache score calculated by multiplying severity and duration. Data on migraine frequency were not presented. The headache score was reduced 16% by amitriptyline and 21% by propranolol. Both treatments were significantly superior to placebo with no significant difference between treatments. Interpretation is difficult because of a high drop-out rate (24 patients dropped out of 54 included). Efficacy was independent of depression and anxiety.

Two studies found no effect of the tricyclic antidepressant clomipramine.[10,11] It is not possible to draw firm conclusion from these studies because of the very small number of subjects treated and because of low methodological quality. Therefore these studies are not presented in Table 16.1.

Zeeberg *et al.*[12] treated 20 patients with the SSRI femoxetine 300 mg daily and 25 patients with placebo. No difference in attack frequency between the treatments could be detected (Table 16.1). Orholm *et al.*[13] found the same result when treating 25 patients with femoxetine 600 mg daily and 28 patients with placebo (Table 16.1).

The SSRI fluoxetine has been investigated in several trials. Adly *et al.*[14] treated nine patients with fluoxetine 20–40 mg per day and nine patients with placebo. The primary efficacy parameter was headache score, but it is unclear how this was calculated. Fluoxetine reduced headache scores significantly more than placebo. Efficacy was not related to depression (Table 16.1). Saper *et al.*[15] treated 29 patients with fluoxetine 20–40 mg/day and 22 patients with placebo, and found no difference

Table 16.1 Summary of randomized, double-blind, placebo-controlled studies of antidepressants in migraine

Study	Drugs tested/Design	*N*	Results
Gomersall and Stuart[2]	Amitriptyline/Crossover	20	AM reduced attack frequency by 42% compared with PL, $p<0.001$
Couch and Hassanein[8]	Amitriptyline/Parallel	100	More patients improved on AM (55%) than on PL (34%), $p<0.05$
Ziegler *et al.*[9]	Amitriptyline - Propranolol/ Crossover	30	Effect of both treatments, $p<0.05$, no difference between treatments
Zeeberg *et al.*[12]	Femoxetine/Parallel	45	No effect
Orholm *et al.*[13]	Femoxetine/Parallel	53	No effect
Adly *et al.*[14]	Fluoxetine/Parallel	18	FL reduced headache score more than placebo
Saper *et al.*[15]	Fluoxetine/Parallel	51	No effect
Steiner *et al.*[16]	Fluoxetine/Parallel	33	Attack frequency reduced more on FL (53%) than on PL (27%), $p<0.05$

AM: amitriptyline; FL: fluoxetine; PL: placebo; *N*: number of patients included in evaluation of primary efficacy parameter; *p*: *p*-value.

between treatments (Table 16.1). Steiner *et al.*[16] treated 17 patients with the long-acting enantiomer S-fluoxetine 40 mg daily and 16 patients with placebo. Patients with depression were excluded. Attack frequency was reduced by 53% by S-fluoxetine, which was significantly more than placebo (27%). The study was methodologically well-performed, but interpretation of the study is made difficult by a large drop-out rate (of the 53 patients included only 33 patients completed) (Table 16.1). D'Amato *et al.*[17] treated 32 patients with fluoxetine 20 mg/day and 20 patients with placebo. Patients with depression were excluded. Fluoxetine but not placebo significantly reduced total pain index, but the two treatments were not tested against each other. Nothing can therefore be concluded about efficacy of fluoxetine and the study is not presented in Table 16.1.

Controlled studies comparing two active treatments. Mathew[18] found amitriptyline 50–75 mg/day less effective than propranolol 120–160 mg/day (42% improvement versus 62% improvement in headache index) in patients with migraine, $p<0.01$. No difference in the reduction of migraine frequency was detected in a study

comparing low dose amitriptyline (25 mg/day) and the SSRI fluvoxamine.[19] A small study comparing amitriptyline with timed-released dihydroergotamine in patients with mixed migraine and tension-type headache indicated that amitriptyline was best for treating tension-type headaches, while dihydroergotamine was superior for migraine like headaches.[20] Andersson and Petersen found no difference between femoxetine 400 mg/day and propranolol 160 mg/day.[21] Kangasniemi *et al.*[22] found that propranolol 160 mg daily reduced attack frequency more than femoxetine 400 mg daily, $p < 0.05$.

Tension-type headache

Placebo-controlled trials. In 1964, Lance and Curran[1] conducted a crossover trial of amitriptyline 10–25 mg three times daily in 27 patients with chronic tension-type headache (Table 16.2). Twelve patients had no improvement during treatment with either amitriptyline or placebo, 12 patients reported a response only to amitriptyline, and 3 patients responded to both treatments. These results were significantly in favour of amitriptyline. The response to treatment was not correlated with the presence or absence of depressive symptoms.

Diamond and Baltes[23] tested two different dosage ranges of amitriptyline, a lower one between 10 and 60 mg/day and a higher one between 25 and 150 mg/day (Table 16.2). All patients were also suffering from anxiety or depression. The results suggested that the lower dose range reduced headache more than placebo, while there was no significant effect of the higher dose range. Amitriptyline also reduced depression more than placebo, which makes it difficult to estimate the specific effect on headache.

Göbel *et al.*[24] evaluated amitriptyline 75 mg/day (Table 16.2). Patients with depression were excluded. Compared with placebo, headache duration was reduced significantly in the last week of the 6-week study, while the intake of analgesics was unaltered. Neither headache frequency nor headache intensity were presented. Nevertheless, as headache duration decreased consistently throughout all 6 weeks of active treatment but not throughout placebo treatment, the study is in favour of an effect of amitriptyline.

A multi-centre trial by Pfaffenrath and colleagues[25] compared amitriptyline 50–75 mg/day, amitriptylinoxide 60–90 mg/day and placebo (Table 16.2). No significant difference was found between the active treatments and placebo for either the primary study end point (a reduction of at least 50% of the product of headache duration and frequency *and* a reduction of at least 50% in headache intensity) or for any of the mentioned secondary efficacy parameters. However, the frequencies of side-effects were similar on amitriptyline and placebo. Usually, amitriptyline has marked side-effects and the inability to detect known side-effects suggests insensitivity of the trial for reasons which remain obscure.

In a three-way crossover study, Bendtsen *et al.*[26] compared amitriptyline 75 mg daily, the SSRI citalopram 20 mg daily and placebo (Table 16.2). The patients had been resistant to numerous previous treatments and were not suffering from depression.

Table 16.2 Summary of randomized, double-blind, placebo-controlled studies of antidepressants in chronic tension-type headache

Study	Drugs tested / Design	*N*	Results
Lance and Curran[1]	Amitriptyline/Crossover	27	Significantly more responders on AM (15/27) than on PL (3/27), *p* not given
Diamond and Baltes[23]	Amitriptyline/Parallel	85	Effect of AM 10–60 mg/day, $p<0.01$, but not of AM 25–150 mg/day
Göbel *et al.*[24]	Amitriptyline/Parallel	53	Effect of AM in the last week of the 6-week study, $p=0.007$
Pfaffenrath *et al.*[25]	Amitriptyline and AO/ Parallel	197	No significant effect of AM or AO, no difference in side effects between A and P
Bendtsen *et al.*[26]	Amitriptyline and CI/ Crossover	34	Effect of AM (headache reduced by 30%), $p=0.002$, no significant effect of CI
Holroyd *et al.*[27]	ADM and SMT/Parallel	144	Effect of ADM (headache reduced by 30%), $p=0.001$, and SMT, $p<0.01$
Fogelholm and Murros[29]	Maprotiline/Crossover	30	Maprotiline effective, $p<0.01$
Langemark *et al.*[30]	Clomipramine and mianserin/Parallel	82	Effect of CL and MI (headache reduced by 22% and 20%), $p<0.02$

AM: amitriptyline; PL: placebo; AO: amitriptylinoxide; CI: citalopram; ADM: antidepressant medication (amitriptyline 83% or nortriptyline 17%); SMT: stress management therapy; CL: Clomipramine; MI: mianserin; N: number of patients included in evaluation of primary efficacy parameter. Data on headache reduction are active drug compared with placebo.

Amitriptyline reduced the area under the headache curve (calculated as headache duration times headache intensity) by 30% compared with placebo, which was highly significant, while citalopram had only a slight (12%) and insignificant effect. Amitriptyline also significantly reduced the secondary efficacy parameters—headache duration, headache frequency, and intake of analgesics.

Holroyd and colleagues[27] treated patients with antidepressants (83% took amitriptyline median dose 75 mg daily and 17% took nortriptyline median dose 50 mg daily) and compared this treatment with stress management therapy and with a combination of stress management and antidepressant treatment (Table 16.2). After 6 months, all three treatments reduced headache index by approximately 30% more than placebo, which was highly significant. Patients with depression were not excluded and data on the relation between changes in mood and headache are not presented. This makes it unclear whether the beneficial effects were due to specific antiheadache effects or to antidepressant actions. However, in

a subsequent correspondence regarding this question the authors claim that reductions in depression scores did not differ between patients who received active drug and placebo.[28] The study is important in demonstrating a long-lasting effect of amitriptyline in chronic tension-type headache.

Fogelholm and Murros[29] treated 30 patients with the tetracyclic antidepressant maprotiline 75 mg daily. Active treatment reduced total pain scores significantly more than placebo. Data are only presented as figures, so the exact percentage reduction cannot be calculated. Efficacy was independent of depression.

Langemark *et al.*[30] treated 26 patients with the tricyclic antidepressant clomipramine 75–150 mg daily, 22 patients with the tetracyclic antidepressant mianserin 30–60 mg daily, and 34 patients with placebo. Patients with depression were excluded. The summed visual analogue scale headache score was reduced by 22% by clomipramine, and by 20% by mianserin compared with placebo. The effect was significant for both drugs.

Controlled studies comparing two active treatments. The selective 5-HT_2 and 5-HT_{1C} antagonist ritanserin was reported as effective as amitriptyline in patients with chronic tension-type headache and depression.[31] This was not confirmed in a subsequent placebo-controlled trial in non-depressed patients.[32] The latter study was only presented as a letter. Holroyd *et al.*[33] compared amitriptyline 25–75 mg/day with cognitive-behavioural therapy. They found a significant effect for both treatments with a tendency to more positive outcomes of cognitive-behavioural therapy. Langemark and Olesen[34] compared the SSRI paroxetine 20–30 mg daily with sulpiride, a dopamine antagonist used as a neuroleptic. Patients improved with both treatments with a tendency to better efficacy of sulpiride. Manna and colleagues[35] compared fluvoxamine 50–100 mg/day with mianserin 30–60 mg/day and found significant effects with both treatments. Bendtsen *et al.*[26] found significantly better effects for amitriptyline than for the SSRI citalopram, $p = 0.04$.

Patients suffering from both tension-type headache and migraine

Morland *et al.*[36] treated 14 patients with mixed migraine and tension headache with the tricyclic antidepressant doxepin 100 mg daily or placebo in a double-blind crossover trial. Active treatment reduced headache index (headache days time severity) by 15% compared with placebo, which was significant, $p < 0.05$. Mathew[18] found that amitriptyline 50–75 mg/day was superior to propranolol 120–160 mg/day (60% improvement versus 52% improvement) in patients with mixed migraine and tension-type headache. Saper and colleagues[15] found fluoxetine 20–40 mg daily more effective than placebo in the last month of a three-month study in patients with chronic daily headache. Mood was improved earlier in the study than headache, and mood improved most in the patients who later reported reduced headache. The authors suggested that the influence of fluoxetine on headache was linked to its effect on mood. In a small study, Krymchantowski *et al.*[37] treated patients with chronic daily headache with amitriptyline or with a combination

of amitriptyline and fluoxetine. No difference could be detected between the treatments. To my knowledge there are no placebo-controlled trials with antidepressants for the other primary headache types or for headache in children.

Discussion

In spite of the extensive use of amitriptyline for the prophylactic treatment of migraine[3] there are only 3 placebo-controlled studies of low to moderate scientific quality to support this use. The reviewed trials indicate that amitriptyline has a prophylactic effect in migraine, but more studies are needed for final proof and for estimation of the size of this effect. Only two of five studies testing SSRIs in migraine reported superiority of active drug over placebo. Both these studies were difficult to interpret. Thus, at present, there is no evidence for an effect of SSRIs for the prophylactic treatment of migraine. However, SSRIs may be helpful in patients with comorbid depression because of their favourable side-effect profile. It is unknown whether other antidepressants, e.g., other tricyclics, other SSRIs or some of the newer antidepressants such as the serotonin/noradrenaline dual reuptake inhibitors may have an effect. There are not enough data to estimate the relative prophylactic effect of antidepressants compared with other prophylactic drugs for migraine.

In chronic tension-type headache, seven out of eight studies of tricyclic or tetracyclic antidepressants reported a significantly better effect with active drug than with placebo. Five out of six placebo-controlled studies found a significant effect for amitriptyline. The two most recent studies reported that headache index was reduced by 30% compared with placebo. The tricyclic antidepressant clomipramine has been found effective in one study and the tetracyclic antidepressants maprotiline and mianserin have been reported effective in one study each. One study found no effect of the SSRI citalopram. It can be concluded that amitriptyline has a statistically significant and a clinically relevant effect in the prophylactic treatment of chronic tension-type headache. However, the effect is of only moderate size. The other tetracyclic and tricyclic antidepressants may also be effective. The SSRIs seem to have no clinically relevant effect in non-depressed headache patients but should be considered in patients with comorbid depression. The newer antidepressants such as the serotonin/noradrenaline dual reuptake inhibitors have not been tested. Based on the present knowledge of chronic tension-type headache pathophysiology, it has been suggested that these drugs could have an effect.[38] Since more effective treatment modalities with less side effects are highly needed for patients with chronic tension-type headache, these drugs should be tested. The few studies conducted in patients with both migraine and tension-type headache indicate that tricyclic antidepressants are effective in these patients.

Compared with the vast number of patients investigated in controlled trials of acute migraine medications very few patients have been included in controlled prophylactic trials. More studies of higher quality are needed to define the exact role of antidepressants in headache prophylaxis and to address the many unanswered

questions, such as what are the optimal dosages? what is the long-term efficacy? and what is the efficacy of antidepressants relative to that of other prophylactic agents? It should be mandatory that future studies control for depression and mood changes and that they adhere as close as possible to IHS guidelines[6,7] and the CONSORT statement.[39]

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17 Antidepressants: mechanisms of action

E. Richelson

Antidepressants, particularly tricyclic antidepressants, are widely used for the prophylaxis of migraine headaches.[1] In fact, the tricyclic antidepressant amitriptyline is reported to be the second most prescribed antimigraine drug, with propranolol being the first.[1] In addition, amitriptyline is the only antidepressant for which there is consistent reports of efficacy for the prevention of migraine headaches,[2] although 11 other antidepressants have been recommended for use.[2] Interestingly, although their effects in the prophylaxis of migraine headaches appear to be unrelated to effects in treating depression, the general theoretical mechanisms of action involved in treating these two diseases are thought to be similar. That is, the down-regulation of certain receptors for serotonin (5-hydroxytryptamine or 5-HT) may play a role.[3,4] However, the serotonergic receptors that are down-regulated may be different for preventing migraine headaches than for treating depression.

This review will present data on the neurotransmitter transporter and neurotransmitter receptor blocking effects of the antidepressants that are recommended for prevention of migraine headaches.[2] This information, from preclinical studies, will show how these effects may relate to both their therapeutic and their adverse effects, as well as why some antidepressants are more likely than others to cause these effects.

Synaptic effects of antidepressants

Most of the effects of antidepressants in the body, whether therapeutic or adverse, occur at the level of the synapse. By either blocking transport of neurotransmitters or blocking certain neurotransmitter receptors, antidepressants alter the magnitude of the effects of neurotransmitters at certain synapses.

When the neurotransmitter binds to its postsynaptic receptor on the receiving neurone, this receptor is activated. However, neurones can also regulate their own activity by feedback mechanisms involving receptors called 'autoreceptors', which are present on their cell bodies and on terminals.[5] An example of an autoreceptor is the 5-HT_{1A} receptor on the somatodendritic region of the raphe nucleus serotonergic neurone. Activation of this autoreceptor, with the overflow of serotonin, inhibits the firing rate of action potentials of this neurone ('negative feedback loop').

For some biogenic amine neurotransmitters (for example, norepinephrine and serotonin), after release they are taken back into the nerve ending. This process is called 're-uptake', or 'transport'. Re-uptake occurs through transport proteins (transporters), which have been molecularly cloned from human and other species. This transport is a mechanism that prevents overstimulation of receptors in the synapse.

One mechanism of enhancing neurotransmission acutely (in the absence of any presynaptic negative feedback loops) is to block this transport with a drug. However, with chronic treatment, adaptive mechanisms occur that can affect this outcome. Specifically, desensitization, which is often followed by down-regulation, can occur with many types of receptors after chronic treatment with a transport blocker. As a result neurotransmission can ultimately be diminished (or be increased, if the desensitized and down-regulated receptors are inhibitory receptors).

Desensitization is the loss of sensitivity of the cell to the neurotransmitter and *down-regulation* is the loss of the receptor protein from the cellular surface. These processes may be the mechanisms of tolerance to certain drugs. In addition, it may explain the therapeutic effects, as well as the reversal of the side effects (e.g. gastrointestinal) of serotonin re-uptake inhibitors (SRIs). It is important to understand, however, that these adaptive mechanisms of receptors may not occur with all receptors and that a specific receptor may or may not adapt, depending upon the cell type in which it resides.

Nonetheless, antidepressants of many types acting by different mechanisms can desensitize certain receptors for catecholamines and serotonin. These effects, which can occur in the absence of down-regulation, are the bases of one hypothesis of their mechanism of action in treating depression.[5] On the other hand, the antidepressant mirtazapine may cause its therapeutic effects in treating depression by directly blocking presynaptic α_2-adrenoceptors, as well as some postsynaptic receptors (e.g. 5-HT_{2A}).[6]

By blocking a receptor with an antagonist, the effects of the neurotransmitter can be selectively and acutely abolished. Very often with chronic blockade, the receptor undergoes another type of compensatory change and becomes more sensitive (supersensitive) to the neurotransmitter. Supersensitivity may be the mechanism of adaptation to some receptor-related side effects of antidepressants and other drugs.

Possible mechanism of action of antidepressants in treating depression: focus on serotonergic neurones

The mechanisms of the therapeutic action of antidepressants in treating depression and migraine headaches remain uncertain. However, there are reasonable theories that can explain the time lag (up to six weeks) to the onset of therapeutic action of antidepressants in both treating depression and preventing migraine headaches.[5] While there is this time lag to the onset of therapeutic effects, side effects occur quickly. Some of these adverse effects can be explained by the acute synaptic affects of antidepressants, while the therapeutic effects can be explained by slow-to-develop adaptive mechanisms, namely, desensitization and, possibly, down-regulation of certain receptors.

Long before these receptor theories of the mechanism of action of antidepressants were proposed, studies on tricyclic antidepressants in the late 1950s and early 1960s strongly suggested that serotonin and norepinephrine played important roles in the mechanism of action of antidepressants. Because of this early evidence, researchers have performed animal studies focusing on the neurones in the brain that synthesize and release serotonin and norepinephrine.

Virtually all the neurones in brain that synthesize serotonin are located in the raphe nucleus. All the neurones that synthesize norepinephrine are localized either in the *locus coeruleus* or in the lateral ventral tegmental fields. Importantly, there is a reciprocal relationship between the noradrenergic neurones of the *locus coeruleus* and the serotonergic neurones of the raphe nucleus, because these neurones project to one another.[7]

On the surface of the serotonergic neurones are either autoreceptors for serotonin or heteroreceptors for other neurotransmitters, such as for norepinephrine. These different receptors are important because most are inhibitory. Somatodendritic autoreceptors inhibit the rate of firing of action potentials, and presynaptic autoreceptors inhibit the synthesis and release of serotonin. Additionally, there are presynaptic α_2-adrenergic heteroreceptors, that when activated by norepinephrine, inhibit the release of serotonin, while the somatodendritic α_1-adrenergic, heteroreceptors activate this neurone upon binding norepinephrine.

With acute treatment with an SRI, there is only a modest elevation of serotonin in the synapse, because of the negative feedback loops that prevent the accumulation of excessive amounts of serotonin in the synapse.[5] However, with chronic treatment with an SRI, changes occur that involve, first, desensitization and then down-regulation.[5] Thus, chronic treatment of animals with an SRI results in desensitization and down-regulation of serotonergic somatodendritic and presynaptic inhibitory autoreceptors. Since these receptors are inhibitory, as a result of removing the negative feedback loops by desensitization and down-regulation of these autoreceptors, there is a marked elevation in synaptic levels of serotonin in the continued presence of the uptake blockade.[5] Not all animal studies support this theory and it has not yet been shown to occur in humans.

Blockade of neurotransmitter transport by antidepressants (Table 17.1)

The vast majority of antidepressants used for treating migraine headaches block the transport of neurotransmitters back into the cells from which they were released. Most of these drugs are more potent at blocking transport of serotonin than transport of norepinephrine (Table 17.1).[8] Some antidepressants (e.g. mirtazapine) very weakly block transport of norepinephrine and serotonin. Paroxetine is the most potent blocker of serotonin transport (Table 17.1). Venlafaxine has been called a serotonin and norepinephrine re-uptake inhibitor based on animal data. However, it is much weaker at the human norepinephrine transporter than at the rat homolog. Therefore, at low dosages (likely below 200 mg/day) it mainly affects serotonin, while at high dosages (e.g. 375 mg/day), it has effects on the norepinephrine transporter.[9] Bupropion is devoid of direct serotonergic effects, because it is so weak at this transporter (Table 17.1).

Table 17.1 Affinities of antimigraine antidepressants for some human neurotransmitter transporters and receptors*

Drug	Affinities+					
	NET‡	SERT§	α_1-adrenergic	Histamine H_1	Muscarinic	5-HT_{2A}
Amitriptyline	2.9	23	3.7	91	**5.6**	3.4
Bupropion	0.0019	0.01	0.022	0.015	0.0021	0.0011
Doxepin	3.4	1.5	**4.2**	420	1.2	4
Fluvoxamine¶	0.077	45	0.013	0.00092	0.0042	0.018
Imipramine	2.7	71	1.1	9.1	1.1	1.3
Mirtazapine	0.021	0.0010	0.20	**700**	0.15	6.1
Nortriptyline	23	5.4	1.7	10	0.67	2.3
Paroxetine	2.5	**800**	0.029	0.0045	0.93	0.0052
Protriptyline	**71**	5.1	0.77	4	4.00	1.5
Sertraline	0.24	341	0.27	0.0042	0.16	0.010
Trazodone	0.012	0.63	2.8	0.29	0.00031	**13**
Venlafaxine	0.094	11	0	0	0	0
Reference compounds						
Desipramine	120	–	–	–	–	–
Clomipramine	–	360				
Diphenhydramine	–	–	–	7.1	–	–
Atropine	–	–	–	–	42	–
Phentolamine	–	–	6.7	–	–	–
Methysergide	–	–		–	–	14

*Data from refs 8,10,11,12 and unpublished data of E. Richelson.
+10^{-7} x $1/K_d$, where K_d = equilibrium dissociation constant in molarity
‡Norepinephrine transporter
§Serotonin transporter
¶Not marketed in the United States as an antidepressant.
Data can be compared both vertically and across the table to find the most potent drug for a specific property and to find the most potent property for a specific drug. The bolded numbers highlight the most potent value for a given property.

Blockade of neurotransmitter receptors by antidepressants (Table 17.1)[10–12]

Most of the newer generation antidepressants are weaker than the older compounds (especially tricyclic antidepressants) at blocking receptors for neurotransmitters. This fact predicts a side effect profile for these newer compounds different from and more favorable than that for older drugs.

At the α_1-adrenoceptor (Table 17.1), the most potent compounds (mainly older generation tricyclic antidepressants), although a little weaker than the antihypertensive drug phentolamine, are likely to have effects clinically at these receptors (Table 17.2). Overall, as receptor blockers, the most potent interaction of antidepressants, especially the classical tricyclic drugs, is at the histamine H_1 receptor (Table 17.1). Some antidepressants are exceedingly potent histamine H_1 antagonists (Table 17.1).

The next most potent receptor blocking effect that is of certain clinical relevance is at the muscarinic acetylcholine receptor. Antidepressants have a broad range of affinities for human brain muscarinic receptors (Table 17.1). The most potent is amitriptyline, which is the most commonly used antidepressant to treat migraine.[1] The SRI paroxetine is unique among the newer compounds for having appreciable antimuscarinic potency, similar to that for imipramine (Table 17.1). Antidepressants also antagonize the 5-HT_{2A} receptor, which may be important for the prevention of migraine headaches. However, few of the drugs in Table 17.1 are potent at blocking this receptor.

Clinical importance of the acute synaptic effects of antidepressants

Blockade of transporters and receptors by antidepressants occurs shortly after a patient has ingested a dose of the medication. Thus, most of the possible clinical effects to be discussed below occur early in the treatment of patients. However, with chronic administration of the drug, adaptive changes may occur. These changes can result in an adjustment to certain side effects, the development of new side effects, and the onset of therapeutic effects. Table 17.2 lists the pharmacological properties and their possible clinical consequences. The reader should keep in mind that, as a first approximation, the drugs that are most potent at the properties discussed (Table 17.1), are more likely to cause these possible effects than the drugs that are weak at these properties.

Although transporter blockade may be related to the mechanism of therapeutic effects of antidepressants in treating depression (Table 17.2), evidence to date suggests otherwise. Specifically, there appears to be no difference in clinical efficacy of antidepressants,[13] while there is a broad range of potencies of antidepressants at blocking this transport (Table 17.1). Blockade of neurotransmitter transport likely relates to certain adverse effects of these antidepressant drugs and to some of their drug interactions (Table 17.2). For example, serotonin transport blockade is the property that causes sexual side effects, seen more commonly with the SRIs than other types of antidepressants.

Table 17.2 Synaptic effects of antidepressants and their possible clinical consequences

Property	Possible clinical consequences
Blockade of norepinephrine transport at nerve endings	◆ Alleviation of depression ◆ Tremors ◆ Tachycardia ◆ Erectile and ejaculatory dysfunction ◆ Blockade of the antihypertensive effects of guanethidine and guanadrel ◆ Augmentation of pressor effects of sympathomimetic amines
Blockade of serotonin transport at nerve endings	◆ Alleviation of depression ◆ Gastrointestinal disturbances ◆ Increase or decrease in anxiety (dose-dependent) ◆ Sexual dysfunction ◆ Extrapyramidal side effects ◆ Interactions with L-tryptophan and monoamine oxidase inhibitors (serotonergic syndrome) ◆ Potentiation of central depressant drugs
Blockade of histamine H_1 receptors	◆ Sedation drowsiness ◆ Weight gain
Blockade of muscarinic receptors	◆ Blurred vision ◆ Dry mouth ◆ Sinus tachycardia ◆ Constipation ◆ Urinary retention ◆ Memory dysfunction ◆ Potentiation of the antihypertensives that block these receptors (e.g. prazosin, terazosin, doxazosin, labetalol)
Blockade of α_1-adrenoceptors	◆ Postural hypotension, dizziness ◆ Reflex tachycardia ◆ Alleviation of depression ◆ Reduction of anxiety ◆ Promotion of deep sleep ◆ Prevention of migraine headaches
Blockade of serotonin 5-HT_{2A} receptors	◆ Alleviation of psychosis ◆ Alleviation or prevention of sexual side effects of SRIs

Serotonin transport blockade is also the property that causes the serious clinical syndrome when a monoamine oxidase inhibitor is combined with an antidepressant that blocks the transport of serotonin (serotonergic syndrome).[14] In addition, researchers have reported adverse interactions between L-tryptophan, the precursor of serotonin, and fluoxetine.[15]

Much more rarely, SRIs can also cause extrapyramidal side effects.[16] Their extrapyramidal side effects are not due to blockade of dopamine receptors, because these SRIs are very weak at this binding site. Instead, it is likely due to increased synaptic levels of serotonin, mediating inhibition of release of dopamine through one of the serotonin receptor subtypes.[16]

α_1-Adrenergic receptor blockade by antidepressants may be responsible for orthostatic hypotension, a most serious, common cardiovascular effect of these drugs.[17] This side effect can cause dizziness and a reflex tachycardia. In addition, this property of antidepressants will result in the potentiation of several antihypertensive drugs that potently block α_1-adrenoceptors (Table 17.2).

Potentiation of the effects of central depressant drugs, which cause sedation and drowsiness, is a pharmacodynamic drug interaction of antidepressants related to histamine H_1 receptor antagonism. This antagonism is probably responsible for the side effects of sedation and drowsiness. Sedation, however, may be a wanted effect in patients who are agitated and also depressed. This property also may be responsible for weight gain.

Although blockade of muscarinic receptors may be related to therapeutic effects, more likely this receptor blockade by some antidepressants is responsible for several adverse effects (Table 17.2). The relatively high affinity of paroxetine for these receptors, distinguishes it from the other, newer, compounds. In addition, it may explain the common complaint of dry mouth and constipation reported in some published clinical trials with paroxetine.[18] We need to be especially cautious in the use of these drugs with the elderly patient, so we avoid or reduce these antimuscarinic effects of antidepressants.

Some antidepressants also block 5-HT_{2A} receptors (Table 17.1). Blockade of 5-HT_{2A} receptors may be a mechanism for both treating depression and preventing migraine headaches. Activation of 5-HT_{2A} receptors may cause anxiety, sleep disturbances, and sexual dysfunction. Therefore, blockade of these receptors may reduce anxiety, promote deep sleep, prevent migraine headaches, and alleviate depression. Antidepressants that are relatively potent at this receptor (Table 17.1) are not likely to cause the types of sexual side effects seen with SRIs.[19] These drugs could, potentially, be used either in combination with an SRI to reduce SRI-induced sexual side effects, or as an alternative antidepressant medication in patients, who had intolerable sexual side effects from an SRI.[19,20]

Conclusions

Reviewing the data on the synaptic effects of the antidepressants that are used to prevent migraine headaches (Table 17.1), one can only conclude that there is

nothing in common with all these drugs that might suggest its mechanism of action in preventing migraine headaches. This is no different from our thinking about their mechanism of action in treating depression, which remains uncertain. However, knowledge of their synaptic effects and how they relate to certain adverse effects and certain drug interactions can help the clinician minimize or avoid these problems in patients being treated for the prevention of migraine headaches.

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18 Other prophylactic anti-migraine agents: riboflavin, feverfew, magnesium, Botulinum toxin, and calcium antagonists

J. Schoenen, L. Di Clemente, and G. Coppola

Introduction

There are two major shortcomings with prophylactic therapies in migraine. The first is that the average efficacy rate of any prophylactic agent does not exceed 50%, the second that most prophylactic drugs are associated with uncomfortable and sometimes intolerable adverse effects. It is therefore of clinical interest that several treatments almost devoid of adverse effects are available for migraine prophylaxis. These are riboflavin, feverfew, magnesium salts, and Botulinum toxin. Some of them are widely used in certain countries despite lacking scientific evidence of efficacy, others have been proven efficacious, but are not considered seriously or not used adequately in migraine. In this article, we will review published data for all these treatments and examine the case of certain calcium antagonists that remain controversial. We will focus for efficacy data on 50% responder rates in absolute and placebo-subtracted values and compare the data with those published in a recent trial for slow release propranolol 160 mg[1] and for valproate,[2] two mainstays of preventive anti-migraine treatment.

A critical analysis of two recent publications on prophylactic treatments in migraine, the recommendations made by the US Headache Consortium[3] and a review article in the New England Journal of Medicine,[4] shows that it is most difficult to propose treatment recommendations solely based on scientific evidence. The US Headache Consortium recommends amitriptyline as a first choice drug for

migraine prophylaxis, although none of the three trials published hitherto is of sufficient methodological quality or provides unequivocal evidence of efficacy for this drug. In the same US recommendations, the positioning of metoprolol as second choice among beta-blockers, behind propranolol and timolol, is also not based on evidence. The US Headache Consortium recommends verapamil as a second choice side by side with metoprolol, whereas Goadsby *et al.* (2002) dismiss verapamil as a drug without proven evidence of benefit. In the latter review, most of the drugs that will be considered in this article, are not even mentioned in summary Table 3 of preventive treatments in migraine. It seems clear therefore that these two sets of recommendations are not only based on trial evidence, but also on clinical experience and thus personal preferences. By the same token, we will mention in the present review our clinical experience as a complement to the evidence coming from randomized controlled trials.

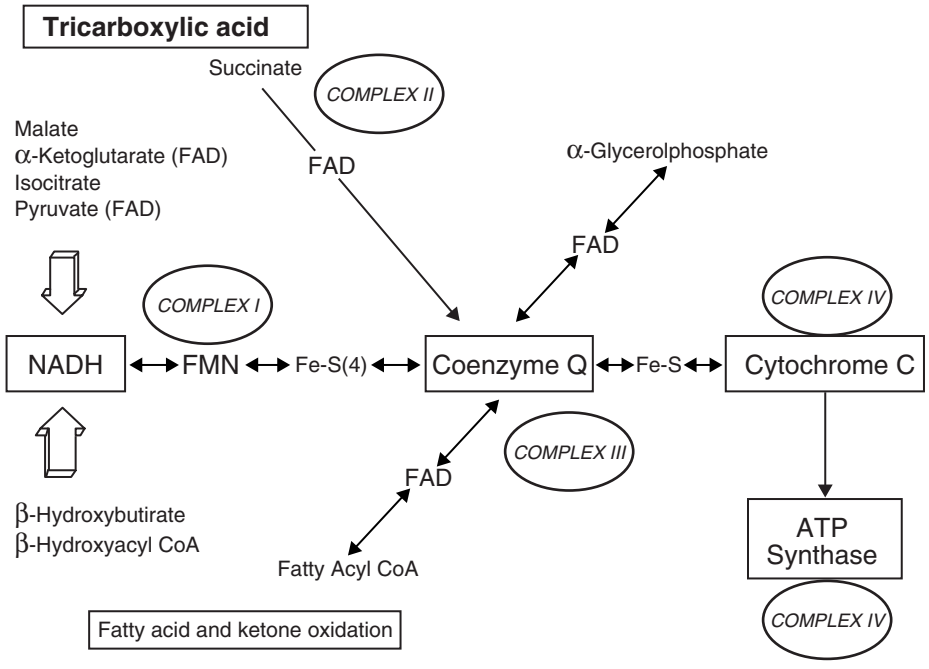
Riboflavin

Rationale

The rationale for using high-dose riboflavin in migraine prophylaxis comes from the observation made by two independent groups[5–7] that on ^{31}P magnetic resonance spectroscopy the mitochondrial phosphorylation potential, i.e. the energy reserve, is reduced by 25–30% interictally in the brain of migraineurs with or without aura. Riboflavin (vitamin B_2) is the precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the activity of flavoenzymes involved in the electron transport chain (Fig. 18.1). Given to patients with MELAS or mitochondrial myopathies on the assumption that at large doses (300 mg/d in children) it might augment the activity of mitochondrial complexes I and II, riboflavin was able to improve clinical and biochemical abnormalities (see ref 8 for a review). After a positive open pilot study,[9] we embarked therefore in a placebo-controlled randomized parallel group trial under the auspices of the Belgian Headache Society.[10] More recently, alternative mechanisms of action for the effects of riboflavin in migraine have been discussed. Riboflavin may indeed counteract inhibition of mitochondrial respiration by NO.[11] It may also act as a precursor in the biosynthesis of vitamin B_{12} which, administered as intranasal hydroxycobalamin, was found effective as a preventive treatment of migraine in an open pilot trial.[12] Riboflavin can also act as a reactive oxygen species scavenger and it can stimulate the activity of methylenetetrahydrofolate reductase, the metabolizing enzyme of homocysteine. Another interaction between riboflavin and NO could be the flavin domain in the NOS gene. Finally, an anti-nociceptive effect was recently found for several B vitamins, including vitamin B_2, in an animal model of chemonociception.[13]

Trial evidence

The Belgian riboflavin trial included 27 patients in the placebo arm and 28 patients in the riboflavin (400 mg once per day) arm. Randomization took place after a 1-month single blind placebo run-in. After 3 months of treatment with riboflavin, the 50%



Mitochondrial electron transport chain (FMN : flavin mononucleaotide : FAD : flavin adenin dinucleotide)

Fig. 18.1 Outline of the mitochondrial electron transport chain and the potential impact of riboflavin at the level of complex I (via flavin mononucleotide-FMN) and complex II (via flavin adenin dinucleotide-FAD). Note that FAD is also a co-factor for methylene-tetrahydrofolate reductase, the metabolizing enzyme of homocysteine.

responder rate for reduction in attack frequency was 56% (NNT : 2.8), for migraine days 59% (NNT : 2.3), and for a migraine index (headache days + mean severity) 41% (NNT : 3.1) compared with respective placebo responses of 19%, 15%, and 8%. The placebo-subtracted 50% responder rate for riboflavin was 37%, which compares favourably with the 23% reported in the valproate trial by Klapper *et al.* (1997) (Fig. 18.2).

Only three adverse events were recorded during the trial. One woman in the riboflavin group had diarrhoea 2 weeks after starting the drug and withdrew from the study. On follow-up, her symptoms disappeared within 72 hours. Another patient receiving riboflavin complained of polyuria but completed the trial. In the placebo group, one patient mentioned recurrent abdominal cramps of moderate intensity but did not interrupt the trial. Comparing riboflavin with placebo, the number of patients needed to treat for adverse effect was 33.3 which again compares favourably with valproate for which the number-needed-to-harm is around 2.4.

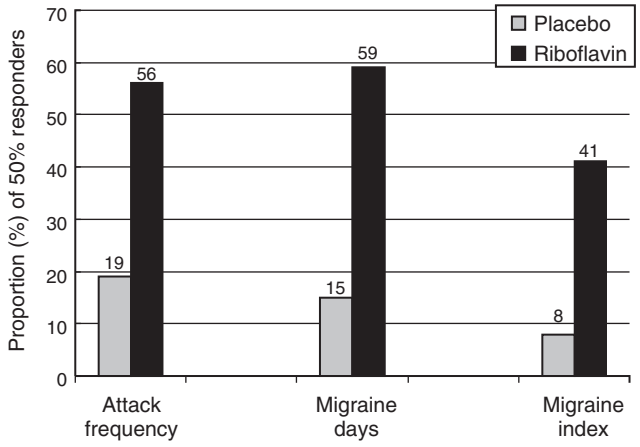


Fig. 18.2 Percentage of 50% responders for attack frequency, headache days, and migraine index (mean severity + headache days) as assessed in the 3rd month of randomization period in riboflavin (400 mg/d) and placebo groups. Numbers-needed-to-treat are indicated.

Clinical experience

In the above-described trial and in clinical experience in over 800 patients, it is obvious that riboflavin has a slow onset of action. The maximal effect on attack frequency does not occur before the 3rd month of treatment. It can therefore be considered as a first choice drug only in moderately disabled patients with a low attack frequency (below 4–5 attacks/month) and not in severe or chronic migraine. Because of its excellent efficacy/adverse effect profile, riboflavin should be considered as a first line preventive drug in childhood migraine. As no teratogenic effects are known for riboflavin, it can also be given during pregnancy, if migraine prophylaxis is warranted. Our clinical impression is that riboflavin may be more effective in migraine with aura, although this could be biased because of the average lower attack frequency compared with migraine without aura. Association of riboflavin with other prophylactic agents, such as beta-blockers, may allow keeping the latter at a dose low enough to avoid side effects. Proper studies of these two aspects are underway.

Adverse events are extremely rare with riboflavin at 400 mg per day. 1% of patients have gastro-intestinal intolerance. We have encountered in one patient an allergic cutaneous rash, which disappeared after withdrawal and recurred after rechallenging the patient with riboflavin. An important difference with most anti-migraine prophylactic drugs is that riboflavin does not induce weight gain. We have shown that riboflavin does not influence habituation of cortical evoked potentials, contrary to beta-blockers which tend to normalize the deficient habituation found interictally in migraineurs.[14]

The beneficial results obtained with riboflavin have initiated trials with other drugs acting on energy metabolism. Positive results were reported in pilot studies of thioctic acid (alpha-lipoate) or coenzyme Q10. Controlled trials with these drugs are underway.

Feverfew (Tanacetum parthenium)

Rationale

Feverfew has been known for its headache relieving potential since medieval times.[15] It has various biological actions. It inhibits interaction of platelets with collagen substrates and 5-HT release,[16] prostaglandin synthesis, and NF-κβ. Its main sesquiterpene lactone, parthenolide, may be a non-specific norepinephrine, serotonin, bradykinin, prostaglandin, and acetylcholine antagonist.

Trial evidence

A review of five randomized controlled trials of feverfew on small samples of patients by Vogler *et al.* (1998) concluded that the clinical efficacy of feverfew in the prevention of migraine had not been established beyond reasonable doubt.[17]

A large, phase II, multicentre, randomized, placebo-controlled study of 3 doses of a CO_2 extract of tanacetum parthenium (Mig-99°) (2.08, 6.25, 18.75 mg t.i.d) was published recently.[18] Only the 6.25 mg t.i.d dose was found to have some efficacy. The 50% responder rate for attack frequency was 27.8% in a sample of 36 patients (Fig. 18.3), but, because of a high placebo response, the placebo-subtracted 50% responder rate was negative (−3.6%). Interestingly, it was decided in the protocol of this study that a subanalysis would be performed on the subset of patients with at least 4 attacks per 28 days during the baseline period. In this 'confirmatory' intention-to-treat sample of 49 patients, the decrease in attack frequency was significant in the 6.25 mg t.i.d group (=19) (−1.8±1.5) compared to the placebo group (−0.3±1.9). The 50% responder rate was 36.8% in the 6.25 mg t.i.d group compared to 15.4% in the placebo group (Table 18.1).

Table 18.1 Sub-analysis of 49 patients having at least 4 migraine attacks during the 1-month baseline before randomization. The amelioration with the 6.25 mg t.i.d. dose is significant

Confirmatory ITT sample (Pfaffenrath *et al.* 2002) *N*=49 patients with ≥4 attacks during baseline				
	FF 2.08 mg t.i.d. (*n*=9)	FF 6.25 mg t.i.d. (*n*=19)	FF 18.75 mg t.i.d. (*n*=8)	Placebo (*n*=13)
Absolute change in attack frequency	−0.2±1.1	−1.8±1.5*	−1.5±1.9	−0.3±1.9
50% responder rate	0	36.8%	37.5%	15.4%

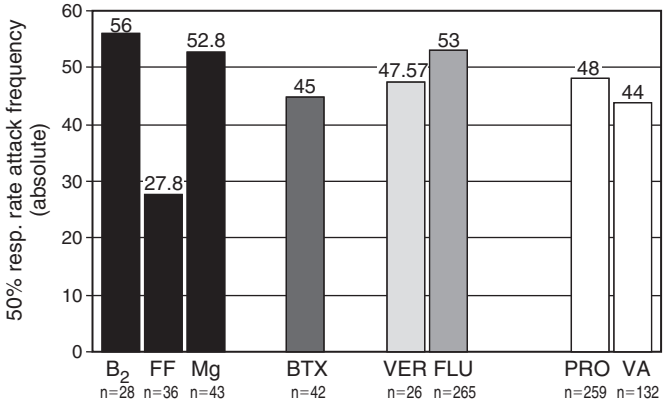


Fig. 18.3 50% responder rates for attack frequency (absolute values) for the riboflavin (B_2), feverfew (FF), magnesium (Mg), botulinum toxin (BTX), verapamil (VER), flunarizine (FLU), propranolol (PRO), and valproate (VA) trials discussed in this chapter. The number of patients in the active arm of each trial is indicated.

Clinical experience

We have no personal experience with feverfew. From the above-mentioned study, feverfew may have an inversed U-shaped dose–response curve. As mentioned, marketed preparations of feverfew contain varying concentrations of parthenolides. It is worth mentioning that a phase III RCT with Mig-99° has just been completed and that it has apparently yielded positive results.

Adverse effects with feverfew are rare, but not inexistent. The most frequent are mouth ulcerations and oral inflammation with loss of taste.

Magnesium

Rationale

Low brain magnesium levels have been detected with ^{31}P magnetic resonance spectroscopy during migraine attacks[19] and interictally in migraine with aura.[20] Between attacks, low magnesium levels were also found in various other biological samples, such as erythrocytes, monocytes, serum, saliva, and cerebrospinal fluid.[21–25] Magnesium is essential for energy metabolism and decreases neuronal excitability via blocking of NMDA receptors, decreases of intracellular calcium, and activation of Na^+/K^+ATPase.[26]

Trial evidence

Two double-blind placebo-controlled studies in parallel groups of patients have been performed in German-speaking countries. One study using a drinkable aspartate

salt of magnesium (20 mmol) was prematurely interrupted after inclusion of 69 patients because of lack of efficacy.[27] In the other trial magnesium dicitrate was used at a 24 mmol dose in 81 patients, 43 receiving the magnesium preparation. In this study,[28] the 50% responder rate for attack frequency was 52.8% (Fig. 18.3) which is well in the range of responder rates reported for propranolol and valproate, but the placebo-subtracted 50% responder rate was only 18.4% which is below that estimated for the classical anti-migraine prophylactics.

Clinical experience

Our clinical experience with high-dose magnesium (450 mg Mg element b.i.d.) in migraine prophylaxis is limited, but we did not find it useful as a monotherapy. Moreover, several patients complained of gastro-intestinal intolerance. In the published trials, diarrhoea occurred in ± 20% of patients and gastric irritation in ± 12%. It remains to be shown that combination of high-dose magnesium with other prophylactic agents may be beneficial, for example in constipated migraineurs.

Botulinum toxin

Rationale

There was no clear rationale for using botulinum toxin type A (Botox®) in migraine prophylaxis, besides the serendipitous observations that certain subjects treated with Botox® for other indications had improvement of their migraine. Botox® inhibits motor and non-motor cholinergic neurones, and thus reduces muscle hyperactivity and spasm, which was the original rationale for its use in tension-type headache. Botulinum toxin type A reduces pain associated with cervical dystonia, achalasia, and rectal fissures.[29] Interestingly, novel experimental data presented at this meeting show that Botox® is able to reduce sensitization of peripheral nociceptors in animal models of pain and hence secondary central sensitization.

Trial evidence

Up to now, the only positive randomized controlled study for botulinum toxin type A in migraine prophylaxis is the one published by Silberstein *et al.* (2000). In this study, 25 units and 75 units of Botox® were compared to vehicle at 9 injection sites spread over the frontal and glabellar region as well as bilateral injections in the temporal region. While there was no difference between the 75U dose and vehicle, 45% of patients (n=42) had at least a 50% reduction in attack frequency with the 25U total dose (Fig. 18.3). The placebo-subtracted 50% responder rate was 21%.

Clinical experience

Botulinum toxin may be useful at certain doses in some groups of migraine patients, but the results of large placebo-controlled randomized trials are eagerly awaited.

An inverse U-shaped dose–response curve may exist. It remains to be demonstrated that individualizing the Botox® injections to each patient, taking into account pericranial tender spots and performing more superficial injections, are more efficient than the standardized injection protocol used in the study by Silberstein *et al.* (2000).

Adverse events occurring with Botox® injections are rare and benign. Mild reversible ptosis may occur.

Calcium antagonist

Flunarizine

Rationale

Flunarizine has calcium channel blocking and anti-hypoxic properties.[30] It enhances the threshold for spreading depression,[31] but it has also an anti-dopaminergic, anti-serotonergic, and anti-histaminic action.[32,33] It was originally developed for the treatment of vertigo[34] and introduced in migraineurs on the basis of the hypoxia theory of migraine pathogenesis.

Trial evidence

There have been 8 double-blind placebo-controlled studies of flunarizine, most of them with the 10 mg dose, 4 comparative studies with pizotifen, 4 with propranolol and 2 with metoprolol. These studies were reviewed in detail by Diener (2000).[35] Recently, a large double-blind comparative trial of flunarizine 5 and 10 mg with slow release propranolol 160 mg was published in Cephalalgia.[1] In this study, which lacks a placebo-controlled group, the 50% responder rate for attack frequency in the flunarizine 10 mg arm ($n=265$) was 53%, compared to 48% in the propranolol arm ($n=259$).

Clinical experience

There is no doubt that flunarizine is an effective drug in migraine prophylaxis. Its efficacy is comparable or superior to most of the other prophylactic agents. Unfortunately, flunarizine induces a number of intolerable adverse effects. The most common are fatigue and weight gain. Moreover, in our experience depressive mood is a frequent adverse effect in migraine patients. This occurs chiefly in migraineurs with a personal or family history of depression but also in other patients. The high prevalence of this side effect, which may be related to the known comorbidity between migraine and depression, is the reason why flunarizine is not 1st nor 2nd choice anymore for migraine prophylaxis in our practice.

Low doses of flunarizine (2.5 mg/day) may be better tolerated, but in our experience they are also less efficient. Flunarizine at the 5 mg dose may be better tolerated in children. We have not encountered a single case of extrapyramidal symptoms induced by flunarizine in our migraine population, whereas these adverse effects are frequent in elderly patients.

Verapamil

Rationale

As mentioned above, verapamil is considered to be a very useful drug in migraine prophylaxis in the US,[3] while it generally receives little consideration in European review articles.[4] Since verapamil is known for its vasodilator properties, its use in migraine is a consequence of the 'vascular' theory of migraine pathogenesis as popularized by H. Wolff : 'initial cerebral vasoconstriction is responsible for the migraine aura, while secondary vasodilatation causes the headache'.[36] As a phenylalkylamine L-type calcium channel blocker, verapamil is able to produce vasodilatation and to inhibit arterial vasospasm, but it is also capable of blocking serotonin release and aggregation of platelets.[37] More recently, it was shown in addition that verapamil can inhibit dopamine release via P-type and, at high concentration, Q-type calcium channel blocking.[38]

Trial evidence

There are only two double-blind studies of verapamil comparing it to placebo in a crossover fashion. In the first study by Solomon *et al.*[36] performed in 12 patients (7 without, 5 with aura), there was a 49% reduction of the attack frequency in the verapamil period (80 mg q.i.d) compared to the placebo period. The effect was already apparent in month 1 without further gain in month 3.

Markley *et al.* (1984)[39] included 14 patients (6 without, 8 with aura) and reported a 56% improvement in the verapamil period of 2 months (80 mg t.i.d.) compared to placebo. In this study, baseline monthly headache frequency was rather high (13.6 for placebo, 11.2 for verapamil) suggesting that interval headaches were included in the assessment.

It is not fair, as in certain review articles, to cite a high drop-out rate in disfavour of verapamil, since most drop-outs occurred during the placebo period (7 in the first, 4 in the second study) and not in the verapamil period (4 in the first, 2 in the second study).

Clinical experience

Although the efficacy of verapamil in migraine prophylaxis is not proven by large randomized controlled trials, clinical experience suggests that it is a useful drug in migraine management. It is our clinical impression that verapamil might be more efficient in patients suffering from migraine attacks associated with ipsilateral autonomic facial signs, which may be related to the fact that verapamil is the most efficient prophylactic agent in cluster headache. Adverse effects are frequent with verapamil, especially fatigue, constipation, leg oedema, and sometimes hypotension.

Other calcium antagonists

Evidence of efficacy in migraine prophylaxis for other calcium antagonists is missing. Contrasting results have been reported for *nimodipine* which is likely to be ineffective in migraine. *Nifedipine* has also provided ambiguous results and is

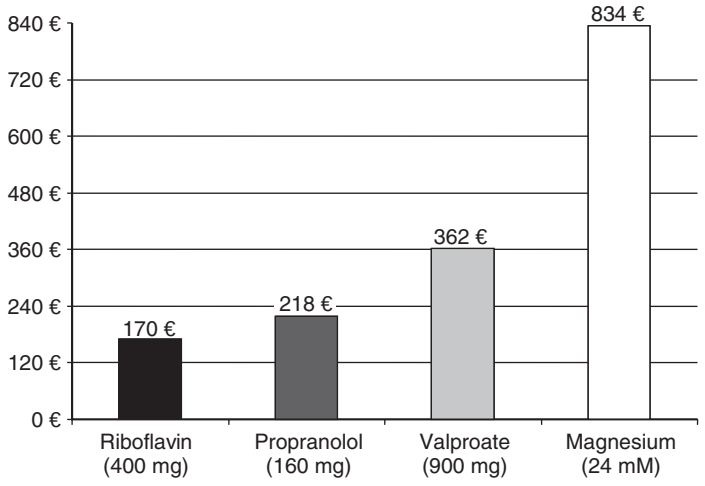


Fig. 18.4 Cost effectiveness of prophylactic anti-migraine drugs as estimated by the ratio of cost in Belgium for a 6-month treatment (in euros) over the placebo-subtracted 50% responder rate for attack frequency.

probably not useful. Only 2 small open studies which are not conclusive are available for *diltiazem*. *Cyclandelate* which has also anti-serotonergic properties, has shown marginal efficacy in some placebo-controlled and comparative trials.

Conclusions

Certain prophylactic anti-migraine drugs quasi devoid of adverse effects may have comparable efficacy to the classical anti-migraine prophylactics with accepted efficacy but known high incidence of side effects, such as beta-blockers or valproate. This is mainly the case for high-dose riboflavin and probably for feverfew, as well as to a lesser extent for magnesium. At present riboflavin seems to have the best efficacy as well as the best cost-effectiveness profile (Fig. 18.4). Further large controlled studies are however needed for these three drugs in order to obtain smaller confidence intervals in outcome measures, and to show convincingly their usefulness in migraine prophylaxis (Fig. 18.5). From their present use, it is clear that their onset of action is slow and that their potential benefit is chiefly for the less severely disabled migraineurs. Because of their favourable efficacy–side effect profile, they may be first choice drugs in childhood migraine.

Botulinum toxin A may be an interesting option in migraine prophylaxis for some patients, but definitive proof of its efficacy in migraine is still lacking. Among the calcium channel blockers, flunarizine stands out for its proven high efficacy in multiple trials. Unfortunately, it frequently induces adverse effects such as weight

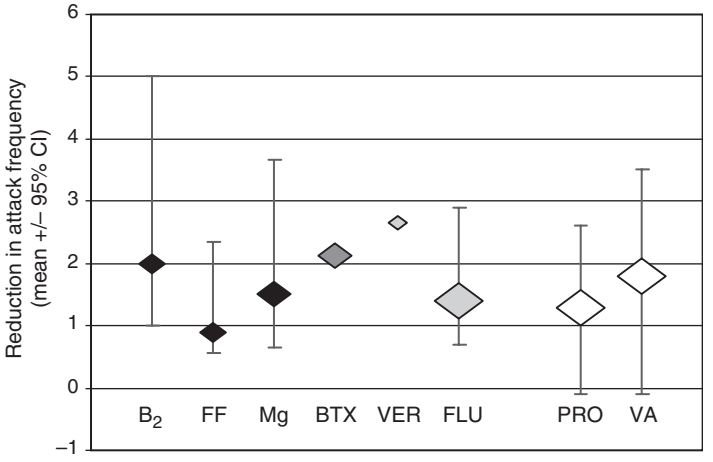


Fig. 18.5 Absolute reduction in monthly attack frequency (means and, when available, 95% confidence intervals) for the various drugs discussed here. Note that the symbol size is proportional to the number of patients included in each trial.

gain and depressive mood which limit its utility. Verapamil seems to be the only other calcium channel blocker which is useful in migraine prophylaxis, although large controlled trials are still missing.

To conclude, Fig. 18.5 clearly suggests that taken together, available drugs only induce a moderate decrease in migraine attack frequency, which underlines the need for more efficient anti-migraine prophylactic treatments.

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19 Treatment of chronic tension-type headache with mirtazapine

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Abstract

Mirtazapine is a novel antidepressant which acts by enhancing noradrenergic and serotonergic neurotransmission via blockade of α-adrenoceptors. Evidence-based studies have shown that overall antidepressants may have an antinociceptive effect in chronic pain. These studies also strongly suggested that serotonergic–noradrenergic antidepressants may have a more consistent antinociceptive effect than the serotonergic antidepressants. In this clinical trial we examined the efficacy of mirtazapine, 30 mg/day, in the treatment of chronic tension-type headache comorbid with major depression in 22 patients by using Visual Analogue Scale(VAS), Hamilton Rating Scale of Depression(HAMD), and Clinical Global Impression Scale(CGI). VAS scores for headache showed significant decrease as early as a week after the start of treatment with mirtazapine. HAMD scores and CGI scores also reached statistical significance from the first month of treatment. Although sedation and weight gain were the most seen side effects, all of the patients except one could tolerate these. In this study, although mirtazapine treated both headache and depression successfully, there was no correlation between the analgesic response and antidepressant response to mirtazapine. This finding supports the idea that analgesic effects of antidepressants might be independent from their effect on depression. This study suggests that mirtazapine is an effective and well tolerated treatment in the treatment of chronic tension-type headache and depression.

Treatment of chronic tension-type headache with mirtazapine

Mirtazapine is a novel antidepressant which acts by enhancing noradrenergic and serotonergic neurotransmission via blockade of α-adrenoceptors.[1,2] It has a significant

advantage even compared with amitriptyline in treatment of depression.[3] Evidence-based studies have shown that overall antidepressants may have an antinociceptive effect in chronic pain. These studies also strongly suggested that serotonergic–noradrenergic antidepressants may have a more consistent antinociceptive effect than the serotonergic antidepressants.[4,5] Antidepressants should have an independent mode of action in chronic pain and the analgesic response seems to come into action much faster than the antidepressant response.[6] There is no study on the therapeutic effect of mirtazapin on headache disorders except a case report on migraine.[2] In this clinical trial we examined the efficacy of mirtazapine in the treatment of chronic tension-type headache comorbid with major depression.

Patients and methods

Twenty-six patients were recruited from the headache outpatient department of the neurology department with the approval of the hospital ethical committee. All patients gave informed consent to participate in the study. All psychological evaluations were done in the department of psychiatry as well as follow-ups of the patients. Inclusion criteria were: age older than 18 years, having both chronic tension-type headache (IHS 1988 criteria) and major depressive disorder (DSM-IV and HAMD-17 $\geq$ 14). Exclusion criteria were: previous failed treatment with mirtazapine; participation in any investigative drug study in the previous month; significant renal or hepatic dysfunction; epilepsy; women who were pregnant or breastfeeding; women of childbearing potential who were sexually active and not using medically accepted means of contraception. The Visual Analogue Scale (VAS, for headache), Hamilton Rating Scale of Depression (HAMD-17, for depression), and the Clinical Global Impression Scale (CGI) were used to assess efficacy. VAS was used in the baseline, 1st, 4th, and 8th weeks of the treatment. HAMD-17 and CGI were used in the baseline, 4th and 8th weeks of the treatment. Mirtazapine (REMERON, Organon) was used in flexible dosing between 15 mg/day and 45 mg/day with a starting dose of 30 mg/day. Tolerability was assessed by registering treatment-emergent adverse events. Results were compared by repeated measures of analysis of variance. To assess the effects of mirtazapine on headache, statistical comparisons of VAS scores were done between (a) baseline and 1st week, (b) baseline and 4th week, and (c) baseline and 8th week. To assess the changes in depression, comparisons of HAMD-17 scores and comparisons of CGI scores were done between (a) baseline and 4th week, and (b) baseline and 8th week. To determine any correlation between changes in headache (via VAS scores) and depression (via Hamilton scores), the differences of VAS scores and HAMD-17 scores between the steps (baseline and 4th week; baseline and 8th week; 4th week and 8th week) were subjected to correlation analysis.

Results

Of 26 patients, one could not tolerate the side effects of mirtazapine and dropped out and 3 did not have the regular follow-ups. Twenty-two of the patients completed

the study. Of 22 patients, 19 were women and 3 were men. Mean age was 37.9 ± 11.6 (20–67) years. All 22 patients started with mirtazapine, 30 mg/day. In one patient the dose was lowered to 15 mg/day from 1st to 4th week and then raised back to 30 mg/day. Most frequent side effects in the 1st week were **sedation** (7 of 22 patients) and **weight gain** (3 of 22) (from **68** ± 13 kg at **1st** week to **71** ± 12 kg at **8th** week). The other side effects were dry mouth (1 of 22), and stomach ache (1 of 22). There was no significant change in blood pressure and heart rate from baseline to 8th week. The VAS, HAMD-17, and CGI scores are shown in Table 19.1. *p* values of the comparisons are shown in Table 19.2. Compared to baseline values, VAS scores showed a statistically significant decrease beginning from the 1st week (Table 19.2). From baseline to 4th and 8th weeks, decrease in the HAMD-17 and CGI scores also reached statistical significance (Table 19.2). There was no correlation between the changes in VAS scores and the Hamilton scores in regression analysis (from 0 to 4th week $p = 0.108$; from 0 to 8th week $p = 0.166$; from 4th to 8th week $p = 0.632$).

Conclusion

In this study, VAS scores for headache showed significant decrease as early as a week after the start of treatment with mirtazapine. HAMD scores and CGI scores also reached statistical significance from the first month of treatment.

Table 19.1 VAS, HAMD-17, and CGI scores (mean value ± standard deviation; minimum and maximum)

Weeks	0	1st	4th	8th
VAS *headache*	**8.9** ± 1.6 (5–10)	**7.6** ± 2.0 (3–10)	**5.9** ± 3.1 (0–10)	**4.9** ± 2.8 (0–10)
Hamilton depression	22.2 ± 5.2 (11–30)	×	12.2 ± 4.8 (0–21)	**8.6** ± 7.3 (2–31)
CGI	**4.9** ± 0.7 (3–5)	×	**3.3** ± 0.9 (1–5)	**2.6** ± 0.9 (1–4)

Table 19.2 *P* values of Paired *t*-test between the visits

Weeks	0–1st	0–4th	0–8th
VAS	0.001*	0.001*	<0.001*
Hamilton	×	<0.001*	<0.001*
CGI	×	<0.001*	0.001*

* statistically significant difference.
× no comparison.

Although sedation and weight gain were the most seen side effects, all patients except one could tolerate these. In this study, although mirtazapine treated both headache and depression successfully, there was no correlation between the analgesic response and antidepressant response to mirtazapine. This finding supports the idea that analgesic effects of antidepressants might be independent from their effect on depression. This study suggests that mirtazapine is an effective and well tolerated treatment in the treatment of chronic tension-type headache and depression. This is a novel study that supports the therapeutic effect of mirtazapine in headache and we have been conducting a placebo controlled double blind cross-over study on chronic tension-type headache without depression.

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20 Botulinum toxin type A in the treatment of refractory headache

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Botulinum toxin type A is being evaluated worldwide as a potential treatment for episodic migraine, chronic migraine, and cluster headaches. According to the revised version of the International Headache Society (2003), chronic migraine (CM) is considered a complication of migraine. Patients with CM usually have a past history of episodic migraine, reporting a process of transformation characterized by headaches that become more frequent over months to years, with the associated symptoms becoming less severe. Patients then develop a pattern of daily or near daily headache that resembles chronic tension-type headache, with a few attacks of full-blown migraine superimposed. They often have daily headaches.

The treatment of CM often poses a major challenge for the clinician. Even when given the best expert care, a significant percentage of these patients still persist with daily or near-daily headaches

Objectives

This study was undertaken to evaluate the efficacy of botulinum toxin type A (BTX-A) in the treatment of refractory primary headache patients who had failed at least 4 preventive medications, and to determine the effects of BTX-A on disability in patients with refractory headaches.

Inclusions

Patients included were ages 18 to 65, with a primary headache diagnosis and previous failure of at least 4 preventive treatments. They were followed for at least 6 months after injections of BTX-A.

Methods

BTX-A was diluted with normal saline to a concentration of 25 U/ml. 100 units were administered to each patient.

Muscles injected included some or all of the following: frontalis, temporalis, corrugator, procerus, occipitalis, semispinalis, splenius capitis, trapezius, paraspinalis, and sternocleidomastoid. Fixed site injections were followed in frontalis, and temporalis muscles bilaterally. A follow-the-pain approach was followed in the other muscles, but all were injected bilaterally.

Data were gathered prospectively by headache diaries, and then reviewed for the following endpoints:

(1) Frequency of headaches.
(2) Intensity of pain.
(3) Number of days with severe headache.
(4) Headache index (frequency × intensity).
(5) Number of pain-free days per month.
(6) Migraine Disability Assessment (MIDAS) Scores.

Endpoints were measured in the month before BTX-A injection (baseline) and monthly in the following 3 months. MIDAS was applied at the baseline and 3 months after BTX-A injections. Statistical analysis was performed using repeated measures of ANOVA with post-test.

Demographics

One hundred subjects, 80% females were treated. Mean age was 43.7 years (SD = 7.8).

Diagnoses

Diagnoses were as follows:

(1) Chronic daily headache (CDH) with analgesic rebound headache/medication overuse (ARH/MOH): 65%.
(2) CDH without MOH: 15%.

(3) Episodic migraine: 12%.
(4) Chronic post-traumatic headache: 8%.

Further clinical information

The average number of days with pain per month was 24.1 (ranging from 5 to 31). Patients used an average of 12.4 preventive drugs previously (4 to 22).

Acute treatments previously used included:

- Butalbital: 48%
- Acetaminophen: 46%
- Opioids: 33%
- ASA: 32%
- Triptans: 18%
- Ergots: 11%

Results

Headache index (frequency × intensity)

A significant reduction at 1 month was noted (22.3 vs 40.3 at the baseline, $p<0.001$). This reduction was maintained for 2 months (21.5, $p<0.001$), and for 3 months (21.7, $p<0.001$).

Number of days with severe pain

A significant reduction at 1 month was noted (2.6 vs 4.9 at the baseline, $p<0.001$). This reduction was maintained for 2 months (2.7, $p<0.001$) and for 3 months (2.6, $p<0.001$).

Number of pain-free days

A significant reduction at 1 month was noted (15.0 vs 8.0 at the baseline, $p<0.001$) and maintained for 3 months (15.3, $p<0.001$).

The percentage of patients who experienced a >50% reduction in headache days were at:

Month 1: 52 (52%) subjects
Month 2: 51 (51%) subjects
Month 3: 46 (46%) subjects

Migraine disability assessment scores (MIDAS)

MIDAS is measured in 3 month periods. A significant reduction was noted at 3 months (19.3 at 3 months vs 33.5 at baseline, $p=0.002$).

Adverse events

No adverse events were noted in the 100 patients including an absence of ptosis, neck pain, or exacerbation of head or neck pain.

Conclusions

Botulinum toxin-A appears to be effective in the treatment of refractory headaches in this open label study. The efficacy was seen at 1 month and maintained for 3 months. Randomized controlled trials are clearly indicated.

Further reading

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21 Botulinum toxin A in the prophylaxis of migraine—a double-blind, placebo-controlled, randomized study comparing frontal and cervical injection

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Introduction

Botulinum toxin A has been suggested to be effective in the prophylactic treatment of headache. However, conflicting results have been reported to date.[1,2] For the prophylactic treatment of migraine, one placebo-controlled and well-designed study has been published showing an efficacy of botulinum toxin A in those patients receiving a small dose (25 U) but not a larger dose (75 U) of Botox® in the pericranial muscles.[3] Another placebo-controlled study, not fully published yet, showed a significant decrease of migraine intensity, but not of migraine frequency and duration, by botulinum toxin A 12 weeks after injection.[4] In addition, some open retrospective studies have been published all showing a positive effect of botulinum toxin A on migraine intensity and frequency using different injections sites and different doses of botulinum toxin A.[5–8]

These latter studies, however, had a small sample size, no standardized injection procedures, no statistical analysis, or no full description of the treatment procedure[2]

and do, thus, not give further scientific evidence about the efficacy of botulinum toxin A. We therefore performed another randomized, double-blind, placebo-controlled, single centre, parallel group study on the efficacy of different doses of botulinum toxin A (Botox®) in the prophylaxis of migraine with a specific focus on different injection sites.

Methods

Patient selection

We enrolled 60 patients with migraine without or with typical aura according to the criteria of the International Headache Society. Patients had to be between 18 and 65 years of age and to suffer from migraine with an average frequency of 2–8 attacks per month in the preceding 3 months. The diagnosis of migraine had to be established for at least one year with an onset before the age of 40. Other types of headache, in particular tension-type headache, were allowed on up to 10 days per month. Exclusion criteria were pregnancy or lactating women, any type of dystonia, any neuromuscular disease, any type of substance addiction including drug-induced headache, treatment with drugs affecting the neuromuscular junction, and changes of drug treatment with a possible migraine prophylactic efficacy within the last 3 months. After giving written informed consent, the patients were asked to keep a headache diary and to return to the clinic after a baseline of 4 weeks. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Münster, Germany.

Treatment procedure

When the baseline diary confirmed the inclusion criteria, the patients were allocated to one of three treatment groups by a computer generated randomization list. One investigator (JVH) who was not involved at all in the remaining study procedure received a sealed envelope with the randomization number. The patients were treated with either 100 U botulinum toxin A in the frontal and neck muscles, or with 16 U botulinum toxin A in the frontal muscles and placebo (0.9% NaCl) in the neck muscles, or with placebo in all muscles. The doses of botulinum toxin A for the different muscles in the different treatment groups are given in Table 21.1. Patients were then asked to keep a diary and to return to the clinic after another 3 months.

Statistical analysis

The primary efficacy parameter was the rate of patients with a reduction of migraine frequency by at least 50% in month 3 as compared to the baseline month. Secondary efficacy parameters were the reduction of migraine frequency, the reduction of days with migraine headache, the reduction of days with moderate

Table 21.1 Doses and injection sites of botulinum toxin A in the different treatment groups (the dose is given for one side, maximum amount of botulinum toxin A 100 U Botox®)

	Treatment group 1	Treatment group 2	Treatment group 3
M. frontalis	4 U	4 U	Placebo
M. temporalis	4 U	4 U	Placebo
M. sternocleidomastoideus	10 U	Placebo	Placebo
M. trapezius	12 U	Placebo	Placebo
M. splenius capitis	10 U	Placebo	Placebo
M. semispinalis	10 U	Placebo	Placebo
In total (both sides)	100 U	16 U	–

or severe migraine headache, the reduction of accompanying symptoms (sum score of photophobia, phonophobia, nausea, and vomiting), the reduction of the total single doses of acute antimigraine drugs, and the total number of possibly or probably drug-related adverse events.

All analyses were performed on data from the intent-to-treat population which was identical with the per-protocol population. We used non-parametric tests with the χ^2-test for qualitative data (Fisher's exact test if applicable) and the Kruskal–Wallis test for quantitative data (Mann–Whitney-U test as post-hoc test). The significance level was set at $p=0.05$.

Results

All 60 patients enrolled in the study could be followed up for the complete study period of 3 months. The demographic data of the three different treatment groups are presented in Table 21.2. There were no significant differences between these groups except significantly more patients with migraine with aura in group 2 as compared to group 1. The rate of patients with at least 50% reduction of migraine frequency (primary efficacy parameter) was 30% in the group receiving 100 U, 30% in the group receiving 16 U, and 25% in the group receiving placebo ($p=0.921$).

The data of the secondary efficacy parameter are presented in Table 21.3. There were no significant differences between the 3 treatment groups with respect to the reduction of the migraine frequency, the number of days with migraine, the number of days with moderate or severe migraine, and the number of acute drugs for the treatment of migraine attacks. The only significant difference could be observed in the sum score of all accompanying symptoms. In the group receiving 16 U botulinum toxin A, but not in the group receiving 100 U, the accompanying symptoms were significantly reduced by 29% in month 3 as compared to a reduction by 5% in the group receiving placebo ($p=0.048$).

Table 21.2 Demographic and clinical data of the 3 different treatment groups. Statistical comparison between the 3 treatment groups by Kruskal–Wallis test

	All patients	Group 1 (100 U)	Group 2 (16 U)	Group 3 (placebo)	Significance
Sex					
Female	83%	80%	80%	90%	$p=0.619$
Male	17%	20%	20%	10%	
Age in years	38 ± 11	37 ± 14	41 ± 9	37 ± 9	$p=0.223$
Tension-type headache					
yes	43%	40%	30%	50%	$p=0.150$
No	57%	60%	70%	40%	
Migraine					
Only without aura	82%	95%	65%	80%	$p=0.023$
With and without aura	3%			–10%	
Only with aura	15%	5%	30%	10%	
Duration of migraine (in years)	22 ± 13	21 ± 14	23 ± 11	22 ± 12	$p=0.770$

Table 21.3 Data of the secondary efficacy parameters in the three treatment groups. The significance levels are given for the comparison between the 3 treatment groups regarding the absolute reduction in month 3 as compared to baseline (Kruskal–Wallis test)

	Group 1 (100 U)	Group 2 (16 U)	Group 3 (placebo)	Significance
Attack frequency				
Baseline	4.0±1.7	3.2±1.8	4.1±1.9	$p=0.343$
Month 1	3.5±1.9	3.0±2.4	3.5±1.5	
Month 2	3.4±1.7	2.8±1.5	3.4±2.4	
Month 3	3.2±1.8	2.5±2.0	3.2±1.8	
Number of days with migraine				
Baseline	6.3±2.4	6.0±3.4	6.3±2.8	$p=0.686$
Month 1	5.6±2.4	5.9±5.0	5.8±2.6	
Month 2	6.2±2.5	5.7±3.3	5.5±3.3	
Month 3	5.0±2.5	5.0±4.0	5.0±3.2	
Number of days with moderate or severe migraine				
Baseline	5.2±1.4	4.5±2.1	5.5±3.1	$p=0.336$
Month 1	4.1±1.5	3.8±2.9	4.8±2.6	
Month 2	4.5±2.1	4.0±2.9	4.8±3.6	
Month 3	3.7±1.5	3.3±2.7	4.0±2.9	
Number of acute antimigraine drugs				
Baseline	6.3±3.7	4.8±2.5	7.1±3.8	$p=0.240$
Month 1	5.2±4.2	4.9±3.2	5.8±3.0	
Month 2	6.1±4.1	5.2±2.9	5.4±2.5	
Month 3	4.7±3.7	4.0±2.6	5.2±3.5	
Sum score of accompanying symptoms				
Baseline	3.4±0.8	3.1±0.8	3.0±0.8	$p=0.215^*$
Month 1	3.4±0.9	2.5±1.1	2.9±0.9	
Month 2	3.2±0.9	2.4±1.1	3.0±0.9	
Month 3	3.0±0.9	2.2±1.3	2.9±1.0	

*$p=0.048$ for the post-hoc analysis of the relative reduction comparing the 16 U treatment group and the placebo group.

The total number of adverse events was significantly higher in the group receiving 100 U as compared to the group receiving placebo. All adverse events were mild and transient. There was no serious adverse event.

Discussion

Our study could not demonstrate any significant efficacy of botulinum toxin A on migraine frequency or severity, or on the psychosocial impact of migraine. This is in concordance with some findings of two previous placebo-controlled studies. In the study of Brin *et al.*,[4] no significant improvement of migraine frequency by botulinum toxin A could be observed. In the study of Silberstein *et al.*,[3] botulinum toxin A showed a significant impact on migraine frequency in the low dose (25 U) but not in the high dose (75 U) treatment group. We cannot explain the different results of the studies concerning the low dose treatment group. It might be that a purely frontal injection of 16 U of botulinum toxin A, as in our study, is not effective whereas a higher dose of 25 U, as in the study of Silberstein *et al.*,[3] is helpful. Interestingly, it was also the low dose treatment group in which we could observe our only significant finding: an improvement of the accompanying symptoms in this treatment group as compared to the placebo group. It seems that the total dosage of botulinum toxin A, at least in the ranges used in the published studies (up to 100 U Botox®) is less important and that other parameters such as injection sites and patient selection are more important in order to yield a positive result from such a study.

Our data clearly contradict the findings in open case series showing a good efficacy of botulinum toxin in the prophylactic treatment of migraine. We interpret these differences as a result of the different study designs and of the placebo effect, which is well known in open studies.

We enrolled consecutive migraine patients without any selection bias except the setting of a supraregional specialized headache clinic. In particular, we did not focus on migraine patients known to be refractory in prophylactic treatment. The demographic data of our patients confirm that we enrolled a typical migraine sample in headache clinics. The placebo rate of 25% for the primary efficacy parameter is also typical for studies on migraine treatment. Therefore, we believe that our study reflects the typical situation of other published migraine prophylaxis studies.

The adverse events reported by the patients and judged by the investigators as possibly or probably related to the study drug were all mild and transient in nature. We observed the typical adverse events known from other studies on botulinum toxin A such as ptosis and neck weakness. Botulinum toxin A appeared to be a safe drug in the doses applied in our study.

Our study does certainly not give any final evidence against the efficacy of botulinum toxin in the prophylactic treatment of migraine. The optimal dose and the optimal injection sites resulting in a possible efficacy remain still to be determined. In the study by Silberstein *et al.*,[3] only frontal injection sites were used. We added also neck injection sites which did not improve the results. It might be that higher

doses injected only in frontal muscles are more effective. However, we observed some typical side effects in the frontal muscles even after 16 U and suggest care be taken with higher doses. In addition, frontal muscle weakness can result in cosmetic changes which might have an impact on migraine by indirect psychosocial mechanisms.

In conclusion, our study does not support the hypothesis that botulinum toxin A is effective in the prophylactic treatment of migraine. However, it might be that other injection sites and other doses of botulinum toxin A are effective in a defined subgroup of patients. Furthermore, our study gives some evidence that a low dose of botulinum toxin A might have a mild effect on the accompanying symptoms of migraine. Further studies should elucidate these specific mechanisms of botulinum toxin A rather than focus on the reduction of migraine frequency. Three placebo-controlled and double-blind studies have now shown that there is no major impact of botulinum toxin A on the migraine attack frequency which could be compared to that of other drugs such as beta-blockers or anticonvulsants. The future role of botulinum toxin A in the treatment of migraine remains, thus, still to be determined. However, it is unlikely that this specific kind of prophylactic treatment will be a competitive alternative to the common drug treatments of migraine.

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22 Description of a prospective, multicenter observational study of headache treatment with botulinum toxin type A: the program to assess treatment strategies (PATS™) registry

S. D. Silberstein, M. A. Stiles, C. Gebeline-Myers, and K. C. Bradley

Introduction

The frequency, severity, and functional limitations associated with primary headache disorders have been shown to significantly reduce patients' perceived health-related quality of life (QoL) and place a substantial financial burden on society.[1–5] Current preventive treatments tend to have a modest effect along with a substantial side effect burden related to vascular or systemic distribution.[6] Botulinum toxin type A (BoNT/A) has shown promise for the preventive treatment of headache in several clinical trials.[7–9] There has been discussion about how BoNT/A should be optimally used for treating headache and which patients are best suited for treatment.

Botulinum Neurotoxin Type A (BoNT/A) has been used in multiple trials for the treatment of various headache types. In addition, many physicians have used

BoNT/A to treat headache patients within their own practice. Many clinicians question why some patients respond so well while others are seemingly unchanged or, in some cases, worsened after treatment. To date there has been no extensive collection of information regarding the use of BoNT/A with regard to injection techniques, location of injections, concentration of product injected, or clinical outcomes. The purpose of this registry is to collect data on variations in current diagnostic and therapeutic management of patients receiving BoNT/A for the treatment of headache. The registry is designed to capture 'usual care' of patients receiving BoNT/A for headache and as such does not specify patient visits or clinical procedures to be conducted. Participating physicians are instructed to treat their patients as they normally would and to use the Program as a means of capturing consistent information among their patients for whom they are prescribing BoNT/A for headaches. The registry is entitled 'The Program to Assess Treatment Strategies' or PATS. It is an internet-based registry directed by Dr Stephen Silberstein at Thomas Jefferson University and administered by Covance Periapproval Services, Inc.

Methodology

Ten headache treatment centers nationwide, will participate in the PATS registry. These centers will recruit a total of 1000 BoNT-naive patients with headache, for whom BoNT/A is being prescribed. Patients are not consented to participate in the Program until after the physician has decided to prescribe BoNT/A for them. Demographic data are collected from each patient at the baseline visit. Clinical characteristics are also collected at baseline and include the following:

- headache history, diagnoses, and prior treatments;
- average headache frequency, duration, and severity;
- the physician's reason(s) for prescribing BoNT/A for this patient;
- indication for BoNT/A use according to IHS criteria;[10]
- concomitant medical conditions and current use of acute and preventive medications.

In addition patients are administered the following questionnaires:

- Headache Impact Questionnaire (HIQ).
- Headache Pain Specific Quality of Life.[11]
- Migraine Disability Assessment (MIDAS).[12]

At the time of injection the following data is captured:

- physician philosophy of injection (i.e. follow the pain, standard injection sites or both);
- Indication for BoNT/A use according to IHS criteria;[10]
- injection sites and muscle tenderness assessments (see Figs. 22.1 and 22.2);

Muscle Group	Tenderness Assessment		Number of Injections		Volume Injected cc's *Total cc's injected per muscle group*		Needle Gauge	Dilution
	RIGHT	*LEFT*	*RIGHT*	*LEFT*	*RIGHT*	*LEFT*		
FRONTAL								
☐ 1. Procerus (mid-line)		____	1 *(auto answer)*	____		____		
☐ 2. Frontalis								
☐ 3. Corrugator								
SIDE								
☐ 4. Temporalis								
☐ 5. Masseter								
☐ 6. Sternocleidomastoid								
POSTERIOR								
☐ 7. Splenius Capitus								
☐ 8. Occipitalis								
☐ 9. Sub-Occipitalis								
☐ 10. Cervical-Paraspinal								
☐ 11. Trapezius								
OTHER								
☐ 12._____								
☐ 13._____								
☐ 13. Mid-Line		____	____	____		____		

Fig. 22.1 The injection data collection form is a complex tool to capture extensive injection information. It can be completed either directly into the web-based application or on paper and then transcribed into the electronic program. The form is designed to capture muscle groups injected; tenderness assessments for each muscle group injected, right and/or left; needle gauge used; and dilution used per muscle group. Investigators are provided with the option to enter additional muscle groups injected in the 'Other' section. The web-based application is also designed to perform the mathematical calculations of total dilution and amount injected.

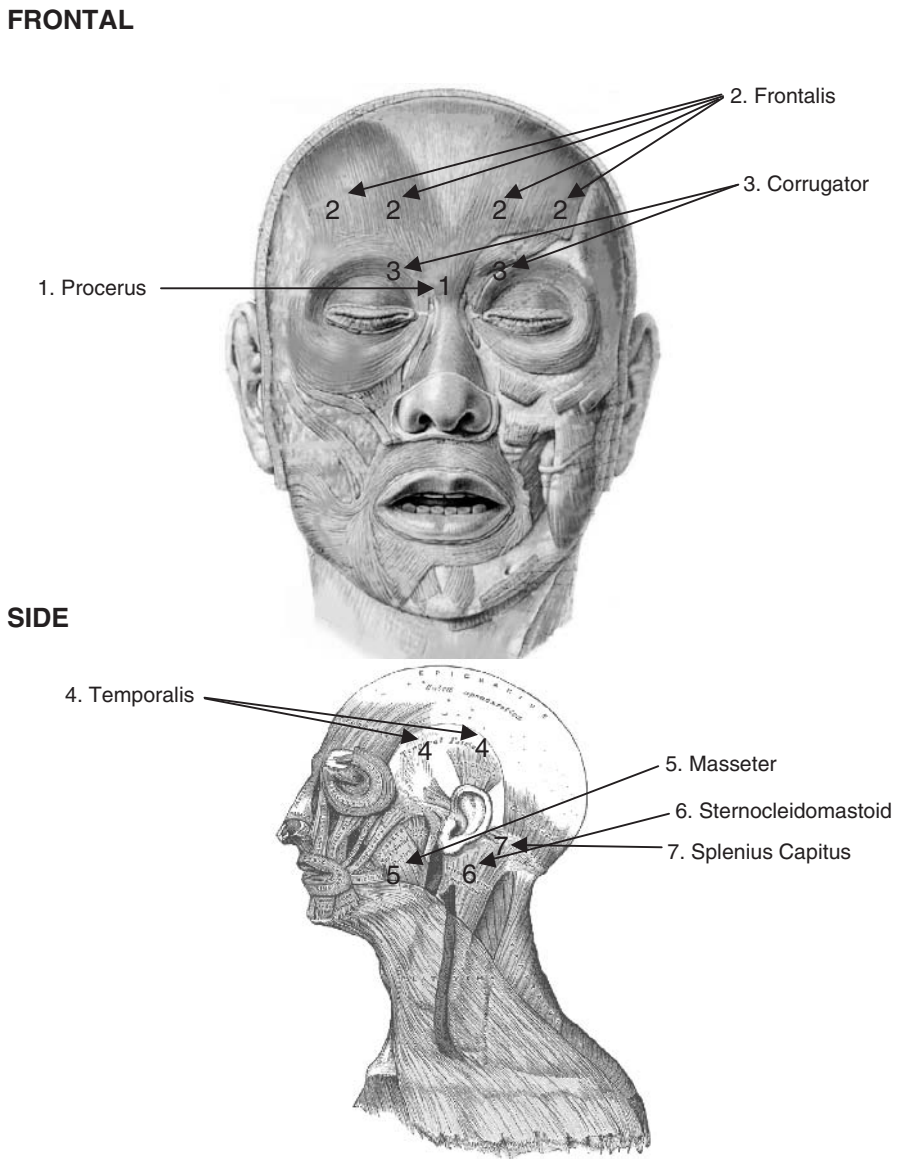

Fig. 22.2 Injection site maps are provided to each participating investigator and are also accessible via the web-based application. They are intended to promote consistency of injection locations reported among all participating investigators.

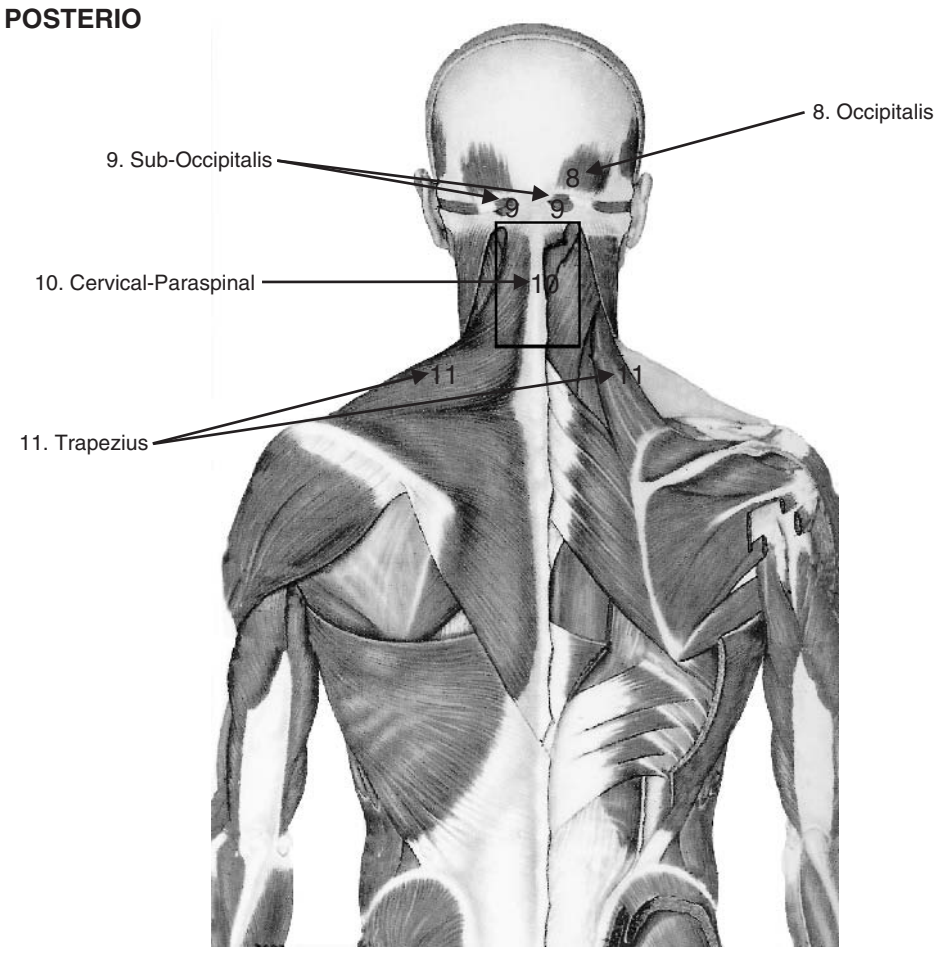

Fig. 22.2 Continued.

- doses, dilutions, and needle gauge;
- patient's impression of injection procedure.

Physicians may decide to re-inject patients at subsequent visits. In the event a patient is re-injected, the aforementioned injection data will again be captured.

Patients are followed for the duration of their participation in the Program (a minimum of 1 year). For those patients who discontinue therapy prematurely, an attempt will be made to continue data collection for six months after their discontinuation. The reason(s) for discontinuation will be documented in the patients' record.

Data are collected at all routine follow-up visits and include:

- patient-reported response to treatment;
- patient administered questionnaires;
- headache frequency, duration, and severity since previous visit;
- physician assessment of the patient's response to therapy;
- occurrence of any serious adverse events and information on specific symptoms perceived to be related to BoNT/A therapy (other adverse events deemed unrelated to BoNT/A therapy will not be collected).

Additionally, patients are asked to maintain a daily headache diary for the duration of their participation in the Program. The headache diary provides patients with a means to capture headache information consistently. This is imperative in the determination of whether BoNT/A seems to have worked for a given patient. The Program has developed a diary that can be used, although a participating physician may use his/her standard collection tool for headache information. Patients are instructed to bring their headache diaries to every office visit so that they may be reviewed with their physician.

For an overview of the registry milestones see Fig. 22.3. For an overview of the study flow, see Fig. 22.4.

Objectives

The primary objectives of this Program are:

- To assess the use, safety, and effectiveness of BoNT/A in usual clinical practice.
- To identify factors that predict successful treatment outcomes in patients receiving BoNT/A for treatment of headache.

Additional objectives of the Program are:

- To describe variations in headache management using BoNT/A (overall and by patient characteristics).

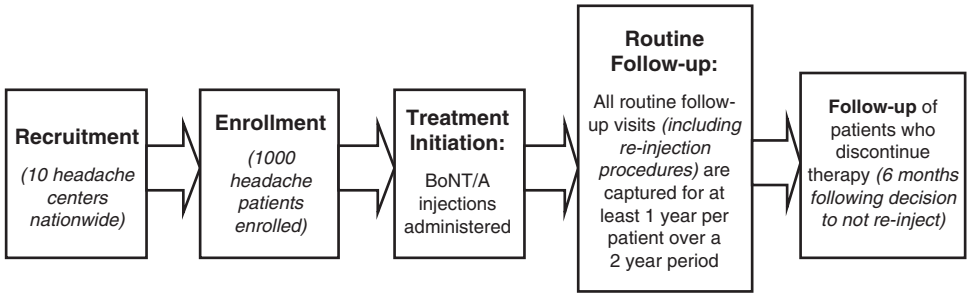

Fig. 22.3 This diagram represents an overview of the PATS registry.

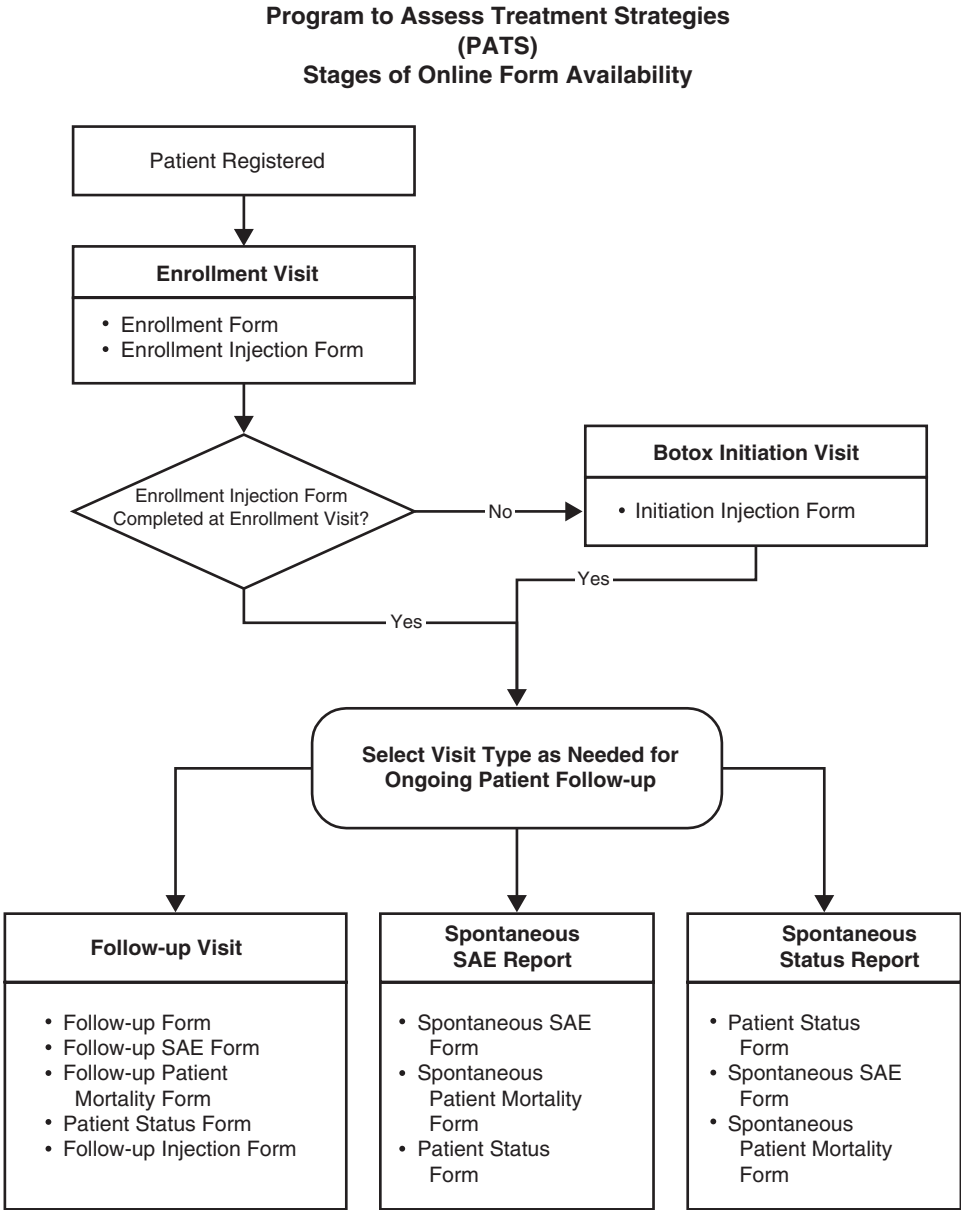

Fig. 22.4 The study flow diagram aids investigators in determining the flow of patient visits as well as the forms that are to be completed at each applicable patient visit.

- To provide participating physicians with information regarding management of patients treated with BoNT/A in their practice compared with the aggregate experience of all physicians participating in the Program.
- To give the medical community an understanding of BoNT/A use in the treatment of headache via scientific meetings, publications, and presentations of Program findings.

Data analysis

Data recorded at the initial and follow-up visits will be analysed to evaluate the temporal trends in headache status and characteristics. Treatment success will be defined as significant reductions in the number of headache days, headache severity or disability, or significant improvements in QOL measures. Data regarding treatment methods employed by the participating physicians (muscle selection criteria, number of injection sites, volume of BoNT/A per injection, frequency of injections) will be related to clinical outcomes. Variables such as headache type and variations in injection technique will be analysed as potential predictors of successful treatment. Patients' demographic and clinical characteristics will also be evaluated as potential determinants of treatment outcomes. Demographic information, clinical characteristics, and other potential factors that may affect patient outcomes will be summarized using descriptive statistics.

Ethical review, patient consent, and confidentiality

An independent Human Research Review Board has reviewed and approved this protocol. Local rules imposed by some institutions require that a participating physician obtain local Institutional Review Board approval before participating in the Program. The Program is conducted according to the recommendations of the Declaration of Helsinki.

Data provided by the patient and the patient's physician are kept strictly confidential. No individual patient will be identified in any way. If Program information is presented in medical journals or scientific meetings, the data will be presented in aggregate. Data entered into the internet-based registry is kept in a confidential form. Patients are not be identified by name anywhere in the electronic application. Patients are referred to as an assigned number and their initials in the Program. Information pertaining to personal medical history will be included in this Program. Entry into the Program is password protected, to assure only authorized users may access the system. Authorized users include the principal investigator and/or delegated staff, and Covance Periapproval Services (registry manager).

Conclusions

Results obtained from this prospective, multicenter observational will provide the most extensive database of the outcomes of BoNT A therapy for headache. In addition to providing data regarding the safety and efficacy of treatment, these data will also be used to derive predictive algorithms to refine the selection of patients most likely to benefit from BoNTA therapy and to optimize the treatment protocol and injection methodology.

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23 Mechanisms of the antinociceptive effect of subcutaneous BOTOX®: inhibition of peripheral and central nociceptive processing

M. Cui and K. R. Aoki

Introduction

Botulinum toxin type A (BoNT-A; BOTOX®) has been used for the treatment of conditions involving excessive muscle contractions, as well as painful pathological conditions such as low back pain, headache, myofascial pain, and migraine. Our group has demonstrated that subcutaneous (SC) BOTOX® inhibits inflammatory pain in the rat formalin model, suggesting a direct action on sensory neurones.[1,2] However, direct evidence that BOTOX® produces pain relief by inhibiting the release of neurotransmitters from sensory neurones in an animal model of pain is lacking. The present study was therefore designed to investigate this possibility using the rat formalin model, examining the effects of BOTOX® on (1) formalin-induced glutamate release, (2) the pattern of formalin-induced Fos-like immunoreactivity, and (3) formalin-induced activation of wide dynamic range (WDR) neurones in the dorsal horn.

Methods

Male, Sprague-Dawley rats (300–350 g) were used for all experiments. Both BOTOX® and formalin were injected SC into the subplantar surface of the hind paw (formalin: 50 µl of 5%; BOTOX®: specified doses in 22 µl bolus).

Glutamate Release Assay

Rats were pre-treated with saline, 3.5, 7.0, or 15 U/kg BOTOX®. Five days later, microdialysis probes were inserted SC into the ventral surface of the paw under general anaesthesia and dialysate was collected every 10 min at 3 µl/min. Three hours after probe insertion, formalin was injected and dialysate was collected for another 1–2 hours, for a total of 4–5 hours. Samples were stored and later analysed for glutamate content using liquid chromatography followed by mass spectrometry.

Fos-like immunoreactivity

Rats received injections of 7, 15, or 30 U/kg BOTOX® for 3 days, followed by formalin injection 3 days later. Two hours after formalin injection, rats were anesthetized and perfused intracardially with PBS followed by 4% formaldehyde, and L4–L5 segments of spinal cords were removed and stored at −80° C. Serial frozen sections (40 µm) were sliced with a cryostat and incubated with primary antibody (rabbit anti-c-fos; Oncogene, 1:5000) for 48 hours at 40° C. Sections were then mounted on slides and incubated with ABC reagent (VECTOR Laboratories) for 1 hour, followed by reaction with diaminobenzidine (VECTOR Laboratories) for 10 minutes. Slides were then coverslipped and examined under bright field microscope.

Extracellular recording of dorsal horn Wide Dynamic Range (WDR) neurones

Rats were pre-treated with 3.5, 15, or 30 U/kg BOTOX®. One day later, animals were anesthetized and laminectomy was performed over the lumbar vertebrae L1–L3. Segments L4–L5 of the spinal cord were exposed. Extracellular recordings of convergent dorsal horn neurones at a depth of 500–900 µm from the spinal cord surface were made with a parylene-coated tungsten electrode (FHC, Inc.). Dorsal horn WDR neurones were identified by their characteristic responses to innocuous and noxious natural stimuli (brush, pinch, and squeeze). Formalin was then administered and recording was performed for approximately 65 minutes (5 minutes before and at least 60 minutes post formalin injection).

Results

All doses of BOTOX® significantly inhibited the peak formalin-induced glutamate release in the paw (Fig. 23.1; $p<0.05$ vs. vehicle, 1-way analysis of variance [ANOVA] followed by Dunnett's test).

BOTOX® also dose-dependently reduced the number of Fos-like immunoreactive cells in the dorsal horn (Table 23.1).

The numbers of Fos-like immunoreactive cells in all BoNT-A groups were significantly different from saline ($p<0.05$), 1-way ANOVA followed by Dunnett's test; $n=3–5$/group.

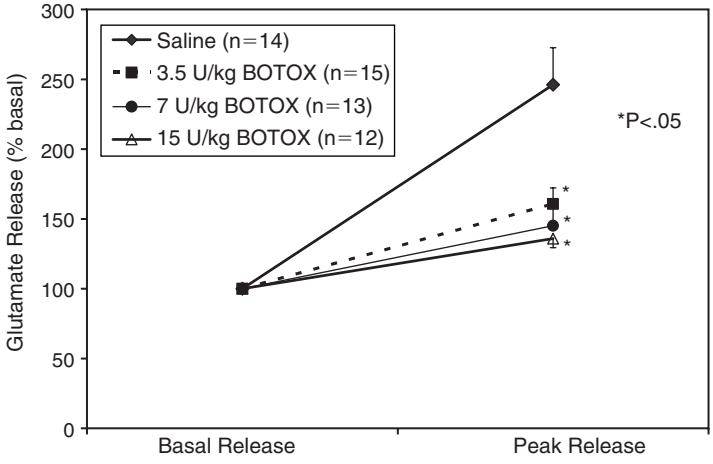

Fig. 23.1 Effects of BOTOX® on the peak formalin-induced glutamate release in the paw (data shown are means ± SEMs).

Table 23.1 Numbers (mean ± SEMs) of Fos-like immunoreactive cells in the dorsal horn in the rat formalin model following various doses of BOTOX®

Laminae	Saline	7.0 U/kg BOTOX®	15.0 U/kg BOTOX®	30.0 U/kg BOTOX®
I, II	64.6 ± 3.8	43.8 ± 5.4	39.3 ± 3.2	12.7 ± 4.0
III, IV	11.2 ± 1.1	11.1 ± 0.4	9.9 ± 0.9	4.0 ± 0.7
V, VI	51.4 ± 3.7	33.4 ± 2.7	31.8 ± 1.2	15.0 ± 4.1

BOTOX® significantly inhibited the excitation of WDR neurones in Phase II but not Phase I of the formalin response (Fig. 23.2; 15 and 30 U/kg doses of BOTOX® were significantly different from saline; 1-way ANOVA followed by Dunnett's test).

Discussion

The results presented here provide evidence that BOTOX® inhibits formalin-induced activation of primary sensory neurones in rats by (1) inhibiting formalin-induced glutamate release in the paw, (2) inhibiting formalin-induced Fos-like immunoreactivity in the dorsal horn of the lumbar cord, and (3) inhibiting the Phase II formalin-induced activation of spinal WDR neurones. It is therefore possible that these effects mediate at least part of the antinociceptive actions of BOTOX® observed in the rat formalin pain model.[1]

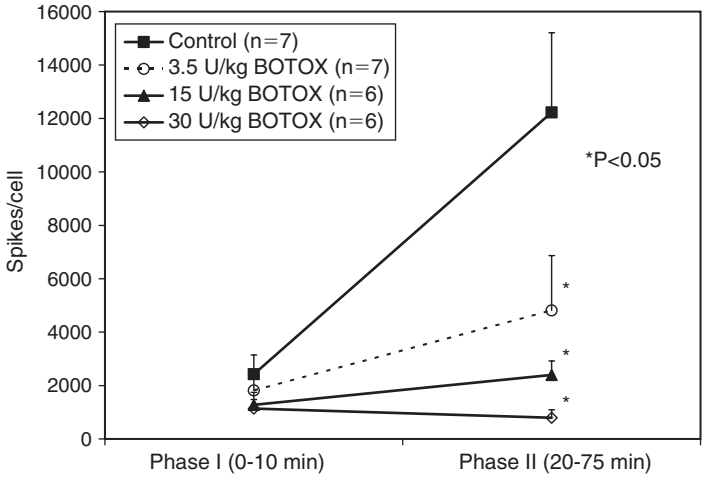

Fig. 23.2 Summary of the inhibitory effect of BOTOX® on the formalin-induced excitation of WDR neurones (means + SEMs). See ref. 1 for dose response effects of BOTOX® on Phase II of formalin-induced lifting and licking of the paws.

Based on these and other results, a model of peripheral and central sensitization may be proposed. Subcutaneous administration of BoNT-A blocks release of neurotransmitters (e.g. glutamate, substance P, and calcitonin gene-related peptide) from peripheral afferent terminals[2,3] through the well-established inhibition of calcium-regulated vesicle-dependent neurotransmitter release.[4] When BoNT-A blocks the release of peripheral neuropeptides, there is an indirect reduction in other inflammatory mediators that are involved in neurogenic inflammation. The peripheral nociceptive nerves are sensitized and are therefore more active and increase the stimulation of the spinal cord resulting in a form of central sensitization.[5–8] Such a blockade would reduce pain and peripheral sensitization. The reduction of peripheral sensitization may then lead to a decrease in pain signals transmitted to the spinal cord by C or A delta fibres and a consequent reduction in the release of substance P and glutamate in the spinal cord, eventually reducing central sensitization. The inhibition of central nociceptive processing at the spinal level was indicated by a decrease in formalin-evoked firing rate and Fos-like immunoreactivity of dorsal horn neurones. Taken together, the combination of reductions in peripheral and central sensitization by BOTOX® contributes to its antinociceptive effect in neurogenic inflammation, a possible mechanism for its clinical efficacy in treating migraine.

Conclusion

Subcutaneous administration of BOTOX® inhibits neurotransmitter release from primary sensory neurones in the rat formalin model. Through this mechanism,

BOTOX® inhibits peripheral sensitization, which leads to an indirect reduction of central sensitization in this model—a possible mechanism for its clinical efficacy in treating migraine.

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24 Survey on expenditure for analgesics in chronic tension headache and its changes following botulinum toxin type A preventive treatment

G. Coloprisco, S. De Filippis, P. G. Santi, G. Fiore, A. Rodio, and P. Martelletti

Abstract

The aim of this study was to investigate the impact of the use of botulinum toxin type A (BoNT-A; BOTOX®; Allergan, Inc.; Irvine, CA) as preventive treatment of chronic tension-type headache (CTTH) on analgesic use and expenditure.

This was a prospective, single-center, 1-year, open-label study of the effect of BoNT-A treatment on acute analgesic use and expenditure in CTTH patients.

A headache questionnaire, which included questions about medication costs, was completed by CTTH patients attending a specialist headache clinic in Rome prior to BoNT-A injections. Repeat injections were administered every 3 months for up to 1 year. Patients were required to complete the questionnaire prior to each injection cycle. A pharmacoeconomic analysis was performed at each assessment to determine the effect of BoNT-A treatment on analgesic use and expenditure.

Three hundred questionnaire were distributed and 296 (98%) were completed. The study population consisted of 67.8% (201) females and 32.2% (95) males, with a mean age of 46.7±16.1 years.

The economic evaluation of the pharmacologic treatment of CTTH was conducted on the 101 (34.12) patients who gave complete information on posology. Pharmacoeconomic data analysis focused on the whole group using analgesics compared to those who self-prescribed and those who turned to health specialists before and after treatment with BoNT-A. Prior to treatment with BoNT-A the median monthly pharmaceutic expenditure per patient was euro (€) 24.30 for the whole group using analgesics, and € 34.93 and € 18.51 for the 'self-prescribers' and the 'prescribed by specialist' groups, respectively. Median monthly pharmaceutic expenditure decreased significantly for the whole group ($p<0.001$), the 'self-prescribers' ($p<0.01$), and the 'prescribed by specialist' group ($p<0.002$) (3rd month: € 13.3, 9.3, 7.2, respectively; 6th month: € 8.9, 9.0, 4.1, respectively; 9th month: € 5.7, 12.4, 3.0, respectively). Data for the 12th month are still under evaluation.

BoNT-A treatment produced significant reductions in both analgesic use and expenditure. The data suggest that consultation with a specialist would be helpful in patients with CTTH. Cooperative studies on cost analysis of chronic daily headaches, including both CTTH and chronic migraine, comparing the economic cost package borne by patient and community both before and after treatment with BoNT-A, are warranted.

Introduction

Tension-type headache (TTH) is the most common form of chronic headache, with a lifetime prevalence in the general population as high as 30%.[1] The socioeconomic burden of TTH includes both direct costs associated with health care utilization and costs associated with missed work due to sickness absence or reduced efficiency. The individual and socioeconomic burden of TTH is substantial. A study of a Danish population reported 870 workdays lost per 1000 people for migraine.[2]

The cost of managing TTH for both patients and health care systems is a critical issue in terms of drug consumption and the treatment of conditions resulting from analgesic overuse.[3,4] Chronic tension-type headache (CTTH) (frequency of headache [HA] ≥ 15 days/month) substantially increases analgesic expenditure in headache disorders.[5] There are few effective preventive drugs for CTTH available. Botulinum toxin type A (BoNT-A; BOTOX®; Allergan, Inc.; Irvine, CA) is a focally acting neurotransmitter from presynaptic nerve endings at the neuromuscular junction, resulting in muscle relaxation. Treatment with BoNT-A has been shown to be safe and efficacious in the treatment of CTTH and migraine.[6–8] Though its mechanism of action in HA disorders in unknown, BoNT-A may have antinociceptive effects apart from its muscle relaxing effects.[9] The aim of this study was to investigate whether preventive treatment of CTTH with BoNT-A may have an impact on analgesic expenditure.

Methods

Design

This was a prospective, single-center, 1-year, open-label pharmacoeconomic study of the effects of BoNT-A treatment on analgesic expenditure in the management of CTTH.

Patients

Included in this study were CTTH in-patients at the Day Hospital of Headache Centre (DHHC) of the University La Sapienza Sant'Andrea Hospital in Rome. The period of the study ranged from March 2002 to January 2003.

Treatment protocol

An anonymous HA questionnaire dealing specifically with analgesic use and expenditure was distributed and completed by the patients prior to first admittance to the DHHC for BoNT-A injections. The protocol has been approved by the institutional Ethic Committee. All patients entered the study signed the informed consent form. Upon admittance to the DHHC, patients were injected with 70 to 100 units (U) of BoNT-A to the referred pain sites. The injection sites were registered in a scheme reporting all the used head/neck injection sites. Repeat injections were administered every 3 months for up to 1 year. Patients were required to complete the HA questionnaire prior to each injection cycle. The use of analgesics and the associated costs were calculated at baseline and during the treatment period on the basis of the data from the questionnaire. Statistical analysis of analgesic use and cost was performed using the student *t* test for paired data.

Results

Three hundred questionnaires were distributed and 296 (98%) were completed. The study population consisted of 67.8% (201) females and 32.2% (95) males, with a mean age of 46.7 years (SD ± 16.1).

The pharmacoeconomic effect of preventive BoNT-A treatment of CTTH was conducted on the 101 (34.12%) patients who gave complete information on posology and completed the entire 1-year treatment period.

The mean distribution of costs was strongly skewed to the right due to a few expensive treatments, therefore, only the median is reported. Pharmacoeconomic data analysis focused on the whole group using analgesics ($n = 101$) compared to those who self-prescribed and those who turned to health specialists before and after treatment with BoNT-A. Prior to treatment with BoNT-A the median monthly pharmaceutic expenditure per patient was euro (€) 24.30 for the whole group using analgesics, and € 34.93 and € 18.51 for the 'self-prescribers' and the 'prescribed by specialist' groups, respectively. Median monthly pharmaceutic expenditure decreased significantly relative to baseline at each assessment point for the whole group ($p < 0.001$), 'self-prescribers' ($p < 0.01$), and the 'prescribed by specialist' ($p < 0.002$) (3rd month: € 13.3, 9.3, 7.2, respectively; 6th month: € 8.9, 9.0, 4.1, respectively; 9th month: € 5.7, 12.4, 3.0, respectively) (Fig. 24.1). Data for the 12th month are still under evaluation.

All *p* values correspond to the 3-, 6-, and 9-month assessment-point values compared to baseline.

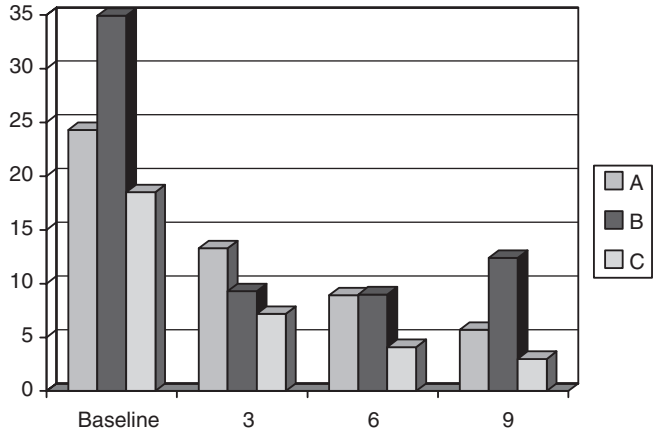

Fig. 24.1 Median monthly pharmaceutic expenditure calculated in € currency. A = whole group (using analgesics) ($p<0.001$); B = 'self-prescribers' ($p<0.01$); C = 'prescribed by specialist' ($p<0.002$).

Conclusions

BoNt-A treatment produced decreases in analgesic use that resulted in significant reductions in analgesic expenditure. Reductions appeared to be cumulative over the 9-month period of observation. The data suggest that consultation with a specialist helps to reduce overall analgesic expenditure and use in patients with CTTH.

Cooperative studies on cost analysis of chronic daily headaches, including both CTTH and chronic migraine, comparing the economic cost package borne by patient and community both before and after treatment with BoNT-A, are warranted. Additionally, a better harmonization in the utilization of this promising therapeutic class, as previously suggested for migraine acute therapy,[10] is necessary.

This financial study shall be accompanied by an economic evaluation to measure the broader expenses incurred by public and private services in the management of CTTH.

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25 Prophylactic treatment of migraine with lomerizine hydrochloride

Y. Hibi, H. Igarashi, and F. Sakai

Introduction

Lomerizine hydrochloride is a novel calcium channel blocker developed for the prophylaxis of migraine.

Although the effect of lomerizine to protect the brain from hypoxia and ischemia was examined in experimental animal models,[1,2] the clinical usefulness of this agent to prevent migraine has not been fully explored.

In this report, we investigated the prophylactic effect of lomerizine in eighteen patients with migraine using our quantitative headache diary.

Purpose

The purpose of our study is to evaluate the efficacy of lomerizine hydrochloride for the prophylaxis of migraine by using visual-analogue scale headache diary.

Subjects and Methods

Eighteen patients with migraine (2 male, 16 female; mean age 41.9 ± 12.3 years) with the indication for prophylactic treatment were evaluated. Clinical evaluation of migraine was checked by diagnosis based on IHS criteria.[3]

All the patients were asked to keep the visual-analogue scale headache diary for a period of 20 weeks. The headache curve, the time-to-pain intensity curve, was plotted when the patients had headache and the data before and after the treatment was compared. The patients were requested to start plotting the migraine scale 4 weeks prior to the initial treatment. Administration of lomerizine

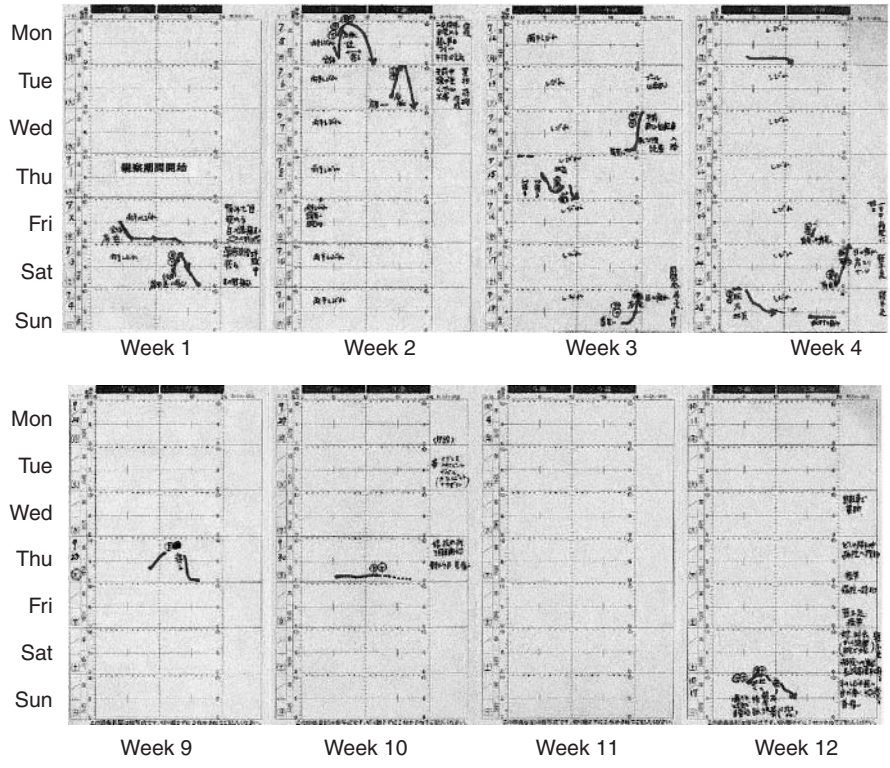

Fig. 25.1 Case presentation: Headache diary before and during the treatment of a 51-year-old female with migraine without aura.

hydrochloride (5 mg) was given orally twice every day for 20 weeks (Fig. 25.1). Headache curve was evaluated by the image analysing program and the comparison was made before and after the treatment of lomerizine.

The headache curves were scanned by an image processor. The image data of each headache curve was measured to calculate the area under the headache curve to obtain the quantity of headache. Frequency, duration, and peak intensity over the 4 weeks period were calculated automatically. Each quantitative index for headache before and after the treatment by lomerizine was compared to evaluate its efficacy.

Our headache diary, which quantitatively analyses the severity of headache is used for this investigation. This diary was analysed in terms of frequency, maximum intensity, duration, and quantity of headache (Fig. 25.2). The mean observation period before and during the treatment was 20 weeks.

χ-square and Wilcoxon *t*-test were used for the statistical analysis. Statistical significance was confirmed when *p*-value is less than 0.05.

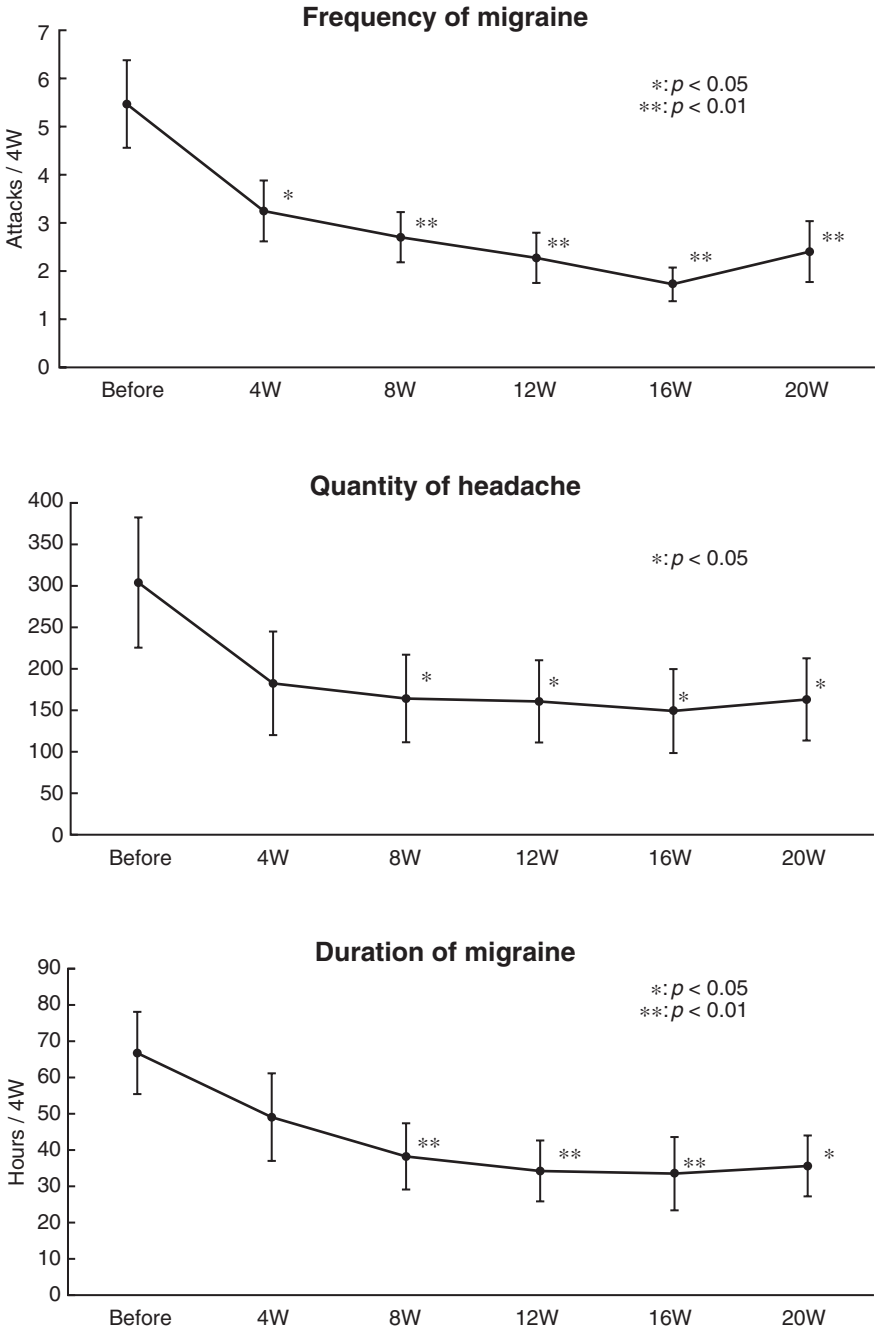

Fig. 25.2 Frequency, quantity, and duration of migraine were decreased by treatment of lomerizine.

Results

By viewing the diary of the patient, physicians were able to distinguish the type of headache according to the IHS criteria. By the administration of lomerizine, the frequency of migraine attack was decreased from 5.5±3.8 to 2.4±2.2** and the maximum intensity of headache was also decreased from 7.5±2.5 to 6.3±3.3. The duration of headache was shortened from 66.3±47.0 to 35.2±28.3* hours/month. The quantity of headache was decreased from 303.1±307.9 to 162.1±168.5* (Table 25.1).

Careful clinical evaluation revealed any further adverse event including extrapyramidal symptoms, weight gain, depression, or drowsiness.

Discussion

Lomerizine(1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)-piperazine dihydrochloride), in experimental animal models, selectively increases the cerebral blood flow by inhibiting Ca^{2+} influx into vascular smooth muscle, resulting in the protection of the brain from hypoxia.[4] Also, the inhibitory action of the agent on neural Ca^{2+} reduces ischemic brain damage.[1,2] The basic mechanism of activity of lomerizine for reduction of threshold of migraine is derived from these factors: (1) by the reduction of the peak amplitude of LVA I_{Ca} in a concentration-dependent manner[5]; (2) by the inhibition of [^{3}H]nitrendipine binding by a negative heterotrophic allosteric mechanism[6]; and also (3) by the inhibitory effect on the cortical hypoperfusion and expression of c-Fos-like immunoreactivity induced by spreading depression and mediated via the effect of Ca^{2+}-entry blockade.[7]

Lomerizine increased the vertebral blood flow to the same extent as the other calcium entry blockers (flunarizine, cinnarizine, nicardipine, and diltiazem), without expansion action of a whole body blood vessels, in animal models.[8]

Other noble agents such as verapamil hydrochloride and flunarizine hydrochloride are used as preventive medicine of migraine conventionally in Western countries. It is assumed that the former is inferior to β-blocker from a point of clinical effect, and the latter is also inferior as a migraine treatment drug with respect to its severe adverse effects. For example, β-blockers cannot be used for asthma patients. Lomerizine, a calcium channel antagonist developed in Japan, is confirmed to be effective for animal models.[4–8] There are, nevertheless, few fundamental examination reports which review clinical results especially the effect on migraine patients. Gotoh *et al*. revealed the efficacy and safety of lomerizine in patients with migraine in an open-controlled and double-blind study.[9,10] The results conclude that the effectiveness of lomerizine is equivalent to that of dimentotiazine in migraine prophylaxis, and that this agent is safer than dimentotiazine.

In this report, the clinical effect of the agent for migraine is examined. Clinical factors such as duration, frequency, and quantity of migraine were significantly improved by the administration of lomerizine. Lomerizine showed a superior effect

Table 25.1 Changes in headache indices 4–20 weeks before and during lomarizine hydrochloride treatment

($n=18$)

	Before	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks
Frequency (attacks/4 weeks)	5.5±3.8	3.3±2.6*	2.7±2.3**	2.3±1.9**	1.8±1.1**	2.4±2.2**
Duration (hours/4 weeks)	66.3±47.0	48.6±51.3	37.9±37.7**	33.8±31.2**	33.3±34.5**	35.2±28.3*
Quantity of headache (4 weeks)	303.1±307.9	181.3±247.7	164.1±212.2*	159.7±177.1*	148.2±175.6*	162.1±168.5*
Peak intensity	7.5±2.5	5.6±2.8	5.4±3.7	5.2±3.6	5.3±3.6	6.3±3.3

* $p<0.05$
** $p<0.01$

in migraine prevention and proved to be the first choice prophylactic drug for migraine since no adverse drug reactions were apparent. These results may indicate that the administration of lomerizine for migraine is useful compared to other drugs. Although frequent administration of lomerizine is required due to its shorter therapeutic half-time, considering the less adverse effects of lomerizine compared to other agents such as flunarizine, clinical use of lomerizine may be a convincing option for the treatment of migraine. The results indicate less adverse effects of lomerizine, in line with the conclusion of the report of Gotoh *et al*.

A headache diary is applied in this study as a tool that can evaluate a drug indication judgment for headache from various angles. The epoch-making maneuver that can evaluate the headache quantitatively, was developed and modified in our Department. The advantage of this method is the quantitative analysis of headache. In this report, this headache diary was effectively used for the evaluation of headache of migraine patients, reflecting significant effectiveness of lomerizine.

Conclusion

In this report, lomerizine hydrochloride showed significant reduction of the frequency, duration, and quantity of headache of migraine and proved to be effective for prophylaxis of migraine. These results demonstrate a convincing case for lomerizine as a new candidate for the prophylactic treatment of migraine.

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26 Prophylactic drugs III: discussion summary

P. J. Goadsby

Selective serotonin reuptake inhibitors (SSRIs) and their use in headache were discussed. Prof Olesen (Denmark) made the statement that there is no clinical trial evidence to support their use in headache. Dr Isler (Switzerland) commented that while they were not necessarily useful in headache *per se* there was a useful effect in enabling patients to cope with their disease. A published controlled trial that showed a possible effect in Chronic Tension-type Headache was considered.[1] Prof Silberstein (USA) pointed out that it was not possible to absolutely dissect out an effect on depression from an effect on headache in that study.

Dr Aoki summarized results from basic experimental studies of Botulinum Toxin A (BotoxA) on nociceptive models, such as formalin injected in the rat forepaw (see Aoki, this volume). It was concluded that BotoxA may have a direct anti-nociceptive effect. It was asked whether this might be within the central nervous system and commented that it was possible although there was no direct evidence. Dr R Hill (UK) suggested studies using antibodies to SNAP-25; Dr Aoki commented that it had been challenging to obtain suitable antibodies.

Issues of the differences between positive studies with BotoxA, such as those published[2]—albeit for one dose, and one presented at the meeting (Barrientois and Chana, this volume), compared to negative studies, such as Schwaag and colleagues (this volume), were aired. Dr Tepper (USA) felt that an important characteristic of the positive studies was multiple injection sites being used, although Dr Evers (Germany) pointed out this was also the case with the negative 75 U arm of the published study and pointed to his recent review.[3] Prof Olesen (Denmark) requested that controlled studies with Botulinum toxin be written up and published as soon as it was practical. It was commented by Dr Aoki that this was part of the ongoing process that would be pursued in order to define the place of Botulinum toxin in headache therapy.

Dr Stovner pointed out that angiotensin II is said to activate NF$\kappa\beta$ which increases expression of inducible nitric oxide synthesis (NOS). He suggested that clinical results with the angiotensin converting enzyme inhibitor lisinopril[4] and the angiotensin II receptor antagonist candasartan[5] might be explained by an interruption of that pathway. Dr Parsons (UK) commented that this had not been established *in vivo*.

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Session V

New targets I

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27 Antagonizing peripheral sensitization in migraine

S. Bolton and C. O'Shaughnessy

Migraine is an episodic brain disorder characterized by attacks of throbbing head pain and sensitization of the cutaneous facial skin. Current research indicates that the dural blood vessels and their neural connectivity with the trigeminocervical complex play a fundamental role in the generation of these symptoms. As such, characterization of this pathway may provide an insight into the pathological processes occurring during a migraine attack and offer new targets for the development of novel anti-migraine treatment strategies.

Utilizing various experimental techniques such as *in vivo* electrophysiology, intravital microscopy and fos immunohistochemistry, several studies have explored the consequences of trigeminal primary afferent neuronal activation both under 'normal' conditions and during sensitized conditions. Findings to date provide significant evidence that the behaviour of second order neurones in the spinal trigeminal nucleus is fundamentally altered during conditions of dural sensitization. This is sufficient to explain many of the symptoms reported during migraine, indicating that sensitization of dural afferents may underlie at least part of the pathophysiology associated with migraine.

Despite observations of migraine-like symptoms as early as 3000 BC, few hypotheses of the origin of the pain are recorded until the 17th century. Dr Willis' *Practice of Physicke* published in 1684 and reproduced in 1963 (Knapp[1]) states that *'the source of pain is not the brain, cerebellum or medulla'* but rather *'distension of the vessels which pull the nervous fibres one from another and so brings to them painful corrugations or wrinklings'*. The theory that cranial vessels and their primary afferent innervation were the source of abnormality underlying migraine was further added to by the observation of Dubois-Reymond in 1859 that the pain of migraine *'mounts synchronously with the pulse of the temporal artery'* but ceases on compression of the carotid artery.[2] However the 18th and 19th century also saw suggestions of a central neuronal component of migraine with Livening's analogy with epilepsy (1873).

This was further supported by Hughling Jackson who described migraine as *'a form of sensory epilepsy with headache and vomiting as an epiphenomenon'* in 1890.[2] Over 100 years later the debate between a peripheral and central dysfunction as a generator of migraine remains a source of controversy amongst researchers.

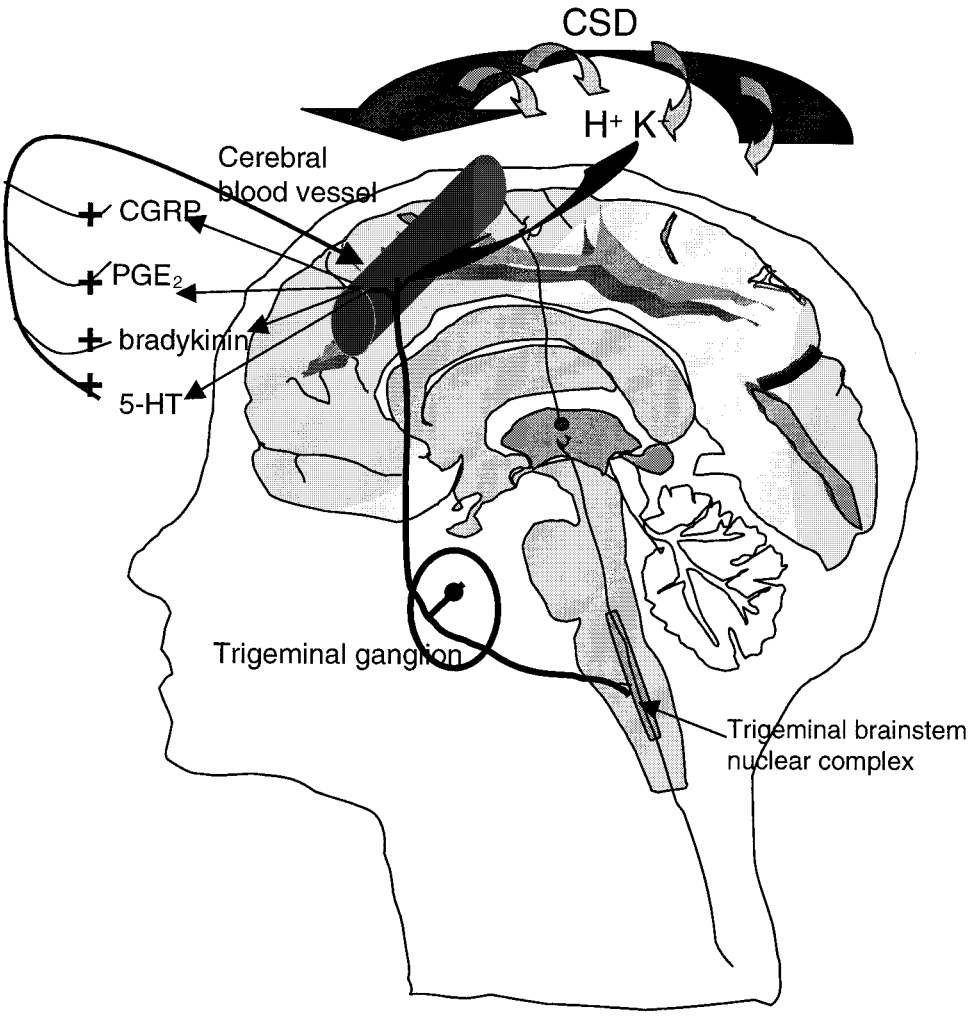
Peripheral sensitization

The development of models which reflect the pain phase of migraine have focused on the sensitivity seen clinically, where patients frequently report pain to normally innocuous stimuli such as head movement and light touch of areas innervated by the trigeminal nerve, including large areas of the face on the side of the headache. This increased sensation is known as allodynia and is often accompanied by hyperalgesia, defined as an amplified response to noxious stimulation. Both phenomena are present in most forms of clinical pain, hence there has been a huge research effort to more fully characterize their underlying cellular mechanisms in the spinal cord, although similar investigations in the trigeminal brainstem nuclear complex (VBNC) have only been evident in the last few years.

At present it is thought that the processes of peripheral and central sensitization are largely accountable for clinical pain sensitivity. Peripheral sensitization describes how peripheral sensory receptors may respond following exposure to algesic mediators that might be released during times of inflammation or tissue injury, whereas central sensitization describes an alteration of the behaviour of second order neurones within the CNS that manifests as either an enlargement of receptive field size, an increased spontaneous firing rate or increased firing rate to peripheral stimuli, or the novel appearance of response to low threshold stimuli that did not previously trigger the cell to fire.

The theory of peripheral sensitization within the dura as a generator of central sensitization has also been extensively investigated (for review see ref. 3). The basis of this hypothesis is that following a cortical disturbance (such as spreading depression), as some believe to be the 'trigger' phase of migraine, potassium and hydrogen ions are released into the extracellular space,[4] resulting in peripheral nociceptor activation and release of mediators such as CGRP, prostanoids, bradykinin, serotonin, histamine, adenosine, neurokinins, cytokines, and NGF from nerve terminals, inflammatory cells, and blood vessel walls. These mediators feedback to further sensitize the peripheral receptors, resulting in a lowered threshold of activation of sensory nerves. In regions where the sensitized nerve terminals innervate the blood vessel walls, the pulsatile flow of blood under these sensitized conditions may then be sufficient to activate these receptors, providing one explanation for the throbbing nature of migraine headache (Fig. 27.1).

This theory has been explored in the anaesthetized guinea-pig[5] and rat,[6] where an inflammatory cocktail was applied to the dural receptive field and the response of second-order neurones in laminae IV and V of the trigeminal nucleus caudalis (Vc) to dural and facial stimulation examined. Profound sensitization to thermal, mechanical, and electrical stimulation of both the dural and FRF were seen that



Spreading depression trigeminovascular activation, and pulsatile blood flow contribute to the development of peripheral sensitization in migraine

Fig. 27.1 Peripheral sensitization in migraine.

lasted for periods up to 10 hours.[5,6] This corresponds well with data from a later clinical study that assessed pain thresholds during a migraine attack with the finding that almost 80% of patients developed cutaneous allodynia ipsilateral to the headache.[7] The study also found that at later time point, allodynia could also be detected in the contralateral head and forearms, which lead the authors to suggest that not only did peripheral sensitization in the dura result in central sensitization of Vc neurones, but also of brainstem neurones such as third order neurones in the

thalamus. Another significant finding of the study was the time-dependence (i.e. the duration which individuals had suffered from migraine) in the development of cutaneous allodynia, implying that the strength of the synapses that facilitate central sensitization increases after repetitive use.

Mechanisms of peripheral dural sensitization

Neurogenic inflammation

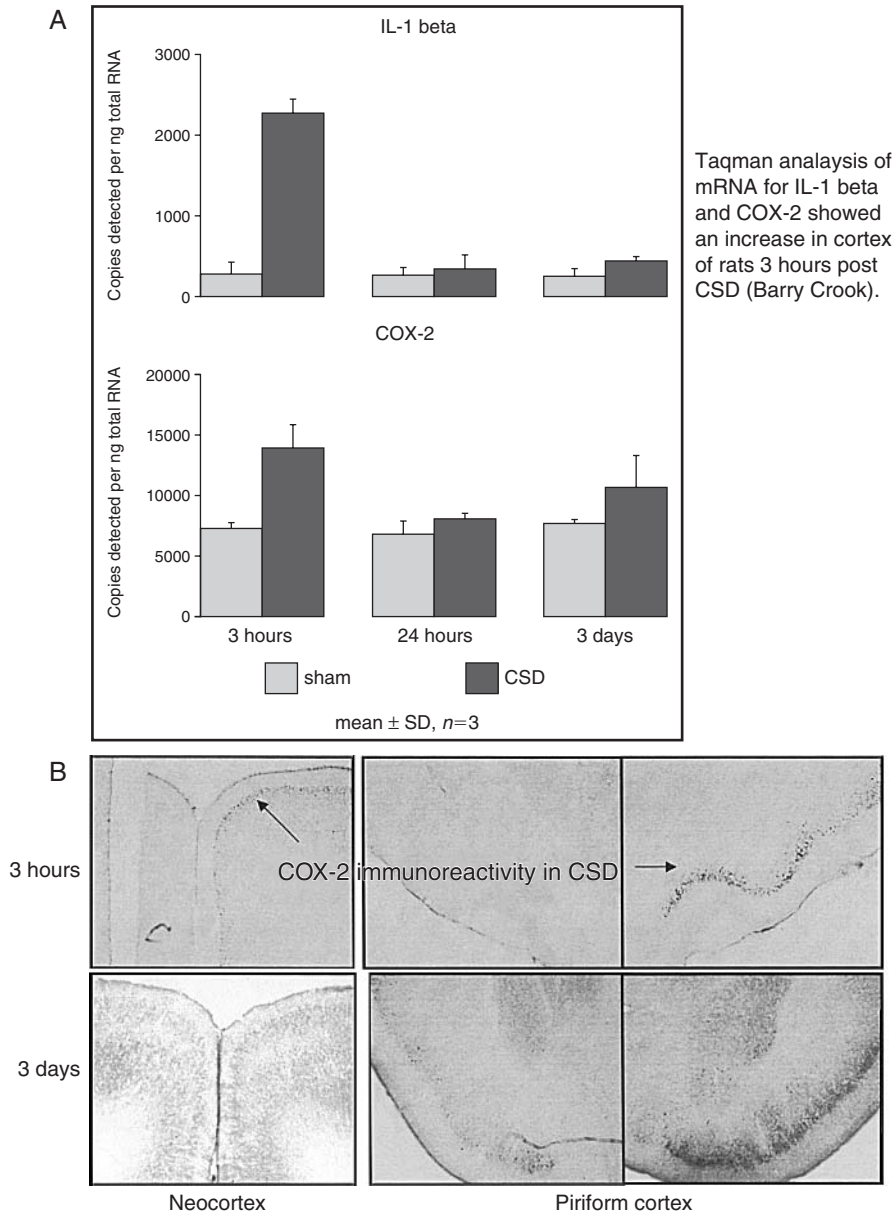
The possible involvement of a neurogenic inflammation within the dura mater during the pain phase of migraine was first suggested by Moskowitz *et al.*[8] who demonstrated that not only could plasma protein extravasation be elicited in dura following stimulation of the trigeminal ganglion[9], but also by cortical spreading depression[10] and following infusion of glyeryl trinitrate (GTN), known to induce migraine in man.[11] Brief infusions (30 minutes) of GTN also resulted in a delayed increase in the levels of several inflammatory markers in the dura, in particular meningeal inducible nitric oxide synthase (iNOS) and the cytokines IL1β and IL6, all showed significant up-regulation between 2 and 6 hours after GTN infusion. Furthermore, dural mast cells appeared degranulated at 4 and 6 hours, providing a further possible site of endogenous inflammatory mediator release following an initial cortical insult.

Studies in our laboratory have shown that mast cells respond to a variety of inflammatory stimuli that would be expected to be present under conditions of peripheral sensitization, such as substance P and NGF. We have also shown that following cortical spreading depression markers, such as cyclo-oxygenase-2 and IL1β, are upregulated in cortex within 3 hours, which further supports the theory that inflammatory cells and mediators may be involved in the sensitization of trigeminal afferents in migraine, and that novel anti-inflammatory therapies will be therapeutic (Fig. 27.2).

Neuropeptides

Calcitonin gene related peptide (CGRP) is the most abundant peptide transmitter found in perivascular sensory trigeminal nerve fibres, where it is colocalized with substance P and other neurotransmitters.[12] In animals, stimulation of these sensory nerve fibres has been shown to cause antidromic release of CGRP with subsequent vasodilatation of the cerebral vasculature. Further evidence for a role of CGRP in the pathophysiology of migraine comes from the observation that the level of CGRP in blood from the external jugular vein, which drains extracranial tissue including the dura and the trigeminal ganglion, is increased during spontaneous migraine attacks.[13] Furthermore, this increased CGRP level is normalized following administration of the anti-migraine treatment sumatriptan.[14]

The ability of CGRP to hyperexcite the trigeminovascular system has also been confirmed in pre-clinical models, where it has been observed to generate dilatation of the MMA, with a subsequent increase in firing of Vc neurones,[15] the increase in Vc neuronal activity was short lived (~6 minutes). However, a role for sumatriptan or



Taqman analaysis of mRNA for IL-1 beta and COX-2 showed an increase in cortex of rats 3 hours post CSD (Barry Crook).

A transient increase in COX-2 in ipsilateral neocortex was seen at 3 hours. A sustained increase was observed in ipsilateral piriform cortex (DC Harrison).

Fig. 27.2 (A) Inflammatory mediators in CSD. (B) CSD induces expression of inflammatory in brain.

CGRP antagonists to reduce this CGRP-induced peripheral sensitization may contribute to therapeutic efficacy (Fig. 27.3).

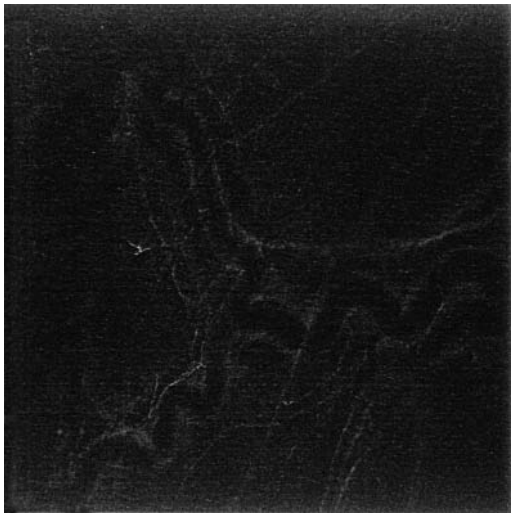
Vanilloid receptors

Vanilloid receptors are implicated in the sensation of thermal and inflammatory pain. They are expressed on C-fibres and can be sensitized on repeated heat, capsaicin, or proton exposure. The agonist activity of pro-inflammatory peptides such as bradykinin is potentiated by protein kinase C-dependent vanilloid receptor phosphorylation.[16] VR1 knock-out mice exhibit deficits in thermal hyperalgesia that accompany tissue injury and inflammation,[17] capsaicin activates trigeminal neurones,[18] and VR1 receptors are expressed in the human trigeminal ganglion,[19] thus raising confidence that blockade of this receptor may be beneficial in migraine.

Prostaglandins

PGs were implicated in the pathology of migraine as long ago as the 1960s, when Bergstrom *et al.*[20] investigated the effects of PGE_1 infusion in healthy volunteers with the finding that 2 out of 3 subjects developed headache and facial flushing. Furthermore, in naturally occurring migraine attacks, PGs have been identified in the saliva of migraine patients,[21] and in sufferers of menstrual migraine a significant increase in the plasma concentration of PGE_2 compared to the headache free period have been reported.[22]

Evidence that PGE_2 may be involved in dural sensitization has now been provided by Ebersberger *et al.*,[23] who showed that in a neurogenic inflammation



Whole mount immunofluorescence showing CGRP immunoreactivity around the MMA following electrical stimulation *in vivo* (Harrison, DC unpublished)

Fig. 27.3 CGRP-immunoreactive fibres in dura mater.

in vitro model, PGE_2, as well as CGRP, release was significantly elevated over basal levels after electrical trigeminal ganglion stimulation and exposure of the dura to inflammatory mediators. The mechanism by which this occurred was further studied by Zimmerman *et al.*,[24] who used ATP and low pH solutions to stimulate the dura in the same model. The authors hypothesized that the enhanced PGE_2 release seen following exposure to ATP, followed activation of $G_{q/11}$ protein coupled P2Y receptors, leading to activation of IP_3 mediated intracellular calcium increase. Interestingly in this study, CGRP release was not detected after exposure of the dura to ATP but was seen after exposure to low pH indicating that during a migraine attack, an initial PGE_2 release with subsequent inflammation and lowered pH may result in CGRP release. This theory has been supported by a study which examined CGRP release from cultured adult rat trigeminal neurones following exposure to PGE_2.[25] Stimulation of EP, DP, and IP receptors evoked CGRP release, and PGE_2 itself could be released from the neurones following treatment with bradykinin via B_2 receptors.[26] Bradykinin has been shown to activate and sensitize sensory afferents that may be of relevence to the pain of migraine.[27,28]

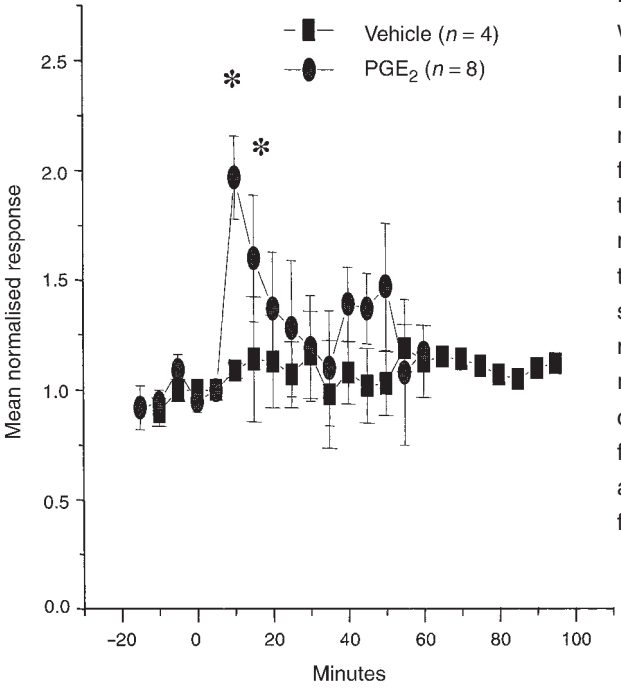
Further to the studies of Burstein *et al.*[6] where exposure of meningeal afferents to a 'soup' of inflammatory mediators, containing histamine, serotonin, bradykinin, and PGE_2 at a low pH, in the anaesthetized rat was reported to increase the response of second order neurones within the TNC, we have carried out a series of experiments in our laboratory, where the effects of PGE_2 alone on dural primary afferents were assessed in a similar model of trigeminal electrophysiology. Here, exposure to PGE_2 (1 mM) resulted in a significantly increased neuronal firing rate above baseline (Fig. 27.4).

These results demonstrate that PGE_2, in its own right, is able to generate sensitization of dural primary afferent fibres innervating the MMA. Furthermore, the increase in afferent input following PGE_2 application is sufficient to alter the behaviour of second order neurones within the Vc over a period that outlasts the peripheral effects, evidenced by increased responses to stimulation in the FRF, which occurred maximally 60 minutes after the PGE_2 stimulation.[29] This corresponds well to clinical data showing cutaneous allodynia on the ipsilateral side of the face occurs approximately 1 hour after the start of a migraine,[7] suggesting that PGE_2 may play a significant role in modulation of the trigeminovascular system under pathological conditions such as migraine.

Summary

The results described here support the hypothesis that following introduction of inflammatory mediators into the peripheral dural receptive field, a sensitization of neurones within the trigeminal brainstem nuclear complex results, and is sufficient to generate an altered neuronal activity that may underlie some of the clinical features of migraine such as headache and facial skin hypersensitivity.

If it is the case that peripheral sensitization is the initiating factor of a migraine attack, then other questions need to be addressed such as the presence of features



Electrophysiological recordings were made as described in Bolton *et al.*, 2002. Data is represented as the mean normalized response to trains of fifty electrical stimuli applied to the MMA, recorded every 5 minutes. PGE_2 was applied at time 0, over the MMA. A significant increases in evoked neuronal activity ($^*p < 0.05$, repeated measure ANOVA) compared to vehicle was seen for 10 minutes after PGE_2 application to the MMA but not following vehicle administration.

Fig. 27.4 Effect of PGE_2 on MMA-evoked activity.

that are likely to have a central origin, for example, premonitory symptoms, the episodic nature of the disease, nausea, and sensitivity to light and sound. Hence current evidence suggests that peripheral sensitization may be secondary to a central dysfunction and, as such, therapies targeted at antagonizing peripheral sensitization are unlikely to block the induction of a migraine, but may well prove to be an effective abortive treatment.

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28 New possibilities for antimigraine therapy via 5-HT receptors?

R. G. Hill, M. J. Cumberbatch, and D. J. Williamson

The study of 5-HT (serotonin) dependent mechanisms has been pivotal in migraine therapy research for many years.[1,2] Indeed, the second seminar in this series devoted the whole meeting to 5-HT mechanisms and more recently a seminar was dedicated to perhaps the most successful product of this field of research, the triptans.[2] The question we are now asking is whether there is significantly untapped potential left in 5-HT receptor mechanisms that will lead to better antimigraine drugs, in particular for use in preventive pharmacotherapy.

We have learned a great deal about the mechanism of action of the triptans since they were introduced (see ref. 3). In particular, the realization that their key mechanism involves agonism at two distinct receptors (5-HT_{1B} and 5-HT_{1D}) raises the question of whether selective agonists stimulating just one of these receptors might have therapeutic advantages. It is also relevant to ask whether the basic mechanisms by which the triptans act can only be exploited for abortive treatment or is there a possibility that preventive use may be feasible?

It has also been found that some of the triptans are ligands for other receptors of the 5-HT_1 family and this has raised the question of whether these receptors in turn constitute novel targets. Lastly, commonly used prophylactic drugs interact with yet other 5-HT receptor families, and although these drugs are notoriously unselective it does raise the question of whether selective ligands for these receptors would provide a better therapeutic option?

Agonism at 5-HT_{1B} receptors

It is now clear that the vasoconstrictor properties of the triptans can be attributed to agonist effects at 5-HT_{1B} receptors.[3] The cranioselective nature of this vasoconstrictor activity (which has been suggested to be an important part of the antimigraine mechanism) can be explained by relative abundance of 5-HT_{1B} receptors in different vascular beds,[4] but it is nevertheless likely that the unwanted constrictor properties

of these drugs on coronary arteries are also due to 5-HT_{1B} agonist activity. Although such coronary events are rare in clinical practice, the use of triptans is contraindicated in patients with known cardiovascular risk factors (see ref. 3 for discussion) thus the probability that 5-HT_{1B} selective agonists might have advantageous therapeutic utility over the existing 5-$HT_{1B/1D}$ mixed agonists seems low. It has been postulated that it might be possible to design a 5-HT_{1B} partial agonist that would retain sufficient efficacy to constrict intracranial arteries but which would have no significant agonism on coronary and other peripheral arteries.[4] Attempts to design drugs with selective efficacy for this and other receptor targets have, in the main, been only partially successful because of the difficulties in extrapolating from the *in vitro* to the *in vivo* situation.

Agonism at 5-HT_{1D} receptors

There are two key non-vasoconstrictor properties of the triptans which have been suggested to explain their ability to relieve acute migraine. These are (1) block of transmitter release from perivascular nerve terminals in the meninges, and (2) block of nociceptive transmission into trigeminal nucleus caudalis. Both effects can be attributed to activation of 5-HT_{1D} receptors in human subjects.[3,5,6] Selective agonists for this receptor may therefore have therapeutic advantages over the unselective triptans that activate both 5-HT_{1B} and 5-HT_{1D} receptors.[7] This topic has been explored in some detail and, in particular, the Upjohn company conducted clinical trials with the selective 5-HT_{1D} agonist PNU-142633 (see ref. 8) but found it ineffective at relieving migraine headache. It should be noted that this agent has lower efficacy at human 5-HT_{1D} receptors than does sumatriptan and it is therefore possible that the hypothesis has not yet been adequately tested. However, in the guinea pig, which has a similar anatomical distribution of 5-HT_{1D} receptors to man, PNU-142633 was effective in reducing neurogenic dural vasodilation.[9] In human isolated coronary arteries a 5-HT_{1D} selective agonist did not evoke contractions at 5-HT_{1D} selective concentrations.[10] The prophylactic potential of this mechanism appears worthy of further study should suitable full agonists at the human 5-HT_{1D} receptor become available.

Agonism at 5-HT_{1F} receptors

Interest in this subtype of 5-HT_1-like receptor as a migraine target stems from the observation that sumatriptan has high 5-HT_{1F} affinity and is clearly an effective antimigraine drug. A selective 5-HT_{1F} receptor agonist, LY334370 (Lilly), has been evaluated in clinical studies against migraine headache.[11] In studies on human isolated blood vessels it was found that there was no correlation between 5-HT_{1F} receptor agonism and the ability of a selection of 5-HT_1-like receptor agonists to contract human isolated middle meningeal arteries.[12] In agreement with this, LY334370 was found not to contract cerebral or coronary arteries, but it was effective at blocking neurogenic extravasation and reduced c-fos expression in trigeminal nucleus caudalis following

a noxious stimulus to the head.[11,13] In a detailed series of experiments, Shepheard *et al.*[13] showed that LY-334370 had no effect on neurogenic dural vasodilation and had no general analgesic properties, but it was effective in reducing the activation of trigeminal nucleus caudalis neurones following electrical stimulation of the dura mater in the anaesthetized rat. Clinical data, from a placebo-controlled double-blind study of oral dosing of LY-334370 in acute migraine, showed that higher doses of 60 and 200 mg were effective against migraine headache. However, this was associated with a greater incidence of central side effects such as dizziness and somnolence than has been reported with triptans.[11] However, the authors pointed out that the high doses needed before treatment with LY-334370 was found effective make it possible that the antimigraine effects were due, at least in part, to 5-HT_{1B} agonism, and likewise the side effects may have been due in part to 5-HT_{1A} agonism.[11] It is therefore still an open question as to whether 5-HT_{1F} agonism *per se* might be a useful prophylactic approach. However, it should be noted that rizatriptan has very low 5-HT_{1F} affinity yet is extremely effective in treating acute migraine, therefore 5-HT_{1F} agonism is unlikely to be essential for the acute antimigraine action of the triptans.[3]

5-HT_7 receptor antagonists

The potential importance of this receptor in migraine has recently been reviewed in detail, so will only be given summary treatment here.[14] There is an abundant 5-HT_7 receptor expression in dural blood vessels and activation of these 5-HT_7 receptors produces a powerful vasodilator response. It has been postulated that 5-HT release preliminary to, or during, a migraine headache might act to produce a 5-HT receptor-mediated dilation which would initiate or exacerbate the headache. If this response is mediated by 5-HT_7 receptors then blocking these sites should have a useful preventive effect. The widespread distribution of 5-HT_7 receptors within the CNS[15] might also suggest an excitatory role in neuronal systems.[14] Evidence from experiments with the available 5-HT_7 receptor antagonists suggests that one important function of this receptor might be in the control of circadian rhythm, although the role of this receptor is not yet fully explored.[1] The ability to test whether blockade of 5-HT_7 receptors has a prophylactic effect in migraine will depend on the availability of antagonist drugs with appropriate properties for clinical use. It has been argued that many of the agents used currently in migraine prophylaxis have appreciable potency as 5-HT_7 receptor blockers,[14] although in experiments on isolated tissues the pharmacology of other receptors appears to dominate. In the spinal cord a role in nociceptive mechanisms has been suggested for 5-HT_7 receptors.[16]

5-$HT_{2B/2C}$ receptor antagonists

The idea that blockade of 5-HT_2 receptors might be effective in the prophylaxis of migraine has been around for some time (see ref. 14 for review). Those drugs

found to have prophylactic efficacy against migraine on empirical grounds, such as cyproheptadine, methysergide, and amitriptyline, have high 5-HT_{2B} receptor activity and are pharmacological antagonists.[14] It has also been reported that the 5-$HT_{2B/2C}$ agonist mCPP evokes migraine in man but, paradoxically, the more potent and selective 5-HT_{2B} agonist, αMe5-HT does not. Immunocytochemical studies reveal that meningeal blood vessels have predominantly 5-HT_{2B} receptors and blockade of 5-HT_{2C} receptors might best be avoided as it is likely to have psychotropic and obesity consequences.[1] Sufficient numbers of agents with mixed pharmacology have been used therapeutically to establish that blockade of 5-HT_{2B} receptors probably does have some prophylactic efficacy against migraine. However, it is probably not worthwhile to evaluate a selective 5-HT_{2B} antagonist as the clinical efficacy of the mixed antagonists is only partial and it has been suggested that many of the agents used currently are equally potent as 5-HT_7 receptor blockers.[14]

5-HT_3 receptor antagonists

There is much evidence linking 5-HT_3 receptors and pain. For example, applying 5-HT to an experimental blister base in human subjects evokes pain and this can be abolished with a 5-HT_3 receptor antagonist.[1] In early clinical trials of 5-HT_3 receptor antagonists, some promising efficacy was seen against migraine but this did not translate into effective treatment. Blockade of 5-HT_3 receptors is proving to be an effective therapy for irritable bowel disorder (IBD),[1] and as there is considerable comorbidity between IBD and migraine, this ongoing use is likely to provide some evaluation of the blockade of these receptors in migraine prophylaxis.

Other 5-HT mechanisms?

Although some antidepressants, notably amitriptyline, have been used successfully for migraine prophylaxis there is no clear correlation with serotonin uptake blockade, and the prophylactic activity could equally well be explained by activity as a 5-HT_7 receptor antagonist.[14] Clues for future research may come from the recent observation that one particular 5-HT-transporter gene polymorphism is associated with an increased risk of migraine.[17] Few, if any, new clues for 5-HT receptor-mediated phenomena in migraine have surfaced in the recent past but it is interesting to note that the T102C polymorphism in the 5-HT_{2A} receptor gene has been associated with migraine aura.[18]

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29 Dihydroergotamine interaction with 5-HT_2 receptors and its relevance to migraine

B. Schaerlinger, P. Hickel, N. Etienne, and L. Maroteaux

Serotonin (5-hydroxytryptamine, 5-HT) receptors have been implicated in the regulation of several psychiatric and neurological disorders related to serotonergic neurotransmission, and specific receptor subtypes have recently been associated with either the pathogenesis or the treatment of migraine headache.[1] A role for 5-HT in migraine has been supported by changes in circulating levels of 5-HT and its metabolites observed during the phases of a migraine attack, along with the ability of 5-HT-releasing agents to induce migraine-like symptoms.[2] The ergot alkaloids semi-synthetic derivative DHE interacts with multiple receptors, at variable receptor affinity, intrinsic activity, and organ-specific access. DHE exhibits alpha-adrenergic and 5-HT_{2A} receptor antagonist activity with only low arterial vasoconstriction potential and behaves as a 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptor high affinity agonist. The long duration of action of DHE appears to result from its main active metabolite, 8′-OH-DHE, which is present at a concentration five to seven times greater than DHE with a long half-life that has been proposed to account for the low rate of headache recurrence observed with DHE.[3] DHE produces selective vasoconstriction in the external carotid artery mediated by 5-$HT_{1B/1D}$ receptors and α_2-adrenoceptors.[4] Both sumatriptan and DHE are effective in aborting migraine headaches. However, headache recurrence is two and a half times as likely with sumatriptan as with DHE.[5] Although still controversial, the prophylactic effect of DHE is believed to be caused through blockade and/or activation of 5-HT receptors including receptors of the 5-HT_{2B} and 5-HT_{2C} subtypes.

Expression of 5-HT_{2B} receptors has been observed on vascular endothelium, and activation of this receptor has been reported to stimulate cGMP via nitric oxide (NO) production.[6] Since stimulation of the 5-HT_{2B} receptors can induce the relaxation of the pig cerebral artery via the release of nitric oxide, it may thus trigger migraine

headache through vasodilation[7] and agents that modulate 5-HT$_{2B}$ receptors either have or may have clinical utility in the therapy of migraine headache.[8]

We have assessed the respective affinity for DHE and 8′-OH-DHE by competition toward [^{125}I]DOI on stably transfected LMTK$^-$ cells expressing human 5-HT$_{2B}$ or 5-HT$_{2C}$ receptors. DHE and 8′-OH-DHE interacted with these receptors at high affinity. The 8′-OH-DHE interacted according to more than one site and affinity was much higher than DHE (K_i = 8.85 ± 0.13) for 5-HT$_{2B}$ receptors (Fig. 29.1). The cGMP levels

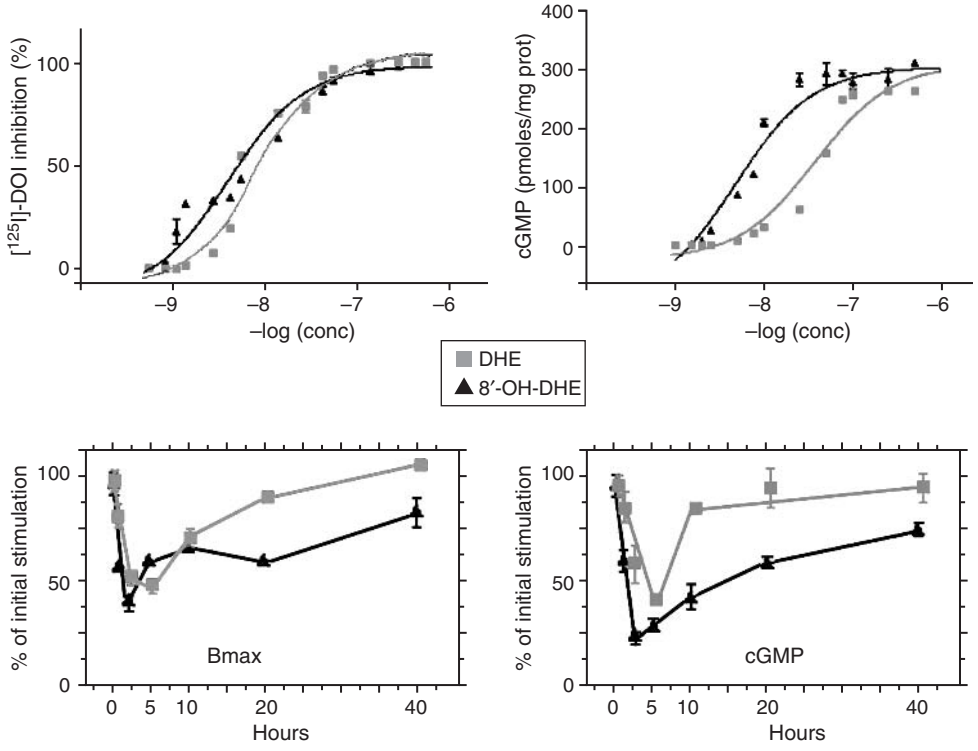

Fig. 29.1 Pharmacology of DHE or 8′-OH-DHE at 5-HT$_{2B}$ receptors. Competition curves against [^{125}I]DOI at 5-HT$_{2B}$ receptors are shown with data points representing the percentage of specific [^{125}I]DOI binding inhibition at each concentration of DHE or 8′-OH-DHE at 5-HT$_{2B}$ receptors. Concentration response curves for cGMP production at 5-HT$_{2B}$ receptors. Data points represent the intracellular cGMP levels for each concentration of DHE or 8′-OH-DHE for 5-HT$_{2B}$ receptors-expressing cells. Values are expressed as pmol per mg of protein. Time course of the Bmax and cGMP levels obtained at 5-HT$_{2B}$ receptors after chronic exposure. Data points expressed as percent of the initial stimulation (maximum) represent the average of the number of specific binding sites or of the cGMP levels remaining for 5-HT$_{2B}$ receptors-expressing cells at each time point after exposure to saturating concentrations of DHE or 8′-OH-DHE. Grey squares: DHE; Black triangles: 8′-OH-DHE.

were evaluated upon stimulation by DHE or 8′-OH-DHE of LMTK⁻ cells expressing 5-HT_{2B} or 5-HT_{2C} receptors and thus, either compounds behaved as agonists. The EC_{50} seems to correspond to high-affinity sites previously identified, the pEC_{50} of 8′-OH-DHE being 8.32 ± 0.09 for 5-HT_{2B} (Fig. 29.1) and 7.83 ± 0.06 for 5-HT_{2C} receptors for cGMP (not shown).

Stably transfected LMTK⁻ cells expressing 5-HT_{2B} or 5-HT_{2C} receptors, exposed to saturating concentration (1 μM) of DHE or 8′-OH-DHE, showed that 5-HT_{2B} and 5-HT_{2C} receptors responded differently to these two compounds, the 5-HT_{2B} receptor being more sensitive to chronic stimulation by 8′-OH-DHE. The number of sites of 5-HT_{2B} receptor and 5-HT_{2C} receptor was much less affected by chronic exposure to DHE and returned to initial values within 10–15 hours. Similarly, the cGMP levels, assessed by radioimmunoassay, showed that the 5-HT_{2B} receptor stimulation of cGMP was more reduced after chronic stimulation by 8′-OH-DHE than 5-HT_{2C} receptors, as previously observed for Bmax, but much less affected by chronic exposure to DHE.

Although it is generally believed that the cellular signal transduction mechanisms activated by 5-HT_2 receptors are indistinguishable, recent data suggest significant differences in their signaling cascades. 5-HT-stimulated IP_3 production has been previously observed at the 5-HT_2 receptors. In response to 5-HT stimulation, 5-HT_{2A} receptor-mediated cGMP generation was reported in C6 glioma cells through NO-dependent pathway. The 5-HT_{2C} receptors expressed in the choroid plexus have been shown to trigger the formation of cGMP formation. Concerning the 5-HT_{2B} receptor, the pharmacological study of pig pulmonary arteries[9] showed that DHE elicited a reversible endothelium-dependent relaxation of precontracted arterial ring segments, associated with an increase in cGMP. The 5-HT_{2B} receptor was also reported to stimulate the relaxation of the pig cerebral artery via the release of NO.[7] For the first time, we have studied long-term effects of DHE exposure and found that 5-HT_{2B} receptors exhibit the most dramatic degree of desensitization with respect to cGMP coupling, 8′-OH-DHE being more effective and permanent. In 5-HT_{2B} receptor naturally expressing cells, as well as in transfected LMTK⁻ fibroblasts, agonist stimulation triggers intracellular cGMP production through activation of endothelial NO synthase.[6] The group I PDZ motif at the C terminus of the 5-HT_{2B} receptor, which is required for recruitment of the endothelial NO synthase transduction pathways, may thus be implicated in this desensitization process.

The long duration of action of DHE resulting from its major active metabolite 8′-OH-DHE and its long half-life can therefore account for the low rate of headache recurrence observed with DHE[3] through long-lasting inhibition of vascular 5-HT_{2B}-dependent second messengers. Furthermore, the activation of 5-HT_{2B} or 5-HT_{2C} receptors inhibits the 5-$HT_{1B/1D}$ receptor function that can be blocked upon concomitant 5-HT_{2A} activation, revealing the antagonistic roles of 5-HT_{2A} and 5-HT_{2B} receptors in regulating the function of 5-$HT_{1B/1D}$, a receptor involved in migraine pathogenesis.[10] The antimigraine action of DHE could, therefore, involve a combination of acute agonist action at 5-$HT_{1B/1D}$ receptors, a long-lasting uncoupling of 5-HT_{2B} receptors, and an insurmountable antagonist action at 5-HT_{2A} receptors that may all be relevant to DHE chronic antimigraine action and should be confirmed on cerebral vasculature (Fig. 29.2).

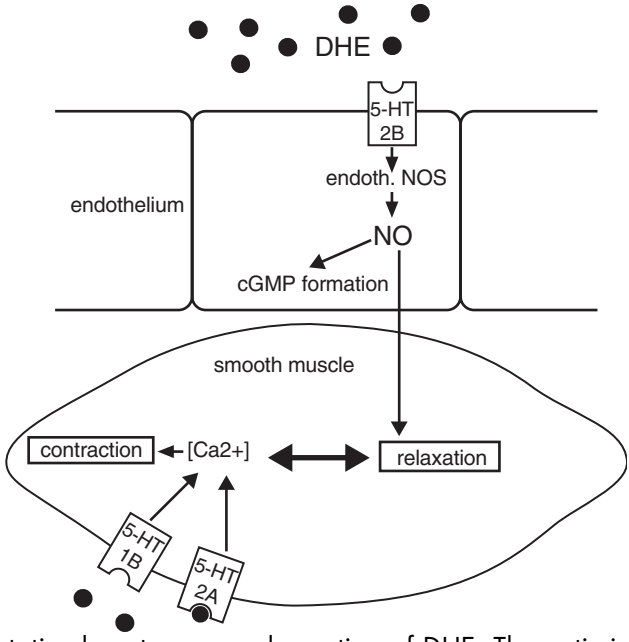

Fig. 29.2 Putative long-term vascular action of DHE. The antimigraine action of DHE may involve a combination of acute agonist action at 5-HT$_{1B/1D}$ receptors, a long-lasting uncoupling of 5-HT$_{2B}$ receptors and an insurmountable antagonist action at 5-HT$_{2A}$ receptors.

These pharmacological data well comfort the preliminary results of the clinical trial 'PROMISE' (Prophylaxis of Migraine with Seglor®). This study indicates a positive action of DHE on migraine as revealed by the number of patients without any attack after 5 months of treatment, the decrease in the number of attacks, in the attack duration, in the pain and attack intensity and in the attack treatment use, and, consequently, the improvement of the quality of life of these patients.

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30 Migraine prophylaxis with drugs influencing the angiotensin system

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Introduction

Various antihypertensive drugs have proven effective in migraine prophylaxis, most notably some of the β-blockers and a calcium antagonist (flunarizin). Contraindications and side effects do, however, limit their use. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AII) receptor inhibitors are extensively used for both hypertension and cardiac failure, and with a very favourable side effect profile. A small open study with ACE inhibitors from 1995 indicated efficacy against migraine,[1] and a meta-analysis involving 12 000 patients who were treated with an AII receptor blocker for other conditions, but in whom headache was registered, indicated that the risk of headache was about one-third lower compared with those taking placebo.[2] In addition, we tried on selected migraine patients first the ACE inhibitor lisinopril and later the AII blocker candesartan, and these trials also indicated a prophylactic effect. For these reasons, our group conducted two studies with almost identical designs, first with lisinopril (in 1999–2000),[3] and later with candesartan cilexitil (in 2001–2002)[4] for migraine prophylaxis.

Patients and methods

The mode of patient recruitment was somewhat different in the two studies. From the outpatient clinic of the Department of Neurology, 35 of 60 (58%) patients were recruited to the lisinopril study but only 3 (5%) to the candesartan study. The remaining (25 and 57 patients) were recruited after a newspaper advertisement.

Inclusion criteria were: age 18–65 years; written informed consent; migraine with or without aura according to IHS criteria with 2–6 attacks per month; debut of

migraine at least one year prior to inclusion; and start of migraine before age 50 years. Exclusion criteria were: interval headache not distinguishable from migraine; pregnancy, nursing or inability to use contraceptives; decreased hepatic or renal function; hypersensitivity to active substance; history of angioneurotic edema; psychiatric illness; use of daily migraine prophylactics at least 4 weeks prior to start of study.

Both studies were conducted as placebo-controlled, randomized, double-blind, crossover studies. First, patients entered a 4-week placebo run-in period. In each study, 60 non-responders to placebo were allocated to treatment according to a randomization list in which 30 individuals received 12 weeks treatment with active medication (lisinopril in the first study and candesartan in the second) followed by a wash-out period during which they received matching placebo tablets. The wash-out period lasted for 2 weeks in the lisinopril study, and for 4 weeks in the candesartan study. Thereafter, these patients entered a 12-week period with matching placebo tablets. The other 30 patients started with a placebo period followed by wash-out and then a period on active substance. In the lisinopril study, in the first week of either 12 weeks period, the subjects received 1 tablet qd (10 mg lisinopril or placebo), and in the following 11 weeks 2 tablets qd (lisinopril 20 mg or placebo). In the candesartan study, patients received 1 tablet throughout the study, containing either candesartan cilexitil 16 mg, or placebo.

At baseline and at the end of the trial, all patients had a complete physical and neurological examination. At the start of the study, and two weeks after the first and second treatment periods, blood analyses were made. Blood pressure and heart rate were recorded at the beginning of all periods of the trials as well as two weeks after the first and second treatment period. Throughout the studies the patients kept a diary with daily recordings of duration and severity[1–4] of headache and severity of accompanying nausea, photophobia, phonophobia, use of symptomatic drugs, and sick leave. The patients stated whether the headache was experienced as migraine or not. The diaries were checked at each visit. On the back of the headache diaries, patients registered all adverse events.

Prior to the study we calculated that with a study group of 60 patients, the power to detect a mean placebo-candesartan difference of 0.6 SD (2-sided $\alpha = 0.05$) would be 93%. To compare end-point variables, and to assess carryover or period effects (not found), the Wilcoxon signed rank test was used.

Results

In the lisinopril study, there were 5 dropouts, 4 in the active period (due to side effects: fatigue,[1] dizziness,[1] exanthema/monoarthritis,[1] or no reason given), and 1 in the placebo period (due to lack of response). In the candesartan study, there were 3 dropouts, 2 in the active period (1 due to depression, 1 with no reason given) and 1 in the placebo period (no reason given). In both studies, there were some non-compliers with regard to tablet intake or diary entries, thus leaving 47 (38 women, mean age 41 (SD 9); 9 men, mean age 43 (SD 5)) and 46 patients (35 women,

mean age 42 (SD12) years; 11 men, mean age 48 (SD 13) years) for the per protocol analysis.

In the per protocol analysis in both studies, there were significantly less headache during the periods on active medication compared with the placebo periods (Table 30.1). The percent of patients with ≥50% less headache ('responders') in the active period compared with the placebo period was for the variable days with migraine, 30% in the lisinopril study and 46% in the candesartan study. For headache severity index, the figures were 32% and 41%. In the intention to treat

Table 30.1 Efficacy parameters and blood pressure in lisinopril and candesartan studies (per protocol analysis) during treatment periods of 12 weeks

	Lisinopril ($n = 47$)			Candesartan ($n = 46$)		
	Mean (SD)	% difference	p*	Mean (SD)	% difference	p*
Days with headache						
Active	19.7 (14)			12.9 (11)		
Placebo	23.7 (11)	17	0.0003	16.5 (11)	22	0.001
Days with migraine						
Active	14.5 (11)			9.0 (9)		
Placebo	18.5 (10)	22	0.0003	12.3 (8)	27	0.001
Hours with headache						
Active	129 (125)			92 (128)		
Placebo	162 (142)	20	0.0002	123 (139)	25	0.001
Severity index**						
Active	297 (325)			189 (271)		
Placebo	370 (310)	20	0.0003	281 (288)	33	0.001
Triptan doses						
Active	15.7 (15)			6.3 (10)		
Placebo	20.2 (17)	22	0.0003	7.7 (10)	18	0.03
Doses of analgesics						
Active	14.5 (23)			12.4 (19)		
Placebo	16.2 (20)	20	0.45	18.3 (31)	32	0.01
Days with sick leave						
Active	2.30 (4.3)			0.85 (1.9)		
Placebo	2.09 (2.5)	−10	0.77	1.52 (2.7)	44	0.054
Systolic blood pressure						
Active	121 (14)			115 (16)		
Placebo	128 (13)	5	<0.0001	126 (20)	9	<0.001
Diastolic blood pressure						
Active	78 (10)			70 (10)		
Placebo	83 (10)	6	<0.0001	77 (11)	9	<0.001

*Wilcoxon signed rank test.
**Headache severity index: headache hours × headache severity.

Table 30.2 Adverse events in lisinopril and candesartan studies

	Lisinopril *N*= 60	Candesartan *N*= 57
Coughing		
Active	8	0
Placebo	3	1
Fatigue		
Active	3	4
Placebo	3	2
Dizziness		
Active	7	11
Placebo	4	9
Tendency to faint		
Active	3	0
Placebo	0	2
Others		
Active	3	17
Placebo	3	30
Total		
Active	24	32
Placebo	13	44

analysis in both studies, results were in general similar though marginally less in favour of the active period than in the per protocol analysis, except for the variable days with sick leave where the difference became statistically significant in the candesartan study (active 1.4 days, placebo 3.9 days, $p < 0.01$)

In the lisinopril study, there were markedly more coughs, dizziness, and tendency to faint in the active than in the placebo period (Table 30.2). In the candesartan study there were no large differences between the two periods except with regard to fatigue, which was quite rare in both periods.

Discussion

A relatively marked migraine prophylactic effect was seen with both lisinopril and candesartan. The effect seemed larger with the latter drug, but it may also be that patients in the lisinopril study were more seriously affected by headache (cfr the higher level of headache in the lisinopril study comparing the placebo periods in the two studies, Table 30.1). Therefore, any comparison between the two drugs with regard to efficacy must be made with great caution.

As to side effects, both drugs were in general well tolerated and there were few dropouts. Evaluation of adverse events was made somewhat differently in the two studies: in the lisinopril study, what were considered as totally benign and innocuous

phenomena were omitted, whereas in the candesartan study all somatic phenomena reported by the patients were registered. The main expected side effects (orthostatic phenomena, dizziness, and fatigue) were probably recorded in much the same way in both studies. In both studies, the counting of adverse events was made before the treatment code was broken, which should assure that no bias was introduced due to knowledge of treatment. It seemed that particularly coughing, but also dizziness and tendency to faint, were adverse events related to intake of lisinopril, but probably not with candesartan. More troubling side effects in the lisinopril study may explain, at least partly, why patients in this study did not have a reduction in days with sick leave in the active period, in contrast to what was found in the candesartan study.

A comparison between candesartan and other drugs used for migraine prophylaxis is difficult to perform because of the differences in design, end points, and patient groups. A meta-analysis of propranolol[5] 160 mg per day for prophylaxis of migraine indicated a relative improvement of 33% with regard to headache severity index with active medication compared with placebo, which is similar to the results of the candesartan study (33% in the per-protocol analysis) but better than the lisinopril study (20%).

Only speculations can be offered as to why medication influencing the angiotensin system has a prophylactic effect in migraine. Migraine without aura is more frequent in subjects with the ACE-DD gene, and migraineurs with this gene also have higher ACE-activity and a higher frequency of attacks.[6] Angiotensin is a circulating hormone, but it is also involved in local functions in many organs, including the brain.[7] It can modulate cerebrovascular flow,[8] influence fluid and electrolyte homeostasis, autonomic pathways and neuroendocrine systems, modulate potassium channels and calcium activity in cells,[7] increase the level of dopamine and the main serotonin metabolite, 5HIAA, and activate NFκβ, which is associated with increased expression of inducible nitric oxide synthase.[9,10]

Lisinopril and candesartan are not contraindicated in asthma, claudication, heart conduction block or diabetes, as are the β-blockers, and they also give less asthenia, sleep problems, and sexual dysfunction. Hence, since they have a favourable side effect profile, are easy to use with one daily dose, and are well known to general practitioners, lisinopril, and particularly candesartan, may become useful tools in migraine prophylaxis.

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31 Naratriptan in the preventive treatment of refractory chronic migraine

A. M. Rapoport, M. E. Bigal, S. J. Tepper, and F. D. Sheftell

According to the revised version of the International Headache Society (2003), chronic migraine (CM) is considered a complication of migraine. Patients with CM usually have a past history of episodic migraine, reporting a process of transformation characterized by headaches that become more frequent over months to years, with the associated symptoms becoming less severe.[1] Patients then develop a pattern of daily or near daily headache resembling chronic tension-type headache, with a few attacks of full-blown migraine superimposed.[1] They often have daily headaches.[2]

The treatment of CM often poses a major challenge for the clinician. Even when given the best expert care, a significant percentage of these patients still persist with daily or near-daily headaches.[4–6]

The triptans represent a benchmark in the acute treatment of migraine. Their mechanism of action is based on the stimulation of specific serotonin (5-hydroxytryptamine; 5-HT) receptors including peripheral 1_B and central and peripheral 1_D subtypes.[7] Naratriptan was the third selective 5-$HT_{1B/1D}$ agonist to be introduced in the US for the acute treatment of migraine.

A previous study by Sheftell *et al.*[8] reported three patients with CM, previously refractory to a wide variety of traditional preventive pharmacologic and nonpharmacologic interventions, that showed remarkable reduction in the frequency and intensity of daily headache after receiving preventive treatment with daily naratriptan.

Compared to other triptans, naratriptan has attractive pharmacological properties for preventive use (even though this use is off label): it has a more gentle adverse effect profile, a longer half-life, and lower recurrence rates when directly compared with other triptans.[9–11]

We aimed to retrospectively review the efficacy of naratriptan in the preventive treatment of 27 patients with refractory CM.

Methods

This review was performed at The New England Center for Headache (NECH), Stamford, CT, U.S.A. Clinical records and headache calendars (diaries) of 27 patients fulfilling the following inclusion criteria were reviewed:

1. Age ranging from 18 to 65 years old.
2. Diagnosis of CM (formerly Transformed Migraine) according to the criteria proposed by Silberstein *et al.*[1]
3. Previous failure of at least 4 preventive treatments.
4. Daily use of naratriptan for no less than 2 consecutive months.
5. Stable dose of medication used to prevent CM in the last 2 months.

The decision to use naratriptan in the patients presented was based on their refractoriness to other preventive therapies (alone and in combinations), as well as on the good results obtained in three previous patients followed in the same headache center (not included in this study).[8] Patients were enrolled in this study no less than 6 months after they had tried and failed an extensive management program.

Once the patient decided to participate in the study, all preventive drugs were stabilized and naratriptan 2.5 mg bid was added. The medication was often begun at one half tablet in the morning and raised every 3 days by half a tablet till the final dose of one tablet twice per day was attained. Headache calendars were reviewed, and the diary results of the month immediately previous to the naratriptan prescription were considered as the baseline. For extremely severe breakthrough headaches, occasional use of fast onset triptans was permitted (after careful explanation that this was an off label use, without controlled safety data).

We considered the following outcomes:

1 — Frequency of pain;
2 — Intensity of pain, measured on a scale ranging from 0 (no pain) to 3 (severe pain);
3 — Number of days with severe headache per month;
4 — Headache index (frequency × intensity);
5 — Proportion of subjects that reverted to an episodic pattern of pain after 6 months of treatment.

The outcomes from number 1 to 4 were compared to the baseline period after 1 month, 2 months, 6 months, and 1 year.

Descriptive statistics were applied. The assumption was that the values were sampled from Gaussian distributions and tested using the normality test of Kolmogorov–Smirnov. Matched comparisons in nonparametric distributions were performed using the Friedman test with post-test. Nonmatched comparisons in nonparametric distributions were performed using the Kruskal Wallis test with post-test.

Results

Our sample consisted of 27 subjects, 20 (74.1%) females. Ages ranged from 18 to 64 years old, with a mean of 44.5 years (SD=12.0; 95% CI: 42.8–52.3). All subjects were followed for at least one year after being given naratriptan. The average length of treatment at the NECH, for these patients, was 5.3 years. The number of preventive drugs tried before inclusion in the naratriptan study ranged from 4 to 21 (average of 7.2). When included, 14 (51.8%) subjects were using 1 preventive drug, 12 (44.4%) were using 2 preventive drugs and 1 (3.7%) was using 3 different preventive drugs. At the moment of the inclusion in the study, 13 (43.1%) patients were overusing acute care medications, despite the previous attempts at detoxification. Four (14.8%) were overusing butalbital compounds; 4 (14.8%), acetaminophen combined with ASA and caffeine; 2 (7.4%), opioids; 2 (7.4%), NSAIDs; 1 (3.7%), ASA.

Of the 27 subjects that completed the evaluation at 2 months (criteria of inclusion), 20 (74.1%) continued to use naratriptan after 6 months and 18 (66.7%) after 1 year of inclusion. All the subjects that stopped using naratriptan except one were acute medication overusers.

At inclusion, 13/27 (43.1%) were overusing acute care medications. At 6 months, 6/20 (30%); at 1 year, 5/18 (27.8%). These differences are not statistically significant.

Figure 31.1 compares the frequency of headache at baseline and after initiation of naratriptan therapy, in those subjects who were overusing acute medications, in non-overusers, and overall. Overall, a statistically significant reduction of headache frequency was obtained in 2 months (15.3 vs 24.1 at the baseline, $p<0.001$), 6 months (9.1, $p<0.001$) and 1 year (7.3, $p<0.001$). Statistical significance also was reached between 6 months and 1 month (9.1 vs 19.7, $p<0.05$) and between 1 year and 1 month (7.3 vs 19.7, $p<0.01$). The same pattern was obtained in the overusers and non-overusers sub-groups.

The mean number of severe attacks per month is presented in Fig. 31.2. Overall, a significant reduction, compared to baseline, was obtained in 1 month (5.6 vs 12.5 at the baseline, $p<0.01$), 2 months (5.7, $p<0.01$), 6 months (2.8, $p<0.01$) and 1 year (2.6, $p<0.01$). The same pattern was verified in the overusers and non-overusers subgroups, the response being more evident in the non-overusers sub-group.

Figure 31.3 displays the headache index. Similarly to the outcome frequency, a statistically significant reduction of the headache index was obtained in 2 months (33.0 vs 56.4 at the baseline, $p<0.001$), 6 months (19.5, $p<0.001$), and 1 year (17.2, $p<0.001$). Statistical significance was also reached between 6 months and 1 month (19.5 vs 42.2, $p<0.05$) and between 1 year and 1 month (17.2 vs 42.2, $p<0.01$). Again, the same pattern was obtained in both subgroups.

Of the 20 subjects that continued to use naratriptan after 6 months of inclusion, 13 (65%) reverted to an episodic pattern of pain (migraine). At one year, 11 (55%) still continued episodic, one (5%) reverted again to CM, and two (10%) were lost to follow-up.

No patients were intolerant to naratriptan in the follow-up period. No one was withdrawn from the study due to adverse events. There were no increased adverse

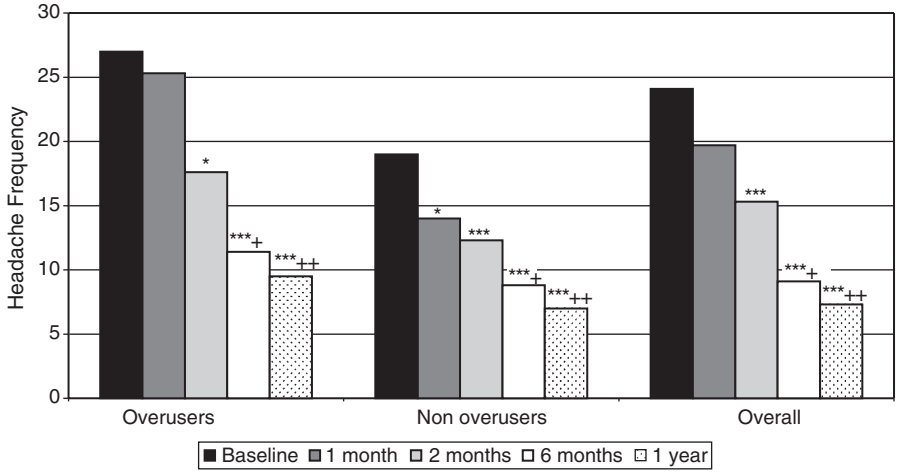

Fig. 31.1 Comparison of the frequency of pain at baseline and after the start of daily naratriptan, overall, and by groups of overusers and non-overusers of acute medication.***$p<0.001$ compared to baseline; $^{+}p<0.05$ vs 1 month; $^{++}p<0.01$ vs 1 month.

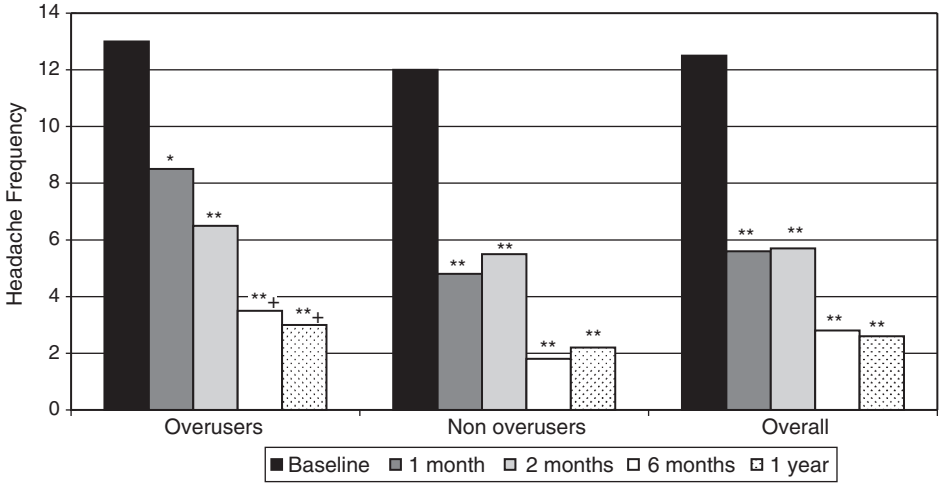

Fig. 31.2 Comparison of the mean of days per month with severe pain at baseline and after the start of daily naratriptan, overall, and by groups of overusers and non-overusers of acute medication; *$p<0.05$ compared to baseline; **$p<0.01$ compared to baseline; $^{+}p<0.05$ compared to 1 month.

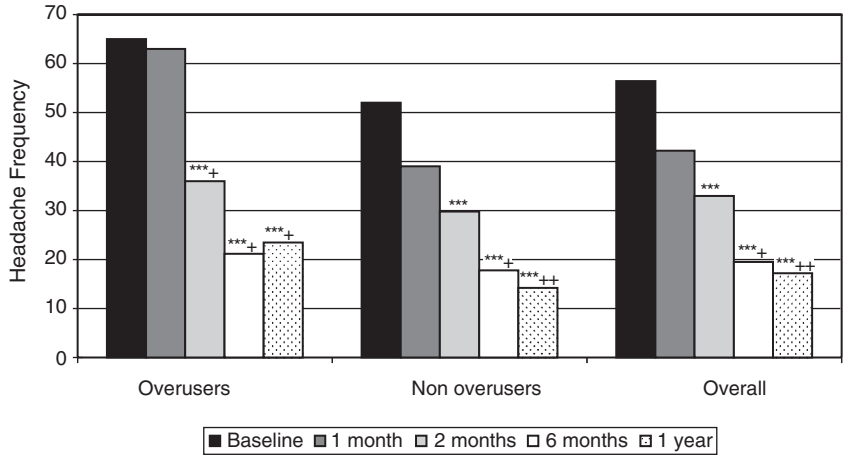

Fig. 31.3 Comparison of the headache index at baseline and after the start of daily naratriptan, overall, and by groups of overusers and non-overusers of acute medication. ***$p<0.001$ compared to baseline; $^{+}p<0.05$ vs 1 month; $^{++}p<0.01$ vs 1 month.

effects to the occasional use of faster acting triptans for severe breakthrough headache, and no significant adverse events associated with the nartatriptan. No EKG or BP changes were noted in any patient.

Conclusions

We present data from 27 patients seen in a tertiary care headache center whom we decided to treat with daily naratriptan based on two factors: 1 – Their refractoriness to other standard preventive therapies (alone and in combination), very frequent headaches, high levels of pain and disability, and good cardiovascular health; 2 – The previous pilot experience of the authors[9] with naratriptan in the preventive treatment of CM.

Our data can be summarized as follow: 1 – Naratriptan is effective in reducing the frequency of CM both in subjects overusing or not acute care medication. Statistical significance was reached in two months and sustained for one year (the duration of the study). Additional statistically significant reduction of the frequency was obtained in 6 months and 1 year, when compared to 1 month; 2 – Naratriptan reduced the amount of severe pain. Significance was reached in 1 month and sustained in 2 months, 6 months, and 1 year; 3 – Naratriptan significantly reduced the headache index beginning at 2 months and continuing for 1 year (the duration of the study). Additional statistically significant reduction of the headache index was obtained in 6 months and 1 year, when compared to 1 month; 4 – A subgroup of subjects receiving naratriptan preventively for CM

reverted to episodic migraine; 5 – Naratriptan is well-tolerated when given for this indication on a daily basis. 6 – The use of occasional doses of fast onset triptans for breakthrough headache was well tolerated in this study, which was not powered as a safety study.

Several cautions must be taken when analyzing our results. First, this is a retrospective open label review of our experience, neither placebo-controlled, nor blinded. Second, only patients with very refractory CM were included, which can significantly underestimate the results of the therapy. Third, we measured neither the disability nor the quality of life of our patients and did not make any inference about the cost-effectiveness of the treatment. Fourth, some of the subjects stopped overusing acute care medication during the study. Part of the benefits could, therefore, be due to analgesic discontinuation, rather than naratriptan efficacy alone. The analysis of the subgroup that did not discontinue the medication during the study showed, however, the same pattern of benefit. Finally, since some patients had difficulty affording the medication, adherence was a problem when prescribing daily naratriptan. To avoid this, we decided to analyze just patients who used daily naratriptan for at least 2 months. This approach could, therefore, have biased the tolerability analysis, since subjects that had tolerated naratriptan for 2 months were more expected to continue to tolerate for the length of the study. Moreover, despite assessment of tolerability, the safety of the chronic utilization of naratriptan was not evaluated by subsidiary exams.

The results of this review indicate that naratriptan must be considered as a potential adjunctive treatment for refractory CM. While naratriptan has neither been submitted to, nor approved by, regulatory authorities for use in the treatment of CDH, these preliminary results are promising. Since CM evolves from migraine, both share pathophysiological mechanisms, especially regarding serotoninergic pathways, and naratriptan is a serotoninergic agonist with a long half-life, our data suggest that naratriptan may have a role in the preventive treatment of chronic migraine pending further controlled studies.

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32 PROMISE study (PROphylaxis of MIgraine with SEglor®)

A. Pradalier, N. Lanteri-Minet, Ch Lucas, and G. Geraud

Objectives and methodology

The objective of the trial was to evaluate the efficacy of Seglor® (dihydroergotamine) in migraine prophylaxis. It was a double-blind, randomized, multicentre, placebo-controlled and parallel group study conducted in GP practice and according to the IHS criteria.[1,2] An important patient management program was also implemented: the 113 investigators were specialized in clinical research and conscious of the importance of patient education, the patients were followed-up during 6 months with 7 visits, the compliance was measured by classical pill counts by the investigator and by electronic caps that registered each open of the bottle.[3] The investigators and the patients were aware of the electronic measurement of the compliance.

A 4-week placebo period (baseline) was followed by a 5 months treatment period with either Seglor® 5 mg bid or placebo. The main criteria was the reduction of the number of attacks. The attack characteristics were established from a patient diary by periods of 28 days.

The assumption used to calculate the number of patients to be enrolled was based on a reduction of the attacks frequency of 55% with SEGLOR and 30% with placebo.

The secondary endpoints were the decrease of the mean and total duration of attacks, the decrease of their intensity, the patient preference and the decrease of symptomatic treatments. The Quality of Life (QoL) was measured by the MSQ questionnaire.[4] Two QoL groups were defined in the ITT population according to the MSQ questionnaire: patients with a good QoL ($MSQ \geq 80$; $n = 53$) and patients with a bad QoL ($MSQ < 80$; $n = 288$).

The statistical analysis compared the baseline results with those of the 4th month (primary criteria) and 5th month study. The Student *t*-test was used for the

quantitative variables, Chi-squared or Fischer test for the qualitative variables and Wilcoxon–Mann–Whitney test for the ordinal variables.

Results

There were 465 patients enrolled, 384 randomized, 380 evaluated for tolerance, and 363 for the ITT analysis of efficacy. They were 39.1 ± 11.2 years old, 80.7% were women and they had 15.7 years of migraine history.

The frequency of attacks was reduced by 57% with Seglor® (from 3.3 ± 1.0 to 1.4 ± 1.4) but without statistical difference against placebo (51%, from 3.3 ± 1.1 to 1.6 ± 1.5). Because of the low number of attacks, any stratification on frequency was possible. The sub-populations study has shown a better efficacy of Seglor® in the smokers population ($p < 0.05$) and a big trend ($p = 0.06$) in patients younger than 40-years-old as well as in patients with zero attacks at the end of the trial ($p = 0.06$).

Seglor® has significantly demonstrated better efficacy ($p < 0.05$) in most of the secondary endpoints, particularly the mean duration of an attack (Fig. 32.1), the total duration of attacks per month (Fig. 32.2), the decrease of symptomatic treatments (antalgics level II, OMS, Fig. 33.3) and the patient preference.

The electronic monitoring of patient's compliance to prescribed therapy did not reveal any difference between randomized groups ($p > 0.05$). Undercompliance was more frequent than overcompliance. In both randomized groups, the compliance decreased over time, compliance to the evening dose is significantly lower than to the morning dose, and compliance during the weekend is significantly lower than during the week days.

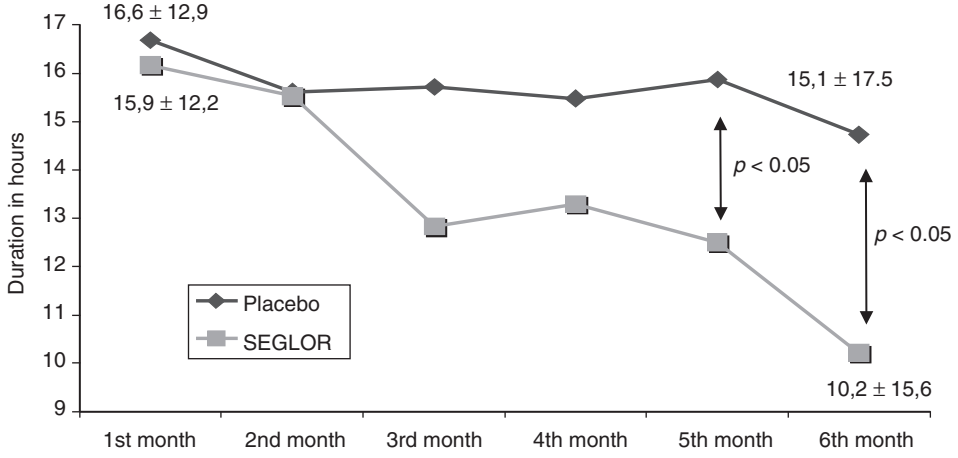

Fig. 32.1 Mean duration of an attack.

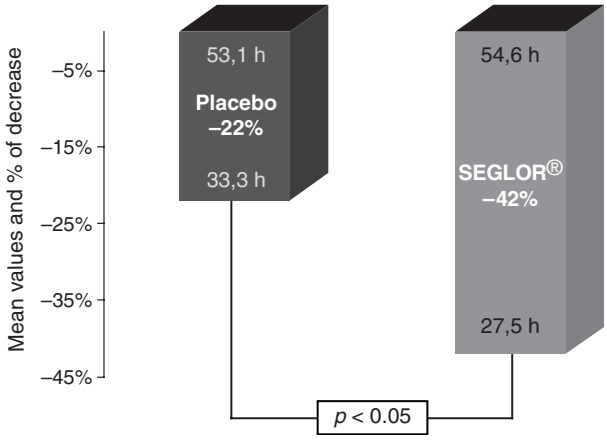

Fig. 32.2 Total duration of attacks per month.

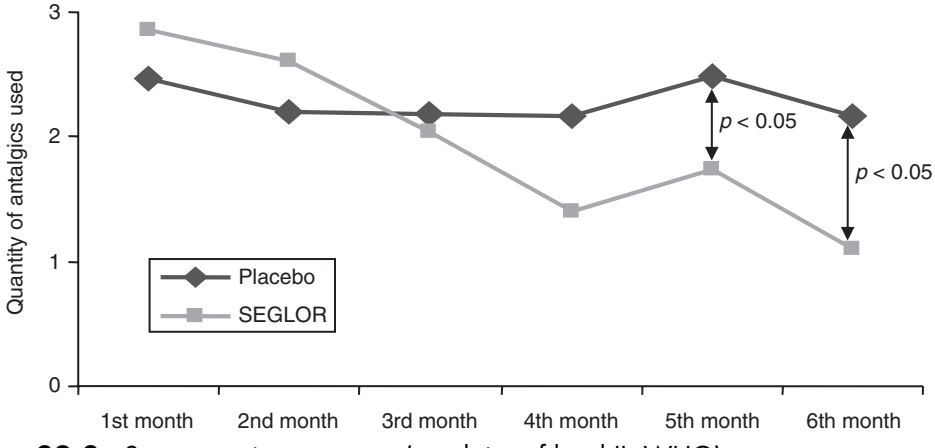

Fig. 32.3 Symptomatic treatments (antalgics of level II, WHO).

The patient's QoL at the inclusion was independent of the attacks frequency ($p > 0.05$) but correlated to their duration ($p < 0.05$) and their intensity ($p < 0.01$). The frequency (Table 32.1) and the duration of the attacks were reduced significantly with Seglor® versus placebo ($p < 0.05$) only in the group of patients with bad QoL. The number of days with pain was also reduced significantly ($p < 0.05$) only in this group.

The tolerance was statistically comparable to the placebo.

Table 32.1 Evolution of the frequency of attacks in the population with bad quality of life

	Placebo		Seglor®
Decrease of the frequency (%)	49	($p=0.01$)	60
Responder rate (%)	55	($p=0.03$)	68

Discussion

PROMISE is the largest trial conducted in migraine prophylaxis with the IHS criteria. The placebo efficacy of this trial can be easily explained: the investigators were very experienced and well trained in conducting clinical trials. Every patient performed 7 visits during 6 months and the compliance was registered electronically. The patients were aware of this fact in order to improve the patient management. The efficacy of this patient management program confirms that a specific program should be recommended to all physicians in combination with any drug prescription.

The mean frequency of attacks was lower than expected (3.3 attacks per month) but the patients are representative of the population seen by GPs. The placebo effect seems to be higher when the frequency is lower (analysis of 13 recent IHS trials). Moreover, up to now, any recognized prophylactic treatment has been able to demonstrate a higher efficacy than placebo when the frequency of attacks during baseline is lower than 4 attacks per month. The electronic monitoring of the compliance did not reveal any difference between randomized groups. This fact could be explained because of the good tolerance of Seglor®. The QoL results have confirmed that the frequency of attacks is not enough to confirm the need of a migraine prophylaxis treatment. The patient's QoL at the inclusion was independent of the attacks frequency. Moreover, our results confirm that only the patients with a bad QoL would benefit from a migraine prophylaxis treatment. In these patients, Seglor® has demonstrated a significant efficacy on the frequency and duration of attacks, as well as on the number of days with pain.

The already known good tolerance of Seglor® was confirmed to be statistically comparable to the placebo one, which is a key issue if we consider the proposed alternatives (beta-blockers and anti-epileptic drugs).

Conclusion

PROMISE brings a real question regarding the main criteria to be used in clinical trials with GPs. The frequency of attacks would not probably be the best statistical criteria in populations with a number of attacks lower than 4 per month at baseline. Some other variables like duration, intensity or the quality of life have to be taken into account too. Among these variables, the patient's Quality of Life seems to be the

best parameter to confirm the need of a migraine prophylaxis treatment. According to the group of patients with bad Quality of Life, Seglor® has demonstrated a significant efficacy on the frequency and duration of attacks and the number of days with pain. The patients with good Quality of Life, independent of the frequency of attacks, do not probably need a migraine prophylaxis treatment.

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33 Serotonin receptors and migraine prophylaxis—the case of dihydroergotamine

M. Hamon, S. Bourgoin, and L. Lanfumey

The place of dihydroergotamine among antimigraine drugs

Important progress has been made for the last decade in the knowledge of physiopathological mechanisms underlying migraine attack. This was achieved notably through extensive investigations on the mechanisms of actions of drugs, such as triptans, which efficiently stop headache when they are administered acutely, immediately after the first clinical signs of a migraine attack.[1] Like triptans, the classical antimigraine drug, dihydroergotamine (DHE), is also effective in the acute treatment of migraine, probably through its ability to prevent activation of the trigemino-vascular pathway, and the associated release of calcitonin gene-related peptide from activated trigeminal fibres.[2] However, in contrast to triptans, DHE is also effective for the prophylactic treatment of migraine,[3] but the mechanisms underlying the latter effect are essentially unknown.

Comparison of the pharmacological profiles of triptans on one hand and DHE on the other hand shows that both types of drugs are high affinity agonists at serotonin 5-$HT_{1B/1D}$ receptors, and convergent evidence strongly supports the view that this property actually accounts for their efficacy to stop migraine attack under acute conditions. Whereas triptans are indeed rather selective ligands of these receptors, DHE exerts additional effects at other 5-HT receptor types as well as at dopaminergic and adrenergic receptors (see ref. 4), and one can wonder whether at least part of these additional effects might be causally related to the unique prophylactic efficacy of the ergot derivative. Indeed, numerous studies demonstrated that selective dopaminergic and adrenergic receptor agonists and antagonists do not exert antimigraine effects,[5] indicating that agonist/antagonist actions of DHE at

these receptors do not contribute to its antimigraine properties. In contrast, other data support the idea that 5-HT receptors different from the 5-$HT_{1B/1D}$ types might be implicated in the prophylactic action of DHE.[6] Among them, the 5-HT_{1A} receptor type, which is recognized by nanomolar concentrations of DHE,[5] is an interesting target to consider because several other antimigraine drugs which are efficient under chronic treatment conditions such as methysergide, cyproheptadine, pizotifen and (–)propranolol also bind with a relatively high affinity to this receptor. Furthermore, 5-HT_{1A} receptors are known to control neuronal excitability,[7] and one can wonder whether this action might participate in the antimigraine effect of DHE under chronic prophylactic treatment conditions.

Dihydroergotamine and its metabolite, 8′-OH-dihydroergotamine, are agonists at central 5-HT_{1A} receptors

In addition to DHE itself, its metabolite 8′-OH-DHE, has to be included in studies aimed at assessing the functional status of 5-HT_{1A} receptors under chronic DHE treatment because of its long half-life and accumulation in tissues up to levels much higher than those of the parent compound under such conditions.[8] Several complementary approaches can be used to assess the effects of ligands at 5-HT_{1A} receptors. We selected *in vitro* binding studies with selective radioligands, quantification of the autoradiographic labeling by [^{35}S]GTP-γ-S of G proteins functionally coupled to the receptors, and electrophysiological recordings of neuronal responses to 5-HT_{1A} receptor agonists and antagonists.[4] Indeed, 5-HT_{1A} receptor stimulation is well known to trigger a hyperpolarization of the plasma membrane of neurones, which, in case of the spontaneously firing serotoninergic neurones, results in a reduction in their firing rate.[9]

Binding studies with both [^{3}H]8-OH-DPAT, a selective 5-HT_{1A} agonist radioligand, and [^{3}H]WAY 100635, a selective 5-HT_{1A} antagonist radioligand, demonstrated that DHE as well as 8′-OH-DHE are recognized with nanomolar affinity (K_i = 8–28 nM) by 5-HT_{1A} receptors in rat hippocampal membranes. As expected from 5-HT_{1A} receptor agonists, both DHE and 8′-OH-DHE were found to enhance the specific binding of [^{35}S]GTP-γ-S to areas where there are concentrated 5-HT_{1A} receptors in rat brain sections (hippocampus, septum, dorsal raphe nucleus: DRN), and this effect could be completely suppressed by the selective 5-HT_{1A} receptor antagonist, WAY 100635. Interestingly, the maximal increase in 5-HT_{1A}-mediated [^{35}S]GTP-γ-S specific binding caused by DHE and its metabolite in the hippocampus was significantly less than that evoked by full 5-HT_{1A} agonists such as serotonin itself and 5-carboxamido-tryptamine (5-CT), indicating that both ergot derivatives act as partial agonists at these 5-HT_{1A} receptors. In contrast, no differences were noted between the maximal effects of 5-HT and 5-CT on one hand, and DHE and 8′-OH-DHE on the other hand, at the level of the DRN, as expected from complete activation

of 5-HT_{1A} receptors by all these compounds in this region. Because the latter receptors correspond to autoreceptors on serotoninergic neurones whereas 5-HT_{1A} receptors in the hippocampus are heteroreceptors located on postsynaptic targets of these neurones,[9] these observations tended to support the idea that DHE and 8′-OH-DHE are full agonists at 5-HT_{1A} autoreceptors but only partial agonists at postsynaptic 5-HT_{1A} heteroreceptors. Indeed, electrophysiological recordings of neurones endowed with these receptors provided a clear-cut demonstration of this inference. As expected from agonists, both DHE and 8′-OH-DHE exerted a negative influence on the firing rate of DRN serotoninergic neurones down to a complete blockade with 30–100 nM of these compounds (Fig. 33.1), like that observed with full 5-HT_{1A} receptor agonists.[9] In contrast, at the level of the hippocampus, direct application of DHE onto pyramidal neurones in the CA1 area hardly affected their membrane potential as a concentration as high as 30 μM was required to produce maximal hyperpolarization, reaching only half of that caused by 5-HT or 5-CT. In this respect, 8′-OH-DHE was more potent than its parent compound because the same partial response was observed with only 0.3 μM of the metabolite. As expected from changes evoked by 5-HT_{1A} receptor stimulation, the effects of DHE and 8′-OH-DHE were completely prevented by WAY 100635 (Fig. 33.1). Accordingly, these convergent data indicated that both DHE and 8′-OH-DHE act as full agonists at 5-HT_{1A} autoreceptors in the DRN, and as partial agonists at postsynaptic 5-HT_{1A} heteroreceptors in the hippocampus. At the latter level, the metabolite is more potent than the parent compound, which has special relevance regarding the effects of long term treatment with DHE (see ref. 8).

Possible relevance of the 5-HT_{1A} agonist properties of DHE and 8′-OH-DHE to their antimigraine prophylactic action

A large body of evidence supports the idea that inhibition of DRN 5-HT neuronal firing in response to local 5-HT_{1A} autoreceptor stimulation is causally related to the anxiolytic action of such an intervention. In particular, other partial 5-HT_{1A} receptor agonists such as buspirone and ipsapirone are well known to decrease anxiety-driven behaviors in relevant animal paradigms through their action specifically at these autoreceptors to inhibit the firing of DRN 5-HT neurones.[9] As migraine attacks are often triggered by stress and/or anxiogenic events, it can be reasonably inferred that the prophylactic action of DHE may be underlain, at least partly, through its own effects, and those of its main metabolite 8′-OH-DHE, at DRN 5-HT_{1A} autoreceptors.

At the cellular level, the stimulation of 5-HT_{1A} receptors always triggers a hyperpolarization, thereby reducing the excitability of neurones endowed with these receptors.[7] Comparison between DHE and 8′-OH-DHE showed that the metabolite, much more than the parent compound, exerted at least a partial agonist action at

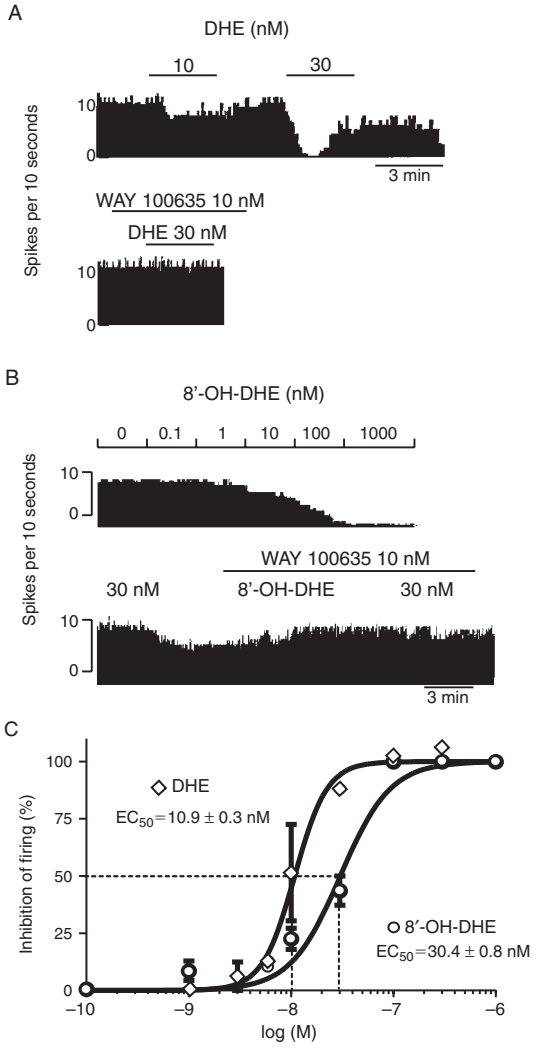

Fig. 33.1 Inhibitory effects of DHE and 8′-OH-DHE on the firing of serotoninergic neurones in the dorsal raphe nucleus (DRN) Experiments were performed using rat brain stem slices. (A–B)—Firing rate histograms (in spikes emitted per 10 seconds) of DRN serotoninergic neurones exposed to increasing concentrations of DHE (A) or 8′-OH-DHE (B). In both cases, the inhibitory effect of these drugs was prevented by the concomitant application of WAY 100635 (10 nM). (C) – Concentration curves of the inhibitory effects of DHE and 8′-OH-DHE on the firing of DRN serotoninergic neurones. Data are expressed as percent inhibition with respect to the baseline firing rate (in the absence of DHE and 8′-OH-DHE). Each point is the mean ± S.E.M. of data obtained in at least 4 individual cells for each concentration ([M] on abscissa) of DHE or 8′-OH-DHE tested. The dotted lines point at the EC_{50} values of the compounds.

both DRN and hippocampal 5-HT_{1A} receptors, suggesting that it probably stimulates 5-HT_{1A} receptors throughout the CNS. A general decrease in the excitability of 5-HT_{1A} receptor expressing neurones can thus be expected, especially under chronic treatment conditions such as those for migraine prophylaxis, because of the long lasting tissue accumulation of 8′-OH-DHE.[8] This effect should notably concern serotoninergic neurones in anterior raphe nuclei whose activation has been proposed as a first event in the hypothetical mechanisms triggering a migraine attack (see ref. 1). Accordingly, 5-HT_{1A} receptor (partial) stimulation by 8′-OH-DHE and, to a lower extent, DHE, might both reduce neurone hyperexcitability, which has been proposed to be causally related to migraine attack,[10] and prevent stress-induced activation of serotoninergic neurones, including those in the DRN which send fibers around blood vessels in the meninges (but this is still a matter of controversy). Through the latter action, 8′-OH-DHE (and its parent compound) might therefore prevent local 5-HT release, and subsequent activation of pial 5-HT receptor types (5-HT_{2B}, 5-HT_7) possibly at the origin of migraine-triggering vasodilation (see ref. 5).

Other 5-HT receptor-mediated effects of DHE and their possible implication in its antimigraine prophylactic action

In any case, these 5-HT_{1A}-mediated actions of DHE and 8′-OH-DHE have to be considered as only one component of the pharmacological profile responsible for the prophylactic efficacy of DHE because selective agonists at 5-HT_{1A} receptors are indeed devoid of clear-cut antimigraine effects.[5] In addition to 5-HT_{1A} receptor stimulation, effects of DHE at other 5-HT receptor types have therefore to be taken into account. Indeed, DHE is a potent agonist at 5-HT_{1B} and 5-HT_{1D} receptors, and this property might also be involved in its prophylactic action, especially because of the long half-life of the ergot derivative (and its metabolite). Through both a resulting long lasting presynaptic inhibition of the release of vasoactive neuropeptides (calcitonin gene-related peptide, substance P) and vasoconstriction of pial vessels, DHE might locally prevent any vasodilation, possibly at the origin of a migraine attack. At the level of 5-HT_{1F} receptors, DHE is also an agonist ($K_d = 0.25\,\mu M$), and this action can result in the blockade of the trigeminal pathway that conveys migraine-associated pain signals.[5] In case of 5-HT_2 receptors, DHE is known to exert an antagonist action at the 5-HT_{2A} subtype and an agonist action at 5-HT_{2B} and 5-HT_{2C} subtypes, the latter being shared with 8′-OH-DHE (see ref. 4). However, under chronic treatment conditions, 5-HT_{2B} and 5-HT_{2C} receptors desensitize (Maroteaux, personal communication), and, finally, the resulting effect of DHE (and its metabolite) is a partial (at least) blockade of all 5-HT_2 receptor subtypes. Because these receptors mediate excitatory actions of 5-HT, such an effect might also contribute to a decreased neuronal excitability (and anxiolytic-like effects) in migraineurs. In addition, inactivation of 5-HT_{2B} receptors should prevent any

vasodilatory action of 5-HT mediated by these receptors. At the level of 5-HT_6 receptors, DHE has been shown to exert a partial agonist action (K_d=15 nM), whereas in contrast it acts as a high affinity antagonist (K_i=10 nM) at 5-HT_7 receptors. Because 5-HT_7 receptors mediate vasodilatory effects of 5-HT, especially in the meninges, and 5-HT_6 receptor blockade is anxiogenic (see ref. 5), it can be inferred that the latter two actions of DHE also possibly contribute to its ability to prevent migraine attacks under chronic treatment conditions.

Clearly, DHE is a unique compound with properties regarding several 5-HT receptor subtypes that all converge to prevent the neuronal and vascular events associated with migraine attacks. At the level of 5-HT_{1A} receptors, we found that its metabolite, 8′-OH-DHE, is even more potent to trigger neuronal events possibly contributing to migraine prophylaxis.[4] Apparently, 8′-OH-DHE is also more efficient than DHE to desensitize 5-HT_{2B} and 5-HT_{2C} receptors (Maroteaux, personal communication). If such differences between the metabolite and the parent compound also concern the other 5-HT receptors relevant to their antimigraine effects, this would mean that 8′-OH-DHE is in fact responsible for the therapeutic effect of DHE under prophylactic treatment conditions.

Acknowledgements

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34 What is the mechanism of action of ACE inhibitors in migraine prophylaxis?

R. Peatfield

Introduction

Cough is a common side effect of angiotensin converting enzyme(ACE) inhibitors. It is believed to be due to the inhibiting effect of these drugs on bradykinin metabolism,[1] and in the management of hypertension it can be circumvented by substituting angiotensin II receptor blocking drugs, which control the blood pressure without inducing cough. I report a patient with frequent intractable migraine, who proved unresponsive to most prophylactic drugs and had side effects when on the only ones that influenced his migraine. He responded well to lisinopril, though the drug induced an unacceptable cough, and when losartan was substituted, his cough soon settled but the migraine recurred.

Case report

A solicitor, now aged fifty, was first seen in 1992 with frequent bifrontal throbbing headaches with visual blurring, but no other focal symptoms. His father, his paternal uncle, and brother were also affected. At presentation his headaches were occurring up to five times weekly, so a variety of prophylactic drugs were tried over subsequent years (Table 34.1). Some control of his headaches was achieved with methysergide, and later topiramate 25 mg daily totally suppressed the attacks, but he developed nausea and severe dysarthria, which prevented him from working. Lisinopril 20 mg daily was tried next—his headaches were again relieved, but he developed a cough which persisted even when the dose was lowered to 10 mg daily.

Table 34.1 Table of prophylactic drugs

Drug	Daily dose	Effect of headache	Side-effects
Pizotifen	1.5 mg nocte	Milder	Impotent
Atenolol	50–100 mg	Helped marginally at first	
Atenolol	200 mg	No help	
Methysergide	1 mg daily	No use	
Propranolol	up to 320 mg	No use	Impotent
Fluoxetine	20 mg	Cheered up, headaches unchanged	Impotent.
Valproate	up to 600 mg	Marginally less severe, frequency unchanged	
	Increase dose to 1.6 G daily	No benefit	Confused, with inappropriate behaviour.
Methysergide	1 → 2 mg tds	Working! 3–4 per week instead of 5–7; stopped at 6 month limit	
Dothiepin	50 mg daily	Did not help, 6 attacks weekly	
Methysergide	6 mg/day all year	5–6 attacks weekly	
Flunarizine	2.5 mg daily	Did not help headache	Very sedative; asleep at the end of the working day, Impontent
Methysergide	2 mg tds, with Naproxen and Naratriptan.	Headaches every 2 days	Couldn't sleep, Snoring, Impotent
Gabapentin	3G daily	Didn't think there had been an improvement; at least 5 attacks a week	Ill Nausea, retching; face red
Topiramate	12.5 mg daily, Increasing slowly	Headache free when on it	Nausea, retching; Dysarthric attacks on 25 mg daily
Lisinopril	20 mg daily	Headaches helped	Speech better, Persistent cough
Losartan	150 mg daily	5–6 headaches weekly, usually at 10pm–2am. Often less intense, but needing 3 S/C Sumatriptans weekly	Cough settled
Topiramate	7.5mg daily from sprinkle capsules	Very modest improvement	None
Imidapril	5mg daily	Awaited	

Lisinopril was then discontinued and losartan substituted. His cough settled within two weeks, but his headaches increased and were occurring five times weekly, even when taking 100–150 mg daily. Topiramate was then tried again, this time at the very low dose of 5 mg daily with modest benefit, and Imidapril (which is said to cause less cough than lisinopril) has just been added.

Discussion

The value of lisinopril for migraine prophylaxis was discovered serendipitously,[2] and has been confirmed in a double-blind trial.[3] No clear consensus has emerged as to its mode of action, as lisinopril is not only an inhibitor of Angiotensin Converting Enzyme (ACE), but it is also believed to alter sympathetic activity, inhibit free radical activity, and increase prostaglandin synthesis.[4] It also hydrolyses encephalins and their precursors.[5] There is evidence that higher ACE levels and certain polymorphisms of its gene are found in migraineurs,[6] though it is not yet clear how this contributes to the pathogenesis of migraine.

Cough is a common side-effect of ACE inhibitors, and is believed to be due to the inhibition of the breakdown of bradykinin and other inflammatory mediators in the respiratory mucosa.[1,7] To circumvent the cough in the management of hypertension, blockers of the angiotensin II receptor have been developed, and recently Tronvik *et al.*[8] have demonstrated that Candesartan 16 mg daily is also effective in the prophylaxis of migraine. This evidence supporting the beneficial effect of angiotensin II receptor blockers implies that these receptors are directly involved, perhaps by interfering with nitric oxide synthesis.[9] This patient's response to lisinopril and not losartan, of course, does suggest that the modes of action of the two drugs might not be identical. It is certainly difficult to reconcile the enhancement of bradykinin activity with the view that headache as a symptom is mediated by a neurogenic inflammatory process in extracranial blood vessels.[10] There are no known differences between candesartan and losartan, so we assume this patient was particularly refractory, and probably in the minority unresponsive to losartan in any case.

Acknowledgement

I am grateful to Professor Lars Stovner for his comments.

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35 Triptans with methysergide

D. Valade

There is a discussion specially in France with the Drug Agency to prove that the contra-indications of Triptans/Methysergide are more theoretical than factual. In this study we present our experience concerning the contra-indication indicated by laboratories according to regulation.

The contra-indications of the triptans include all the D.H.E. and particularly Methysergide as prophylactic treatment. Is it realistic? Because when you look at the prescriptions of the practitioners, there is a lot of association but no adverse event.

I give you my experience on the last one hundred patients treated with the association, Methysergide/Triptans.

The distribution was the same as migraine in general population: 15% male and 85% female with a mean age of 46.8 years (18–65 years).

All migraineurs according to IHS criteria were suffering from migraine since an average of 24.6 years (3–42 years), with a frequency of attacks: 4.2 per month (1–12), on a scale of intensity: mild = 1, moderate = 2, severe = 3, very severe = 4; an average of 3.04.

All patients were on Methysergide: 7% one per day, 29% two per day, 70% three per day, during an average of 21.1 months (1–66). All the patients interrupted the drug for 1 month every 6 months.

Triptans were prescribed: 29% Zolmitriptan, 44% Sumatriptan (per os and Spray), 17% Naratriptan, 10% Sumatriptan subcutaneous.

The necessary 2 hours delay between the Methysergide and Triptan intake was always respected.

The association of the two drugs was an average of 1.4 years (6 months to 4 years). Only 1 patient stopped the treatment because of gastric side-effects; however, no patient stopped for adverse event linked to the association Methysergide/Triptan. All the patients were active and most patients suffered from more severe attacks than normal migraineurs.

In our practice we have had no problem with the combination Methysergide/Triptan, as long as the 2 hours interval between the 2 drugs is respected. Therefore, this theoretical contra-indication should be suppressed or may be changed in caution for use.

36 New targets I: discussion summary

J. Olesen

Two posters from France demonstrated the potential of modern techniques for studying agonist receptor interaction and the subsequent intracellular cascade of events using dihydroergotamine (DHE). This substance is a 5-HT_{1A} receptor agonist, a mechanism known to give antianxiolytic effects. The effect was shared with the main metabolite of DHE. DHE is also a potent agonist at 5-HT_{1B} and 5-HT_{D} receptors. At the 5-HT_{2B} receptor both DHE and its metabolite induce desensitization, which perhaps could be responsible for its prophylactic effect. DHE is also a 5-HT_{7} receptor antagonist. Thus, DHE seems to have all the desired properties of a universal antimigraine agent in relation to the 5-HT receptors. Nevertheless, it is a fairly poor prophylactic agent as was illustrated by a large double-blind study, presented as a poster, that showed no significant difference between active and placebo. A possible positive effect of this study may have been missed due to an unusually high placebo effect of around 60%. Further studies are planned in more severely effected patients. Celestine O'Shaugnessy had given an excellent account of the various possible mediators of migraine pain. This led to a discussion of the differences between spinal cord mechanisms and trigeminal mechanisms. So far, no marked differences have been shown between the two systems regarding any of these neurotransmitters or receptors. In functional assays Ray Hill and his group have, however, shown different responses to 5-$HT_{1B/D}$ receptor agonists and this seems to be the only difference so far known between the two systems. It was pointed out that very significant differences must exist since, for example, nitroglycerine leads to marked headache but no pain in other parts of the body. The same is true of histamine, CGRP, and Sildanafil. This dramatic difference in response must indicate a similarly marked difference in nociceptors or pain pathways. Further reflecting our relative ignorance about the trigeminal system is the fact that we are still not completely sure about mechanisms of action of the triptans. Some patients respond beautifully to one triptan but not at all to another although they belong to the same class of drugs and as far as we know, have the same mechanisms of action. This led to discussion of 5-$HT_{1B/D}$ receptor agonists for migraine prophylaxis. In the early days, the triptans were presumed to have both acute and prophylactic activity, but recent studies have shown that giving a triptan early during a migraine attack of slow onset does not abort the attack! Similarly, sumatriptan

injection given during the aura has no efficacy at all, while sumatriptan is effective in migraine with aura when given during the headache phase. Dr. Hill had data indicating that there was no superfast tolerance to a single dose of a triptan. However, on repeated application there was a decreased efficacy and perhaps, if the triptans were used too early, this tacyphylactic effect could explain why it did not work pre-emptively. In an open trial, presented as a poster, Naratriptan was given as 2.5 mg bid to highly treatment refractory patients with very frequent migraine. Patients were followed for at least one year and a significant reduction of headache frequency was obtained, suggesting that Naratriptan may have a role in the prophylaxis of migraine. However, since there was no placebo control, this could just as well be a time effect also called regression towards the mean.

This brought up a discussion of the limits between triptan therapeutic effect and triptan-induced medication overuse headache. It is now clear that the use of triptans for 10 days a month or more often leads to medication overuse headache that can be treated only by a triptan-free period. When used for long-lasting attacks usually associated with menstruation, the prophylactic use of a triptan for approximately a week did not lead to triptan-induced headache.

The discussion subsequently focused on the possibility that the pharmaceutical industry had actually been overlooking compounds that might be inactive for acute attacks, but active in prophylaxis, having so far focused almost exclusively on the development of acute treatment. It was pointed out that it is much more expensive to develop prophylactic drugs than acute drugs, primarily because longer toxicology is needed, but also because the drug trials take longer and are more expensive. Substances like the NK_1 receptor antagonists might be effective. According to Dr. Silberstein, one such drug had been tried in the USA and was found negative, but other substances might be more brain penetrating and might therefore have better efficacy. Another substance with potential in prophylaxis is a Pfizer substance with extremely high potency in preventing neurogenic inflammation. The case was made that if toxicology is available for two or three months then a proof of concept trial concerning the prophylactic use of a substance is easy and cheap to do compared to the development of drugs for other indications. It was pointed out that industry has an obligation to look into this possibility, because no highly specific compounds are available for the prophylactic treatment of migraine. There is a very large unmet need.

Lastly, two posters describing the use of antihypertensive agents for migraine prophylaxis were discussed. An ACE inhibitor, Lisinopril, had been effective in a substantial subset of migraine patients with modest side effects of the type well known for ACE inhibitors, i.e. mainly persistent coughing. The somewhat unexpected efficacy of Lisinopril had led to a trial of an angiotensin receptor blocker, Candesartan. The study included 60 patients in a crossover design and, thus, had a greater power than provided by using 3–400 patients in a group comparison of design. Reduction in the headache index was approximately 30% compared to placebo, i.e. a therapeutic gain of 30% which is comparable to betablockers. Furthermore, a reduction in triptan use and a 44% decrease in sick days due with migraine as well as an improved quality of life could be shown. Very importantly,

side effects were no more frequent than after placebo. It was recommended that Candesartan should be used as the drug of first choice for migraine prophylaxis because of the absence of side effects. However, one study in one centre is not enough evidence to promote a drug to this status. The manufacturer, Astra Zeneca, was encouraged to support more studies with this important compound. Likewise, other producers of angiotensin receptor antagonists should try their compound for migraine prophylactics.

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Session VI

New targets II

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37 Nitric oxide and its signalling pathways: a rich source of potential targets for migraine therapy

P. J. L. M. Strijbos and A. A. Parsons

Introduction

Nitric oxide (NO) is a simple chemical molecule, yet it participates in highly complex and varied biological activities. It has been implicated as a key messenger molecule in diverse processes including neurotransmission in the central and peripheral nervous systems, vasodilation and host defence signalling during infection, tissue trauma, and neurological disorders.[1,2] In the context of headache, NO may be involved at a multitude of levels. For example, NO mediates vasodilation of dural blood vessels, NO and its synthesizing enzymes are expressed in migraine relevant tissues such as the dura, spinal trigeminal nucleus, and other somatosensory nuclei in the brain, and NO regulates the release of a host of vasoactive molecules including CGRP, serotonin, and substance P.

In the current review, we describe key aspects of the biology of nitric oxide that are relevant to migraineous headache, and highlight opportunities for the development of new therapeutic approaches to migraine.

Nitric oxide: a reactive gas

Throughout the body, NO acts as an unconventional neuronal messenger by virtue of the fact that it has unique properties of reactivity, diffusibility, and degradation. Unlike conventional neurotransmitters, NO is probably not stored, nor released in a vesicular manner, but is generated *de novo*. The activity of NO terminates when it reacts chemically with its targets. As a highly lipophilic molecule, spatial signalling of NO is not restricted to defined synapses or its origin of synthesis, but potentially

it can innervate multiple cells in a manner limited only by diffusion.[3,4] Therefore, NO can contribute to both anterograde and retrograde, autocrine and paracrine signalling. In contrast to the prevailing dogma, NO shows remarkably little reactivity with most cellular components and its targets are highly selective and limited. Nevertheless, NO can interact with:

- heme and non-heme containing Fe proteins
- Fe–S containing proteins
- proteins with labile cysteine-containing residues
- proteins with the potential for oxidation of tyrosine residues
- other reactive oxygen and nitrogen species

Nitric oxide also does not interact with specific membrane-bound receptors, but it can exert very discreet biological effects by the interactions outlined above. Examples of these types of reactions have been well documented in the literature, and include interactions with the heme-containing proteins guanylate cyclase[5] and hemoglobin.[6] Iron–sulphur containing proteins modified by nitric oxide include aconitase[7] and mitochondrial proteins.[8] Further, NO can modulate the activity of proteins by interaction with cysteine residues and this mechanism has been described for an interaction with p21ras leading to activation of the MAPK pathways[9] and also modulation of the NMDA channel.[10,11] Nitric oxide has also been shown to interact with tyrosyl residues within PG endoperoxide[12] and ribonucleotide.[13] It is generally thought that physiological signalling by NO occurs predominantly through an interaction with guanylate cyclase, leading to the production of cGMP. Pathological signalling of NO, on the other hand, is thought to involve an interaction with other reactive nitrogen- and oxygen species, with subsequent formation of potentially more reactive oxidant species (for review see ref. 14)

Excess production of NO and interaction with other reactive nitrogen/oxygen species is associated with cellular pathology. Of these, the formation of peroxynitrite, a product of the interaction of NO with superoxide, appears particularly important. Peroxynitrite is a potent oxidant, capable of evoking lipid peroxidation and modification of nucleic acid residues and protein function.[15]

Formation of nitric oxide

The discovery that NO produced from L-arginine was the endothelium-derived relaxing factor reported originally by Furchgott and others,[16–18] created the impetus to identify and characterize the enzymes responsible for the synthesis of NO. It is now established that NO can be produced by a series of enzymes called NO synthases, which utilize the amino acid L-arginine for NO synthesis, with the concomitant production of citrulline. A neuronal NOS was the first isolated and characterized isoform[19,20] and found to be similar to NADPH-cytochrome P450 reductase. Much research over the last 10 years has provided a detailed description of the properties of the various mammalian NOS isoforms. The original nomenclature

was based on the source of the purified enzyme with rat cerebellum, endothelium and murine macrophage providing key sources of the neuronal, endothelial, and inducible enzymes, respectively. It should be noted, however, that the NOS enzymes are expressed also by cell types other than those in which they were originally identified. As such, an alternative nomenclature has been suggested: nNOS: NOS1, eNOS: NOS2; iNOS: NOS3.

Critical roles for NADPH, flavin adenine dinucleotide (FAD) and flavin adenine mononucleotide (FMN), heme, zinc, and tetrahydrobiopterin in the production of NO have been described. FAD, FMN, Zn, and heme play key structural roles in the oxidation-reductase activity of the enzyme (for review see ref. 21) Tetrahydrobiopterin has been suggested to play a crucial role in dimerization of the inactive NOS monomers and stabilization of resultant bioactive enzyme.[22]

Some of the key properties of the NOS enzymes are summarized in Table 37.1.[23] The most notable differences relate to the control of their expression and enzyme activity: nNOS and eNOS are constitutively expressed enzymes and produce NO in a transient, calcium-dependent manner. iNOS, on the other hand, is not normally expressed, but is induced readily in response to a wide variety of cellular stressors, including tissue trauma, inflammation, and pathological neurotransmission. Moreover, calmodulin has a high affinity for iNOS rendering it essentially Ca^{2+}/calmodulin independent. This allows iNOS to produce NO in a continuous fashion, the extent of which appears restricted only by its protein stability. In contrast, calmodulin has a much lower affinity for the constitutive NOS isoforms, such that NO production by these enzymes closely mirrors cellular calcium transients. Thus, NO generated by iNOS occurs in a transcription-dependent manner and is relatively uncontrolled. Indeed, it has been suggested that the amount of NO generated by iNOS may be as much as an order of magnitude greater than that produced by eNOS and nNOS. These properties render iNOS particularly relevant to a wide range of disorders, including migraine, and suggest that iNOS may represent a key therapeutic target.

Transcriptional regulation of inducible NOS was first described in murine macrophages (incidentally, the expression and regulation of iNOS in human macrophages is controversial). Interestingly, it appears that eNOS and nNOS can be transcriptionally regulated also. For example, nNOS expression can be evoked by glutamatergic transmission,[24] hypoxia, and steroid hormones.[25] A variety of promoter sites have been implicated in controlling nNOS gene expression, including AP-1, NFκB and Hif-1. Similar control of eNOS by shear stress, cytokines, and hypoxia have also been described. These data demonstrate that the constitutive NOS isoforms also can be induced upon trauma.

With respect to iNOS expression, the transcription factor NFκB appears important. Stimuli such as lipopolysaccharide, interleukins, TNF-α and oxidative stress have been shown to evoke iNOS expression by translocation and activation of NFκB. NFκB is a transcription factor which provides a link between membrane signalling events and changes in gene transcription in a variety of cell types. Following membrane receptor activation, the NFκB heterodimer translocates, through phosphorylation and degradation of inhibitory (IκB) subunits, to the nucleus where it binds to DNA and

Table 37.1 Properties of nitric oxide synthase isoforms

Parameter	Active homodimer		
	Neuronal NOS (NOS1)	Inducible NOS (NOS2)	Endothelial NOS (NOS3)
Mass	160 kDa	125–130 kDa	135 kDa
Expression	Constitutively expressed	Not normally expressed	Constitutively expressed
Calmodulin binding	Ca^{2+}/calmodulin dependent	Ca^{2+}/calmodulin independent	Ca^{2+}/calmodulin dependent
Vmax (nmol/min/mg)	7	1000	5
Protein varients	μ, α, β and γ tissue specific isoforms		
Post translational modifications	Specific phosphorylation sites present	Specific phosphorylation sites present	Myristoylation, palmitolylation, phosphorylation sites present
Protein–protein interactions	PSD-95, caveolin 3, phosphofructokinase M		Cavelolin1, HSP90, bradykinin receptor
Major biological role	Neurotransmission	Cytotoxicity/pro-Inflammatory	Vasodilatation

induces subsequent iNOS gene transcription. Other transcription factors have also been implicated in the expression of iNOS including PPAR, AP-1, and hsp-70.

In summary, NO can be formed in many cell types and organ beds by comparable enzymatic processes which can be up-regulated in response to a variety of traumatic events. The regulation of NOS expression is complex and involves a plethora of transcriptional and post-transcriptional events which offer potential targets to interfere with aberrant NO production.

Endogenous inhibitors of nitric oxide synthases

The role of NO in (patho)physiological processes has been studied mainly with the use of inhibitors of NOS. A wide range of different agents is available that inhibit NOS either non-selectively (e.g. L-N^G-monomethyl arginine [L-NMMA]) or that inhibit more selectively a specific NOS isoform (e.g. nitro-L-arginine [L-NA: nNOS]; L-nitro isoleucine [L-NIL: iNOS).

It is important to note that the body generates several arginine analogues that can act as endogenous NOS inhibitors. For example, L-NMMA is a naturally occurring amino acid that is produced by protein arginine methyltransferases (PRMTs[26]) and non-selectively inhibits all three NOS isoforms. An additional two methylated arginines are known to exist endogenously, namely symmetric dimethylarginine (SDMA) and asymmetric dimethyl arginine (ADMA). Only the asymmetric methylarginines (ADMA and L-NMMA) inhibit NOS enzyme activity but they do not discriminate between the various NOS isoforms.[27,28] Under normal conditions, the concentration of ADMA and L-NMMA is kept low by dimethyl arginine dimethylaminohydrolase (DDAH), which catalyses their conversion to citrulline and dimethylamine or monomethylamine, respectively. It seems plausible that this pathway represents an endogenous mechanism for the regulation of NO production by competitive inhibition. Indeed, pharmacological blockade of DDAH elevates ADMA levels and coincidentally inhibits NOS enzyme activity. Note that two isoforms of DDAH have been identified, namely DDAH1 and DDAH2, with the former isoform expressed predominantly in neuronal cells and tissues, and the latter expressed more widely, particularly in vascular tissues.[27] It is tempting to suggest that DDAH represents a novel target to limit pathological NO production, although this approach may fail to provide isoform-specific NOS inhibition. We have previously reported that the expression of DDAH1 is up-regulated following cortical spreading depression (CSD), a phenomenon implicated in migraine visual aura, highlighting the possibility that dis-inhibition of the NOS pathway may be responsible for the increased NO production detected during CSD, and possibly migraine headache.[29,30]

Nitric oxide in migraine

It has been known for some considerable time that glyceryl trinitrate (GTN), an exogenous NO donor frequently prescribed for treatment of angina pectoris,

is capable of evoking headaches both in normal volunteers as well as pain-free migraineurs. More specifically, when administered intravenously to non-migraineurs, GTN triggers an immediate headache of mild to moderate intensity.[31] The magnitude of the headache responses is dose-related, and appears to resemble migraine headaches (as defined by the IHS) although no phono- or photophobia, or nausea was reported. In analogy to the short half-life of NO in other systems, GTN-evoked headache in normal subjects is of fast onset but short lasting, and can be augmented by agents that prolong NO actions, such as *N*-acetylcysteine.[32] Similarly, the NO donor isosorbate mononitrate causes longer-lasting headaches, possibly because of its extended half-life.[33]

Importantly, when administered to pain-free migraineurs, GTN evokes headaches also, albeit of a very different nature. Like healthy volunteers, migraineurs exhibit an early, short-lasting headache response to GTN, although its intensity is worse when compared with that of non-migraineurs. However, unlike healthy volunteers, migraineurs suffer a second, delayed headache which resembles more closely a migraine-like headache. This occurs, on average, 5 hours after infusion of GTN and is of a severe nature. Thus the exaggerated immediate response of migraineurs to GTN suggests that they may be more sensitive to the actions of GTN (NO?). Indeed, GTN evokes greater arterial vasodilation in migraineurs than in healthy volunteers,[34] an effect which is likely to be caused directly by NO. Incidentally, this arterial dilation may not be critical to the development of headache;[35] see below.

The delayed, migraine-like headache may not involve a direct role of NO. Following system administration, GTN is very short lasting; it becomes undetectable in plasma within minutes of administration and the half-life of GTN metabolites is approximately 40 minutes. Therefore, the delayed headache response to GTN is more likely caused by NO effectors, and could involve cGMP-dependent pathways or interactions with other reactive species. Indeed, systemic administration of GTN has been shown to up-regulate various components of the NO-cGMP pathway, including guanylate cyclase in the dura mater and nNOS in the spinal trigeminal nucleus.[36,37] Moreover, the NO-cGMP pathway at various regions of the somatosensory pathway appears critical for nociceptive signalling in the rat.[38]

Interestingly, co-administration of sumatriptan with GTN reduces subsequent headaches, and prevents large arterial dilation.[39,40] It has recently been suggested that sumatriptan may scavenge directly various free radicals, including NO when derived from a chemical donor.[41] It would be of interest to establish whether sumatriptan, and indeed other triptans, scavenge authentic, endogenous NO. Alternatively, using the relatively poor NO donor SNP (sodium nitroprusside) as a stimulus, it has been shown that sumatriptan inhibits dilation of the dural vasculature,[42] possibly by reducing CGRP release from trigeminal afferents.[43,44]

How relevant are these findings to spontaneous migraine?

In an exploratory, but pivotal study by Olesen and coworkers[45] it has been shown that inhibition of endogenous NO synthesis in migraineurs confers headache relief.

More specifically, using a double-blind study design with use of some historical placebo control subjects, significant headache relief was observed at 2 hours after intravenous infusion of the non-selective NOS inhibitor L-NMMA (hydrochloride salt: 6 mg/kg). Headache relief was obtained in 10 out of 15 patients studied (67%), compared with 2 out of 14 placebo-treated patients (14%), with significant improvements also in phono- and photophobia, but not nausea. These preliminary data support the concept that endogenous NO mediates headache pain during migraine.

Analogous data have been obtained in patients suffering chronic tension-type headaches. Using a randomized double-blind crossover trail of 16 patients with chronic tension-type headache, the ability of intravenously infused L-NMMA (6 mg/kg) was evaluated using visual analogue score of any reductions in headache intensity as primary endpoint.[46,47] The mean pain score was reduced from 49 to 33 following infusion of L-NMMA, whereas the placebo-recipients failed to report benefits (44 to 40). Increased hardness of facial muscles is one of the most prominent features of chronic tension-type headache and it has been suggested that central sensitization (sensitization of spinal dorsal horn neurons following prolonged nociceptive afferent input from myofascial tissues) may be involved. It was observed that, in analogy to headache, muscle hardness in tension-type headache patients was significantly reduced also by L-NMMA.[48]

Histamine has been widely used experimentally to induce headache in healthy volunteers and migraine-like headaches in migraineurs, and exhibits several features akin to GTN. For example, both substances elicit an immediate headache response during the period of infusion followed by a secondary migraine-like headache that occurs several hours later. Like GTN, histamine has been shown to dilate cranial arteries, but unlike GTN, histamine does not cross the blood–brain barrier and therefore acts exclusively on the luminal face of endothelial cells. It has been shown *in vitro* that histamine can act on endothelial H1 receptors to evoke NO production, an effect that is reduced by non-selective NOS inhibitors.[49] However, when this hypothesis was tested in the clinic, L-NMMA inhibited some of the vascular effects of histamine, but failed to provide headache relief.[45,40] These findings suggest that endogenous NO is unlikely to mediate histamine-evoked headache, and that histamine and GTN probably trigger a headache response through distinct mechanisms. This is further emphasized by the finding that headache evoked by GTN is not affected by mepiramine, an H1 antagonist. Further, in the rat, GTN has been shown to evoke inflammation of the meninges and concomitant expression of iNOS in perivascular mast cells,[50] on a timescale comparable to the delayed migraine-like headache response in man. Importantly, the relatively selective iNOS inhibitor L-NIL reduced both meningeal inflammation and mast cell degranulation. It is unclear whether endogenous NO is capable of evoking mast cell degranulation in the human dura, but if this were the case, histamine antagonists might be expected to be efficacious in spontaneous migraine.

Taken together, these data strongly support the concept that endogenous NO can mediate nociceptive signalling in primary headaches, and that NOS represents a valid target for therapeutic intervention.

Oustanding issues

The pivotal studies described above clearly demonstrate that NOS inhibition provides headache relief. However, due to the non-selective nature of the inhibitor used, it is unclear through which NOS isoform this efficacy was obtained.

Intravenous administration of L-NMMA triggers a broad spectrum of vascular changes, and indeed inhibits NOS throughout the body.[51,52] L-NMMA (i.v.), at clinically effective doses, decreases cardiac output and increases mean arterial blood pressure and systemic vascular resistence.[53] This suggests that the efficacy of L-NMMA may involve systemic vasoconstriction, although an effect on regional cerebral blood flow has been discounted.[45] The possibility that L-NMMA achieves migraine efficacy through inhibition of nNOS and/or iNOS, or in fact through inhibition of all three isoforms has not yet been addressed. However, a related non-selective NOS inhibitor L-NAME (L-nitro-arginine methyl esther, moderately more selective for nNOS than L-NMMA) inhibits NOS throughout the brain[54] and has been shown to inhibit the activity of the trigeminal nucleus caudalis, following electrical stimulation of the middle meningeal artery.[55] Based on these findings, it can be envisaged that combined inhibition of eNOS and nNOS may offer benefits in migraine. However, the potential detrimental effects on blood pressure and normal CNS/PNS function following complete inhibition of eNOS and nNOS, respectively, may prevent their clinical use. Moreover, the role of iNOS in migraine headache is currently unclear, but may offer advantages due to its opportunistic expression.

Further studies are required to identify the site of action of NO, the NOS isoform involved, and the events coupling a migraine trigger to NO synthesis and subsequent migraine. With the development of clinically suitable NOS inhibitors with varying levels of selectivity, these questions will hopefully be answered.

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38 Calcitonin gene-related peptide and migraine

H. Doods, S. Just, M. Schindler, W. Eberlein, W. Engel, K. Rudolf, and K. Arndt

Although the so-called triptans are efficacious and are generally well-tolerated drugs for the treatment of migraine headache, there is still a need for improvement of migraine therapy. The relatively low number of patients becoming pain free in addition to the relatively high number of patients experiencing a recurrence of headache and lacking consistency of relief, together with the potential for cardiovascular adverse effects, reflect the limitations of the triptans as the present therapeutic standards.

Since the introduction of triptans to the market, several other treatment approaches targeting different aspects of migraine pathogenesis have reached clinical status, but most of them failed or showed no real therapeutic advantage. Our approach at Boehringer-Ingelheim was specifically directed at the neurovascular aspect of migraine pathogenesis after our attention was drawn to observations made by Edvinsson and Goadsby.[1] They demonstrated that the levels of the potent vasodilator Calcitonin Gene-Related peptide (CGRP) is increased in the jugular blood during a migraine attack. In order to evaluate the role of CGRP in experimental migraine models and to answer the fundamental question whether migraine headache is related to the release of CGRP, we initiated a programme with the aim to design and synthesize a small molecule CGRP antagonist.

Our efforts resulted in the identification of BIBN4096 (Fig. 38.1), the first potent and selective CGRP antagonist that is available for human clinical studies.[2] A Proof of Concept study, in migraineurs,[3] with this compound revealed that CGRP antagonism is a novel and effective approach to treat acute migraine headache and answered a fundamental pathophysiological question—namely that CGRP-release during migraine is indeed related to migraine headache.

Calcitonin gene-related peptide and migraine

It has been hypothesized for many years that migraine headache is associated with vasodilatation of meningeal blood vessels, although the trigger could not be

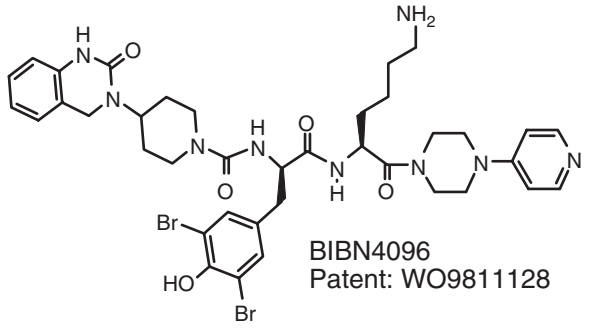

Fig. 38.1 Chemical structure of BIBN4096BS.

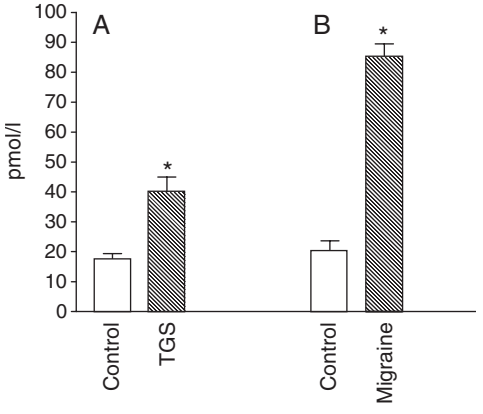

Fig. 38.2 (A) Stimulation of the trigeminal ganglion in rats results in an increased release of CGRP. (B) CGRP levels are increased in migraine patients during an attack (data taken from ref. 1).

identified. The first evidence that CGRP could be an important player originates from studies by Goadsby and Edvinsson who analysed the levels of various neuropeptides during migraine attacks.[1,4,5] They observed a marked increase in CGRP levels in blood drawn from the external jugular vein (Fig. 38.2). The involvement of CGRP in migraine headache has been demonstrated in migraine patients suffering from common and classical migraine.[6] Further support that CGRP could be involved in migraine came from a study where CGRP was infused in migraineurs. In 8 out of 10 patients tested the infusion elicited delayed migraine-like headaches.[7] Interestingly, also in cluster headache patients CGRP levels are increased.[8] Unfortunately, little is known about the exact time course of CGRP release prior to, or during, migraine or cluster headache. However, it seems that headache relief is associated with a reduction of elevated CGRP levels.[8,9]

The trigger mechanism for CGRP release has not yet been fully elucidated. It has been hypothesized that peripheral stimuli contribute to the release of CGRP from

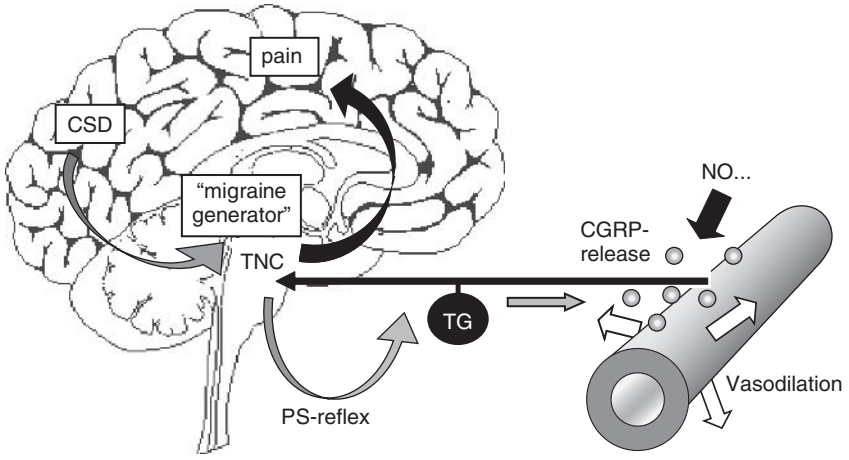

Fig. 38.3 Pathways involved in trigeminovascular activation.

trigeminal nerves. Nitric oxide (NO) might be an important mediator in this respect. It has been demonstrated that early activation of the NO cascade is accompanied by the release of CGRP during spontaneous migraine attacks.[10] Moreover, CGRP levels are increased following a cluster headache attack evoked by the NO-donor nitroglycerine.[11,12] Also preclinical studies show that there is a link between the NO pathway and CGRP release.[13–15] An endothelial origin of NO following stimulation of e.g. serotonin, histamine or acetylcholine receptors on endothelial cells can be suggested. A potential contribution of parasympathetic nerves should be considered, as parasympathetic autonomic disturbances have been described for migraine and cluster headache patients.[16,17] In addition, CGRP-dependent parasympathetic reflex vasodilation is observed in animals following trigeminal nerve stimulation (Fig. 38.3).[18,19]

Recent findings, however, favour the view that disturbances within the CNS might initiate a migraine attack. Cortical spreading depression (CSD) and/or brainstem activation have been proposed as primary triggers leading to activation of the trigeminal vascular system.[20] Studies in migraineurs support the hypothesis that migraine aura results from CSD.[20–22] Moreover, CSD in rats can activate trigeminovascular afferents and consequently dilates the middle meningeal artery.[23] NO as well as CGRP seem to be involved in pial artery dilatation in rats elicited by CSD. Not in line with the hypothesis that CSD is an important trigger for migraine headache is the absence of aura in most patients. However, it cannot be excluded that CSD-like events also occur in patients without aura, but is clinically silent in these patients. Besides cortical activation, a dysfunction of the brainstem could be involved in the activation of the trigeminal pathway. Although activation of the brainstem has been observed in patients during migraine attacks,[20,24] it remains unclear how this phenomenon could result in an antidromic activation of the trigeminal vascular system.

Disturbances of the central nervous system may not only activate the trigeminal vascular system but could also lead to sensitization of central and/or peripheral neurons. In this respect, an association between migraine and sensitization, measured as cutaneous allodynia, has been convincingly reported.[25,26]

Irrespective of those many unsolved questions the clinical findings clearly suggest the involvement of CGRP in the pathophysiology of migraine and provided a sound rationale to test a CGRP antagonist for the treatment of migraine headache.

CGRP receptors

CGRP is a 37-amino acid peptide identified in 1982[27] and belongs to the family of peptides including calcitonin, adrenomedullin, and amylin.[28] CGRP is present in two forms, α- and β-CGRP, derived from different genes which differ by three amino acids in humans.[29] CGRP is widely distributed both in the central nervous system and in the periphery, and induces a wide range of biological effects.[28,29] The peptide is for instance a very potent vasodilator, especially in the cerebral circulation, which is densely innervated by CGRP containing nerves.[30]

Historically, CGRP receptors have been divided into two classes based on pharmacological studies, namely CGRP1 and CGRP2. CGRP1 receptors show a preferential affinity for the peptidic antagonist CGRP(8-37) as well as the non-peptidic antagonist BIBN4096.[29,31,32] Despite the pharmacological evidence for CGRP receptor heterogeneity,[32–34] so far molecular cloning efforts resulted only in the identification of one CGRP receptor, which is pharmacologically identical with the CGRP1 receptor.[35] The functional CGRP1 receptor consists of a classical seven transmembrane receptor component (termed calcitonin receptor-like receptor; CRLR), which shares 55% sequence homology with the calcitonin receptor, and an associated receptor activity modifying protein (RAMP 1). RAMPs are a family of at least three distinct small single-membrane spanning domain proteins that determine the selectivity of CRLR for e.g. CGRP over adrenomedullin. Co-expression of CGRP with RAMP1 results in CGRP1 receptor pharmacology, whereas for instance co-expression with RAMP2 produces an adrenomedullin receptor.

BIBN4096

The first antagonists for the CGRP receptor were carboxyl-terminal peptide fragments of CGRP such as CGRP(8-37)[36] and CGRP(27-37).[37] However, the peptidic nature as well as the potency of those antagonists limits their use, especially for clinical investigations. Accordingly it was our aim to identify a potent small molecule CGRP antagonist in order to investigate the hypothesis that CGRP is involved in migraine headache.

A high-throughput screening campaign resulted in the identification of dipeptide-like compounds that showed weak affinity for the CGRP receptor. Lead optimization

resulted in the generation of a class of potent CGRP antagonists, the prototype being BIBN4096[2] (Fig. 38.1). The affinity and antagonistic properties were determined using SK-N-MC cells that endogenously express the CGRP-1 receptor. In studies employing ^{3}H-BIBN4096 a K_d value for the human CGRP receptor of 0.045 nM was observed.[38] In displacement studies using ^{125}I-CGRP as the radioligand BIBN4096 had a K_i value of 0.014 nM. Performing binding studies employing tissues from different species it turned out that BIBN4096 possesses a pronounced species selectivity, namely a high affinity for primate CGRP receptors (e.g. marmoset cortex; K_d=0.08 nM) and a much lower affinity for CGRP receptors of non-primate species, for instance rat spleen (IC50=6.4 nM) or guinea pig spleen (IC50=9.8 nM). BIBN4096 possesses affinity for human vascular CGRP receptors in the low nanomolar range[39–41] and is able to reverse CGRP-induced vasodilatation (Fig. 38.4). Interestingly, it seems that BIBN4096 discriminates (approx. 10-fold) between the vascular effects of α- and β-CGRP.[42] The same has been reported for the peptidic antagonist CGRP(8-37).[43] So far there is no sound explanation for this finding, but it might indicate that α-and β-CGRP interact with different CGRP receptor subtypes/conformational states or RAMP/CRLR complexes.

BIBN4096 was investigated in three *in vivo* models related to migraine. Measuring facial blood flow following antidromic stimulation of the trigeminal ganglion has been suggested as a model to examine drugs that interact with the trigeminal vascular system.[44] Antidromic stimulation results in the release of CGRP (Fig. 38.2) and subsequently an increase in blood flow can be observed in blood vessels innervated by the trigeminal nerve. BIBN4096 dose-dependently inhibits the increase in facial blood flow evoked by stimulation of trigeminal ganglion both in rats (Fig. 38.5) and marmoset monkeys. Due to the fact that the compound exhibits species selectivity,

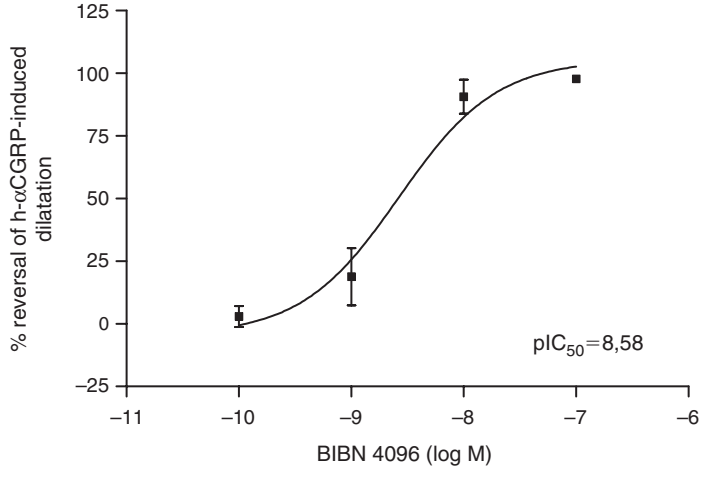

Fig. 38.4 Ability of BIBN4096BS to reverse h-α CGRP induced dilation in human middle cerebral artery (data provided by Pharmagene).

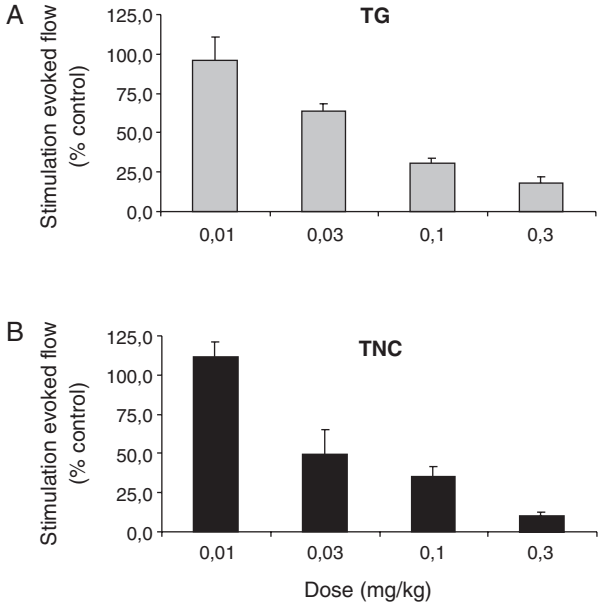

Fig. 38.5 Dose-dependent reversal of neurogenic vasodilation in rats by BIBN4096BS elicited by trigeminal ganglion or trigeminal nucleus caudalis stimulation.

BIBN4096 is more potent in the marmoset monkey (ID50 = 3.2 μg/kg; i.v.) compared to the rat (ID50 = 62.8 μg/kg; i.v.). In another series of experiments in rats, not the trigeminal ganglion, but the brainstem was stimulated. This also caused an increase in facial blood flow that could be blocked by BIBN4096 (Fig. 38.5). Taken together these results show that BIBN4096 is able to inhibit the vascular responses due to antidromic stimulation of the trigeminal nerve, regardless of whether the stimulation occurred peripherally (trigeminal ganglion) or centrally (brainstem).

Measuring the effects of drugs on arteriovenous anastomotic blood flow has been proposed to be predictive for antimigraine activity.[45] The involvement of arteriovenous anastomoses in migraine is supported by the observation that during migraine the oxygen saturation difference between arterial and jugular venous blood is decreased, and is normalized by treatment or spontaneous elevation of the attack.[45,46] Intracarotid infusion of capsaicin in pigs increased total carotid, as well as arteriovenous anastomotic, blood flow and decreased the difference between arterial and jugular venous oxygen saturation. These responses to capsaicin were dose-dependently blocked by BIBN4096 (0.1–1.0 mg/kg, i.v.). The infusion of capsaicin approximately doubled the jugular venous plasma concentrations of CGRP.[47]

BIBN4096 did not show any vasoconstrictor activity or cardiovascular side effects in several *in vitro* studies employing isolated vessels of different species, including human vessels, or in animal experimental models, while CGRP-dependent dilatation can be potently inhibited.

The *in vivo* experiments showed that vasodilator responses due to the release of CGRP can be effectively antagonized by BIBN4096 in several animal models and species. Although the preclinical pharmacological data were encouraging, still the question 'does CGRP really play a role in the pathophysiology of migraine headache or is the increase in CGRP just an epiphenomenon?' needed to be answered.

Clinical experience with BIBN4096

In a Phase I study[48] the safety, tolerability, and pharmacokinetics of BIBN4096 following single intravenous administration of rising doses (0.1–10 mg, infused over 10 minutes) in 55 healthy volunteers (male and female) was evaluated. No clinically relevant changes in blood pressure, ECG, respiratory rate, and routine clinical laboratory tests were observed. Adverse effects (AE) were few, transient, and most mild in severity. Approximately, two-thirds (11 of 16) of all AEs related to active treatment occurred at the highest dose of 10 mg and consisted mainly of transient and mild parenthesis. No serious AEs were reported. The local tolerability after intravenous administration was good. Overall it is concluded that BIBN4096 is generally well tolerated at all dose levels and appears to be a safe compound.

In a Proof of Concept study 85 migraineurs were treated with different doses of BIBN4096 (0.25–10 mg given intravenously over 10 minutes).[3] A group sequential adaptive treatment assignment was chosen to achieve the trial objective with a comparatively low number of patients. Patients were included in the study provided the attack had not lasted more than 6 hours, was moderate to severe and not improving. Migraine headache was evaluated on a scale of mild, moderate, or severe pain. Most patients received the 2.5 mg dose ($n=32$) and the results obtained with this dose will be discussed. The headache response at 2 hours after treatment for the 2.5 mg dose was 65.6% and after placebo it was 26.8% (11 of 41 patients) (Fig. 38.6). A difference between BIBN4096 response rates and placebo response rates was apparent after 30 minutes. The pain free response at 2 hours was 43.8% compared with 2.4% (1 of 41) for placebo (Fig. 38.6). The recurrence rate was 19.0% for the 2.5 mg dose compared with 45.5% for placebo. Also in this study the compound showed a favourable safety and tolerability profile comparable to the study in healthy volunteers.

Conclusion

BIBN4096 is the first potent and selective small molecule CGRP antagonist. In pharmacological studies it was shown that BIBN4096 is able to reverse CGRP-induced vasodilatation in human cerebral vessels and exhibits activity in animal models related to migraine. Phase I studies showed that i.v. administered BIBN4096 is well tolerated.

A Proof of Concept study clearly showed the CGRP antagonist BIBN4096 is effective in the acute treatment of migraine headache attacks. Thus, it can be concluded

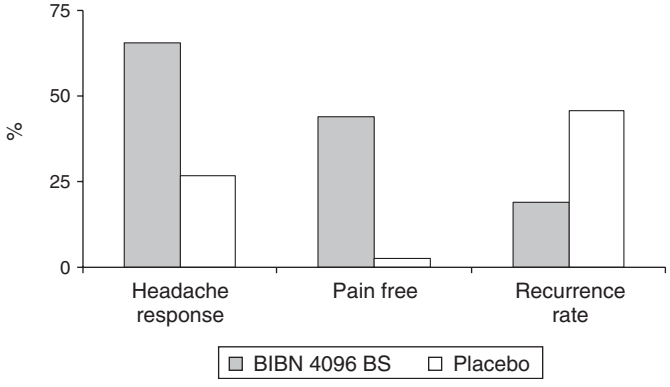

Fig. 38.6 Effect of BIBN4096BS (2.5 mg; i.v.; $n=32$) in migraineurs on headache relief, painfree response and recurrence rate vs. placebo ($n=41$).

that CGRP plays an important role in the pathophysiology of migraine headache. Accordingly, CGRP receptor antagonism is a valid and novel approach for the acute treatment of headache. However, further clinical studies are required to establish the true potential of this novel class of drugs.

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39 Phosphodiesterases, cyclic nucleotides, and their role in migraine

C. Kruuse and J. A. Beavo

Introduction

The signalling molecule nitric oxide (NO) has long been known to play a major part in pain mechanisms along with the neuropeptide calcitonin gene-related peptide (CGRP). Both inhibitors of NO synthase (NOS) and CGRP receptor antagonists have within recent years proven effective in the treatment of migraine. NO is released from endothelial cells or neurons and works mainly by increasing intracellular concentrations of cyclic guanosine monophosphate (cGMP) in adjacent cells through activation of soluble guanylate cyclase (sGC). CGRP is released from the sensory nerve fibres and seems mainly to exert its actions by increasing intracellular cyclic adenosine monophosphate (cAMP). Since both pathways involve production of cyclic nucleotides, a crosstalk between cAMP and cGMP seems very likely and the intracellular enzymes regulating the degradation of these second messengers, cyclic nucleotide phosphodiesterases (PDE), are interesting targets for investigating this interaction and for finding new principles of migraine treatment.

Cyclic nucleotide phosphodiesterases

Intracellular signalling includes production of the second messengers cAMP and cGMP, which in turn regulate a variety of functions by interaction with protein kinases, ion-channels, guanine nucleotide exchange factors, and phosphodiesterases (Fig. 39.1). The intracellular levels of cGMP and cAMP can be regulated in three ways: through production via the adenylate and guanylate cyclases in the cell, by efflux from the cell, or by degradation by the intracellular cyclic nucleotide phosphodiesterases (PDE).[1] The degradation mechanism has proved the most amenable to pharmacological intervention.

The PDEs catalyse the hydrolysis of the 3′5′-cyclic nucleotides to 5′-nucleotides and thereby inactivate the cyclic nucleotide signalling pathway.

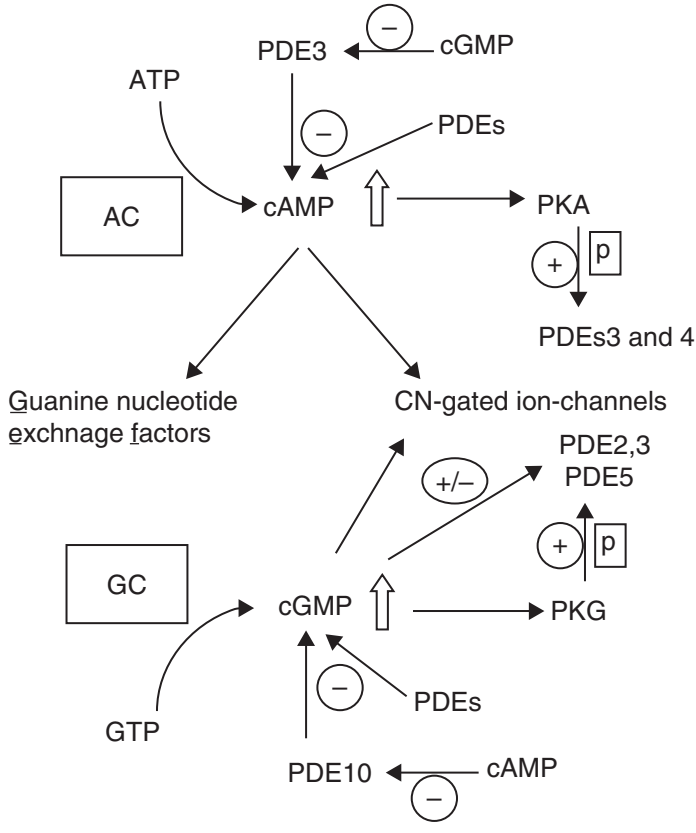

Fig. 39.1 Action and regulation of cyclic nucleotides. The PDEs and possible actions related to neurons or smooth muscle cell functions are shown above. Increases in cyclic nucleotides activate cyclic nucleotide-dependent protein kinases, cyclic nucleotide-regulated guanine nucleotide exchange factors (GEFs), and cyclic nucleotide-gated ion-channels (CN-gated ion-channels). The cAMP and cGMP pathways can interact by inhibition of PDEs, thus inhibiting degradation of each other. Only cGMP is reported to directly activate PDEs, this has so far not been observed for cAMP. The specific cGMP hydrolysing PDEs are PDE5, PDE6, and PDE9 and the specific cAMP hydrolysing PDEs are PDE3, PDE4, and PDE7. PDE2 and PDE10 hydrolyse both cAMP and cGMP. GC, guanylate cyclase; AC, adenylate cyclase; PKA, cAMP dependent protein kinase; PKG, cGMP dependent protein kinase; –, inhibits; +, activates; p, phosphorylation.

PDEs comprise a superfamily of enzymes. To date, eleven different PDE families have been described, i.e. PDE1–PDE11. Each PDE family differs in affinity for cAMP or cGMP, kinetic properties, mode of regulation, cellular and tissue distribution, and sensitivity to PDE inhibitors.[1,2] For a review of types, distribution, and mode of regulation see Table 39.1.

Table 39.1 PDE families, distribution and relevant PDE inhibitors

PDE family	Substrate	Regulation	Cellular distribution	Tissue distribution	Selective PDE inhibitors
PDE1	cGMP (and cAMP)*	Ca^{2+}/CaM-stimulated	SMC, nerves, olfactory nerve cells	Brain, lung, heart, vasculature	8-MM-IBMX (partially)
PDE2	cAMP and cGMP	Stimulated by cGMP	Goblet cells, olfactory nerve cells, endothelial cells	Adrenal cortex, brain, heart, corpus cavernosum, vasculature	(EHNA)
PDE3	cAMP (cGMP)#	Inhibited by cGMP	SMC, platelets, adipocytes	Liver, heart, corpus carvernosum, vasculature, brain	Milrinone Cilostamide Cilostazol
PDE4	cAMP	Feedback phosphorylation by PKA	Lymphocytes, Sertoli cells, SMC, endothelial cells, multiple other cells	Brain, lung, testis, vasculature	Rolipram, and many others
PDE5	cGMP	cGMP binding to GAF domain, phosphorylation by PKG	SMC, platelets, purkinjie cells	Corpus cavernosum, lung, vasculature, brain, peripheral nerves	Zaprinast, (Dipyridamole) Sildenafil, Taldalafil Vardenafil

PDE6	cGMP	Activated by transduction	Photoreceptor outer segments	Retina	No selective inhibitor available
PDE7	cAMP	Regulation unknown	T&B-lymphocytes Dendritic cells	Skeletal muscle, White blood cells	No selective inhibitor available
PDE8	cAMP	Regulation unknown	Multiple cell types	Testis, eye, liver, skeletal muscle, heart	No selective inhibitor available
PDE9	cGMP	Regulation unknown	Multiple cell types	Spleen, kidney, small intestine, brain	No selective inhibitor available
PDE10	cAMP and cGMP	cAMP inhibits cGMP hydrolysis	Multiple cell types	Brain, thyroid, testis, brain (caudate)	No selective inhibitor available
PDE11	cGMP and cAMP	Regulation unknown	Multiple cell types	Skeletal muscle, testis, pituitary	(Dipyridamole) (partially selective)

Most PDE families consist of several genes each of which can encode several different proteins. These different PDEs are commonly differentially distributed in tissues, cells, or subcellular compartments. For reasons of simplicity only information on the overall PDE families is given. PDE inhibitors in parentheses are known to affect other molecules than PDE, e.g. adenosine. Few of the inhibitors are absolutely isozyme selective.
*Mainly the PDE1C subtype. # Only at slow rate. SMC, smooth muscle cells.[1,2,15,32,33]

PDEs consist of a catalytic domain near the carboxy terminus, and regulatory domains in the amino terminus, such as calmodulin-binding, membrane targeting or non-catalytic cyclic nucleotide binding domains (GAF domains), and protein kinase phosphorylation sites.[3] The catalytic domain includes an ~270 amino acid region. This region is highly conserved among the different families. In general, members within families show a 65% or more amino acid sequence homology, but less than 40% homology between families.[1] Each family often includes more than one gene, and each gene may encode several tissue-specific splice variants. For instance, in the cGMP inhibited PDE3 family the two isoforms are products of different but related genes. Furthermore, they show different sub-cellular and cellular localizations indicating a difference in their functional role. In most species PDE3A is expressed in smooth and cardiac muscle cells and platelets, whereas PDE3B is found in adipocytes, beta cells, and several types of white blood cells.[4] Likewise, in the PDE1 family, PDE1C is active in human proliferating smooth muscle cells but not in quiescent cells.[5] In the PDE5 family three different splice variants have been found but a distinct functional difference for each has not yet been described. Due to the differential distribution and physiological function of PDEs between tissues in general, and between vessel types and vascular beds in particular,[1] the regulatory properties with regard to cyclic nucleotide concentrations and effects may vary between tissues. This makes individual PDE isozymes excellent cell type specific pharmacological targets.

Distribution of PDEs

Vascular tissue

Previous research has described the distribution of PDEs in vascular smooth muscle cells from tissues other than the brain as being PDE1, PDE3, PDE4, and PDE5.[3] In endothelial cells from bovine aorta only the cGMP-stimulated PDE2, which degrades both cAMP and cGMP, and PDE4 family members have been found.[3] The role of PDEs in regulation of smooth muscle relaxation has been investigated in a wide range of tissue and vascular beds. The cAMP degrading PDE4s are of major importance in regulation of lung bronchial diameter[6] and the cGMP-inhibited PDE3 is a possible key regulator of renal vascular tone.[7] Furthermore, in all smooth muscle cells the cGMP-degrading PDE5 is shown to be of major importance, and administration of a selective PDE5 inhibitor is effective in the treatment of erectile dysfunction due to its interaction with the NO-cGMP pathway.[8]

In cerebral arteries from different animals, several PDE families (PDE1, PDE3, PDE4, and PDE5) have been found to be present and active.[9,10] The identification and relative importance of the different PDEs has, however, not yet been established in human cerebral arteries. In studies on other animals, most non-selective and selective PDE inhibitors induce cerebral artery dilatation, although with different potency depending on species and vessels tested. Selective PDE3 inhibitors usually show effective endothelial independent relaxation whereas PDE1, PDE4, and PDE5 inhibitors elicit endothelial dependent relaxation.[10–12]

Brain

In the brain the presence of PDE4 has long been known and investigated. Among those isozymes that hydrolyse cGMP, both mRNA and protein of PDE1 and PDE5 also have been localized to several different brain regions. For PDE5 highest levels were found in the cerebellum and hippocampus and in the superior cervical ganglion.[13] The PDE1 expression patterns were more widely spread and varied with isozyme.[14] PDE 10, an isozyme that hydrolyses both cyclic nucleotides, is highest in the putamen and caudate nucleus region.[15] In rat PDE5 was also found in the sensory nerves of the dorsal horn and medulla oblongata (personal communication, D. Giordano). The mRNA distribution of another cGMP specific PDE, PDE9, was recently studied in the rat brain using *in situ* hybridization and its distribution was found to largely overlap the distribution of NO synthase with very strong representation in the olfactory bulb, insular area, dentate gyrus, basal forebrain, and Purkinje cells, and strong representation in the trigeminal nucleus.[16] However, as finding mRNA is no certain indication of an actual function of the enzyme in these areas, further studies are needed to elucidate the sub-cellular localization and functional role of this enzyme.

Regulation of PDEs

Inhibition of PDE activity is possible either by cyclic nucleotides themselves as in the case of PDE3 or by relatively selective and specific competitive inhibitors of the active site. Inhibitors of PDEs used as modulators of cyclic nucleotide responses, can increase the intracellular concentration of either cAMP or cGMP or both, especially when used in conjunction with an agonist of the respective cyclase. The first PDE inhibitors described were the non-selective and the non-specific inhibitors methyl-xanthines, which also affected other signalling systems.[17] Within recent years, following the increasing knowledge of the PDE enzymes, the function and selectivity of the known PDE inhibitors has received increasing attention and has been widely investigated.[17] Most of these inhibitors bind to the active site on the enzyme and are competitive with substrate. Most of them are relatively lipophilic compounds. The differential cellular and subcellular distribution and possible unique functions of the various PDEs makes the design of selective PDE inhibitors for specific diseases very attractive.[3,17] Thus, PDE inhibitors are being developed for a wide variety of medical conditions and constitute a rapidly expanding group of new drugs. The most recent and well known is the PDE5 inhibitor sildenafil, which is used for treatment of male impotence.[18] The other PDE5 inhibitors vardenafil and taldenafil are just in the final stages of FDA approval. In cerebral disorders, the PDE3 inhibitor milrinone shows promising results in the treatment of cerebral vasospasm after subarachnoidal haemorrhage[19] and the more selective PDE3 inhibitor cilostazol has been shown to prevent the onset of silent brain infarction in patients with type II diabetes.[20] Dipyridamole, a less selective PDE5 inhibitor than sildenafil which also inhibits adenosine

re-uptake, is currently used in combination with aspirin for the secondary prevention of stroke.[21]

Activation of some PDEs by small molecules is also possible. For example, cGMP has long been known to stimulate the cAMP hydrolysing activity of PDE2 and Ca^{2+}/CaM is known to activate PDE1s. Recently, PDE5 was also found to be directly activated by cGMP binding to the GAF domain at low substrate concentrations, as a feedback mechanism, presumably by a mechanism similar to PDE2. These GAF domains originally described only in PDEs are now known to be present in a variety of other proteins.[22] It has been known for some time that PDE5 can be phosphorylated and activated in the intact cell by the cGMP-dependent protein kinase (PKG); however this requires concomitant binding of cGMP to the regulatory domain.[23]

So far drug development has mainly concentrated on finding and refining compounds that inhibit the PDE enzymes, but with the increasing knowledge of the mechanisms of activating the PDEs, it seems likely that this will be the new target of drug development, with similar potential of finding agents that act on specific tissues or physiological functions.

PDE and migraine

By administering compounds that stimulate cAMP or cGMP production, an insight into the pain and migraine generating mechanisms has been provided.[24,25] More recently, administration of selective PDE inhibitors to cause accumulation of the endogenously produced cAMP or cGMP has begun to add to this knowledge.[26]

In healthy subjects NO donors, including histamine, which activate endogenous production of NO in the smooth muscle cells, induce a mild short-lasting headache concomitant to a dilatation of the large cerebral arteries and no change of cerebral blood flow. The PDE5 inhibitors dipyridamole and sildenafil, which cause accumulation of cGMP, induced a short-lasting mild headache in almost all subjects. A few subjects reported headache of stronger intensity and characteristics fulfilling the diagnostic criteria for migraine pain. With dipyridamole a concomitant dilatation of the large cerebral arteries was seen which outlasted the headache. With sildenafil, on the other hand, no dilatation of the cerebral arteries was seen.[27] Pentoxifylline, the non-selective but probably cAMP accumulating PDE inhibitor, caused neither a headache nor did it change cerebral hemodynamics[28] but the PDE3 inhibitor cilostazol, which is thought to increase cAMP more specifically, did cause headache very similar to sildenafil in most of the healthy subjects. In this case a dilatation of the large arteries was found (personal communication, S. Birk).

When administering similar drugs in patients suffering from migraine without aura, NO donors cause a headache similar to the patients' usual migraine attack with a time lag of approximately 5 hours in 8 out of 10 patients.[29] The NO donors induce an initial increase in large artery diameter of the brain which, in most of the patients, had returned to baseline before the migraine headache appears. Sildenafil was also highly effective in causing a migraine attack in 10 of 12 migraine patients

and this with a time lag of 4.5 hours, but very uniquely, without causing initial dilation of the cerebral arteries.[26] This could indicate that the initiation of the migraine process may be independent of an initial dilatation of the large cerebral artery but activated by an increase in cGMP. It is therefore quite possible that the location of this process may be in perivascular pain-sensitive nerve fibres or in more centrally located neurons involved in the pain process since dilatation of cerebral arteries was not crucial to initiating the headache or the migraine attack.

Further studies are needed using cAMP selective PDE inhibitors to investigate and understand the role of cAMP and thus CGRP in the pain process. Most importantly the target tissue is still not fully elucidated, but studies of the distribution of cyclic nucleotides, PDE families, and other cyclic nucleotide related molecules may bring us closer to understanding the role of the cyclic nucleotides and in which cells or tissue the processes may be initiated.

One target tissue believed to be involved is the vascular smooth muscle cells, since the pain sensitive areas in the brain are found around the arteries, the venous sinuses, and the dura. It has been proposed that cyclic nucleotide accumulation causes dilation of the cerebral arteries and perhaps the venous sinuses, and thus mechanically activates the perivascular pain-sensitive nerve fibres or promotes generation of pain-inducing neuropeptides and increases excitability of the nerves. Another likely target tissue may be the neurons in the trigeminal ganglion or the second-order neurons in the trigeminal nucleus since the sensory nerves innervating the vascular structures and dura derive from the trigeminal nerve. Substantial evidence points to the primary involvement of the trigeminal system in headache-generating mechanisms perhaps with a secondary involvement of the vascular system.[30] How the trigeminal system is activated is, however, not fully understood, but in light of the results of sildenafil, cGMP is likely to be involved at some point. However, whether the increase in cGMP causes increased excitability at the level of the nerve terminals or more centrally in the neurons is still to be investigated.

Future prospects

It is still not known which cells may contain the headache-generating mechanism or where they are situated in the brain. The above studies using PDE inhibitors tells us that accumulation of cGMP is involved in the pain process and that vasodilatation may only be an epiphenomenon rather than playing a causative role in the mechanisms. Future studies may concentrate on the distribution of CGRP, sGC, and PDEs in the trigeminal ganglion and perivascular nerves both in animal models and in humans. Because of possible species variance in the distribution of PDEs, it seems of crucial importance to include studies in human tissue. Finally, since vasodilatation may not be an initiating factor in migraine, animal models studying the neuronal effects of cyclic nucleotides need to be developed. Rat models may not be optimal since their PDE distributions seem to differ from that in humans, at least regarding the smooth muscle cells[5] and perhaps also neurons, so other animal models should be looked for.

From the present knowledge of cyclic nucleotides and migraine, it would be interesting to investigate the effect of compounds which activate PDEs or decrease the effects of cGMP and cAMP since they may prove just as useful in migraine treatment as NOS inhibitors[31] and CGRP antagonists. For example, developing agents that bind to the GAF domain of PDE5 in a similar way to cGMP should activate the enzyme and decrease the intracellular levels of cGMP. Such an agent could be useful in both acute and prophylactic treatment of migraine. Another possible future target to investigate would be the cyclic nucleotide-gated ion channels since this may play a role in the physiological effects of both the cAMP and cGMP pathway, and may be a site for common actions in the pain pathways.

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40 The prostaglandin-E_1-analog misoprostol in the prophylactic treatment of refractory cluster headache and trigeminal neuralgia

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Introduction

Chronic cluster headache is a severe disease extremely affecting the quality of life. In many cases, the common prophylactic treatment options are unsatisfactory and do not lead to a continuous freedom from pain. Trigeminal neuralgia is a rare, although typical, brainstem symptom of multiple sclerosis (MS) occurring in about 2% of all MS patients.[1] In most cases, the semiology of this type of trigeminal neuralgia cannot be differentiated from the idiopathic form of trigeminal neuralgia and the principles of treatment are similar for both types. The pathophysiology of trigeminal neuralgia associated with MS is not fully understood. It has been suggested that demyelinating plaques in the entry zones of the trigeminal roots are responsible for the lancinating pain by ephaptic conduction. Inhibition of T-cell functions by prostaglandins could be a mechanism to decrease their inflammatory activity in the plaques and, thus, could be a specific therapy of this type of trigeminal neuralgia.[2]

Misoprostol is a prostaglandin-E_1-analog substance which has been approved for the treatment of drug-induced gastritis and duodenitis and of gastric and duodenal ulcer.[3] In 1995, misoprostol was investigated in the treatment of trigeminal

neuralgia associated with multiple sclerosis.[4] These patients did not respond to the conventional therapy such as carbamazepine and other anticonvulsants or baclofen. In six out of seven patients, misoprostol showed a good efficacy with complete or nearly complete abortion of the lancinating pain.

Since drug alternatives for the treatment of refractory chronic cluster headache and refractory trigeminal neuralgia in MS are lacking but urgently warranted, we designed two small prospective, double-blind, crossover studies on the efficacy of misoprostol in these specific conditions. Furthermore, the efficacy of a substance with prostaglandin-E_1-analog pharmacological properties would give an interesting insight into the pathophysiology of cluster headache and trigeminal neuralgia in MS.

Methods

We enrolled eight patients with chronic cluster headache according to the criteria of the International Headache Society (IHS) who had insufficient relief from standard prophylactic treatment but good relief from standard acute treatment. In addition, we enrolled five consecutive patients with a diagnosis of trigeminal neuralgia (diagnosis 12.2.1 or 12.2.2) according to the IHS criteria and with a probable or definite MS according to the Poser criteria.[5] The clinical and demographic features were recorded based on the patients' history. We included only patients who did not respond to conventional treatment with at least one anticonvulsant drug in a usual dose (e.g. at least 1200 mg carbamazepine) or who could not tolerate treatment with anticonvulsant drugs.

Patients gave informed consent to participate in these studies. They were treated with 2×300 µg misoprostol per day for 14 days. After a wash-out period of another 14 days, patients received placebo for 14 days twice daily. The order of treatment period was randomized. They were asked to record the number of neuralgic attacks or of cluster attacks per day, the average pain intensity of neuralgic attacks per day (visual analogue scale from 1 [= very mild pain] to 10 [= most intense pain]), the duration of cluster attacks, and all adverse events in a diary for the total time period of six weeks. Then, the patients came back to the hospital and the diary was analysed. Concomitant medication for the treatment of MS (e.g., interferon therapy) and for the treatment of cluster headache (e.g. sumatriptan) was allowed but had to be constant during the study period. Analgesic, anticonvulsant, and antidepressive therapy had also to be unchanged during the study period.

The primary efficacy parameter was the reduction of the number of neuralgic attacks or of cluster attacks per day by more than 50% (responders). We also calculated the average number of attacks and the average pain intensity per day for the two different study periods (placebo versus verum) and the possibly or probably drug-related adverse events.

Results

All patients completed the study period. The cluster headache patients were aged between 28 and 53 years, all were male. Six patients had chronic cluster headache

evolved from the episodic form, and two patients had chronic cluster headache unremitting from initial onset. The mean duration of liability to cluster headache was 14.0±6.0 years; the chronic form had been present for a mean of 6.6± 7.6 years. In Table 40.1, the treatment data are presented. One patient was a responder with a decrease of attack frequency in the misoprostol treatment period by more than 50%. Only one patient reported drug-related side effects (fatigue) in the misoprostol and placebo treatment period, respectively.

Four patients in the trigeminal neuralgia study were female and one was male with the relapsing-remitting subtype of MS. The age was between 34 and 70 with a mean duration of MS of 12.4±7.3 years. Trigeminal neuralgia was present for 61±72 weeks in these patients. The right trigeminal nerve was affected in four cases, all patients were affected in the second branch. The previous drugs which had no effect on the trigeminal neuralgia were carbamazepine (5 cases), gabapentin (4 cases), amitriptyline (1 case), and oxcarbazepine (1 case). Table 40.2 shows the treatment data of the patients with trigeminal neuralgia. There was a significant decrease both in frequency and in attack intensity during the misoprostol treatment as compared with placebo treatment. Four patients were treatment responders with an attack frequency during misoprostol treatment of less than 50% as compared with placebo treatment. One patient complained of severe menorrhagia, no other side effects were observed in this study.

Table 40.1 Efficacy parameters during misoprostol and during placebo treatment in eight patients with refractory chronic cluster headache. The data are presented as arithmetic mean with standard deviation. Statistical comparison by Wilcoxon-test. (ns denotes not significant)

	Placebo	Misoprostol	Significance
Attacks in treatment period	26.1±12.0	25.1±11.0	ns
Duration of untreated attack	63±20	58±11	ns
Number of drug-related side effects	$n=1$	$n=1$	

Table 40.2 Pain features of the five patients participating in the study on trigeminal neuralgia during placebo treatment and during misoprostol treatment. The data are presented as arithmetic mean with standard deviation. Statistical comparison by Wilcoxon-test

	Placebo	Misoprostol	Significance
Attacks per day	15.8±9.1	3.6±6.7	$p<0.01$
Pain intensity (VAS 1–10)	7.6±2.3	2.1±2.6	$p<0.01$
Number of drug-related side effects	$n=0$	$n=1$	

Discussion

The most important finding in our sample is that the patients with refractory trigeminal neuralgia associated with MS showed a remarkable benefit from the treatment with misoprostol, whereas patients with chronic cluster headache did not benefit from the study. We, thus, could confirm a previously reported observation[4] with our double-blind, placebo-controlled design. Misoprostol can be regarded as an alternative drug if anticonvulsants are not effective or not tolerated. Unfortunately, we could not detect any factors predicting the therapeutic response of the patients.

The sample of our study shows the typical features of trigeminal neuralgia associated with MS such as predominance of the right side and of the second branch, higher frequency in older patients, and occurrence about 12 years after onset of MS, and more often in the relapsing types of MS. Therefore, we believe that our sample is representative for the clinical phenomenon of trigeminal neuralgia in MS patients.

There were only mild and transient adverse events in the total sample. One patient, however, could not take misoprostol longer than the study period, although it gave her complete relief from the pain, because of menorrhagia. This is a typical and well-known side effect of misoprostol.[3]

We cannot conclude from our data on the mechanisms of action responsible for the efficacy of misoprostol. However, in experimental models of MS it has been shown that prostaglandins of different types are able to suppress the inflammatory activity, in particular of T-cells.[2] This might lead to a decrease of demyelination in the MS plaques and, thus, to a reduction of the ephaptic nerve conduction which is responsible for the pain also in MS associated trigeminal neuralgia although the inflammation in the region of demyelination in the nerve root entry zone is very limited.[6] However, this hypothesis is very preliminary and the data of our study do not allow any further speculations. In chronic cluster headache, the mechanisms responsible for the attack induction must be different from those in trigeminal neuralgia. The inflammatory processes involved in the pathophysiology of chronic cluster headache seem not to respond to prostaglandin-analog activity.

In conclusion, our data suggest that treatment with misoprostol 600 μg per day is a treatment option in refractory trigeminal neuralgia associated with MS but not in chronic cluster headache. It is safe and effective in the majority of patients with trigeminal neuralgia but not in all.

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41 New targets II: discussion summary

R. G. Hill

This last session of the seminar covered a large amount of pharmacological territory in a search for novel mechanisms that might be exploitable for the preventive treatment of migraine. The interesting data on the prophylactic effect of ACE blockade with lisinopril or candesartan[1,2] illustrates that we still have much to learn. Of particular interest in this study was the efficacy of the ACE inhibitors in reducing the occurrence of all headaches, not just migraine. Clearly confirmatory studies are needed but as this is an extremely safe class of drug the prospects for further clinical use are attractive.

In discussion, the issue of the well-described polymorphism in ACE was raised and it was encouraging to learn that a *posthoc* analysis is being performed to see if there is any correlation with the efficacy of treatment and the presence or absence of the polymorphism. Schouenen[3] had perhaps the most challenging assignment in dealing with a spread of topics from Ca^{2+} channel blockers to riboflavin. Clearly there are treatments which are used and found effective in some countries but not in others and the scientific rationale for these differences in clinical practice is not always completely clear. This issue underlines the need for international seminars such as this so that opinions and data can be adequately shared.

The review of CGRP-related mechanisms and the pharmacology of BIBN 4096[4] was a pointer to perhaps the one new and exciting, but also rational, approach to headache treatment on the near horizon. There was universal disappointment when we were told we must wait for several months more before we could see the clinical data from their proof of concept study.

The potential role of PDE5 in headache was a novel area introduced to us in the last lecture of the seminar.[5] Following the extensive use of the selective PDE5 blocking drug, sildenafil, in the treatment of erectile dysfunction it became apparent that headache is one side effect of this treatment. PDE5 as an enzyme has interesting properties and can be activated both by a process involving phosphorylation and by an alternative route, suggesting that it has two catalytic activity states. This probably means that it would be feasible to design a positive modulator for this enzyme that might conceivably have utility against headache. In the discussion of the poster session, we learned that both male and female subjects experienced headache following administration of sildenafil with 10/12 subjects experiencing

headache after drug treatment but only 2/12 after placebo. In contrast to the headache following treatments causing NO release, no changes in cerebral blood flow, including those indicated by transcranial doppler measurements, nor any changes in systemic blood pressure were seen.

It was shown in another poster presentation that the prostaglandin E-related agonist misoprostol was effective when given twice daily for 2 weeks in patients with trigeminal neuralgia resistant to standard treatment with anticonvulsants. Both frequency of attacks and the pain intensity experienced were reduced by misoprostol. In a separate cohort of patients suffering from refractory cluster headache, however, misoprostol was ineffective. Discussion revealed that the effect of treatment was rapid in onset but that the EP receptor mediating the effect was currently unidentified. Studies on GTN precipitated headache were described as a means for comparison of various potential antimigraine drugs in a controlled volunteer trial. Migraineurs were found to experience migraine in a consistent fashion after GTN administration. Prophylactic administration of propranolol for 2 weeks had detectable peripheral haemodynamic effects but was ineffective at blocking GTN precipitated migraine. However, a similar study with valproate showed that prophylactic administration of this drug could reduce the probability of a GTN triggered migraine. This data suggests that this may be a useful strategy for studying new drugs, although in discussions it was admitted that the desire of patients to use rescue medication during the experiment was a complicating factor. A surprising result was reported with the novel drug tonerbasat, where some subjects treated with this agent experienced a hypotensive episode when subsequently given GTN. In discussion it was revealed that this agent had not been shown to have any direct vascular or sympatholytic activity. The conclusion of the experimenters was that the interaction was likely to involve a reduction in sympathetic outflow by an as yet unidentified mechanism.

The lively discussion in this last session of the seminar showed that this field of research is a vigorous one. It also underlined how much we still have to learn about the underlying mechanisms of headache generation and, in particular, how to design more effective preventive treatments.

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