Migraine Prevention Trials and Optimized Acute Therapy: Translating Lessons Learned into Clinical Practice

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Current Pain and Headache Reports 2008, **12:**220–223
Current Medicine Group LLC ISSN 1531-3433

Different classes of drugs, discovered by serendipity, have been used successfully for migraine prevention for more than 40 years. The progressive knowledge of migraine pathophysiology, brain hyperexcitability, and the specific neurotransmitter systems involved in pain perception has driven the attempts at targeting two crucial mechanisms: the restoration of nociceptive dysmodulation and the inhibition of cortical hyperexcitability. The success of modern research trials with preventive migraine agents (mainly neuromodulators) and optimized treatment of acute attacks with drug combinations aimed at low serotonergic function, neurogenic inflammation, and central sensitization has translated into better outcomes for patients and physicians. Trials combining preventive migraine agents with nonpharmacologic behavioral headache management have yielded additional benefits over either approach alone. With the clinical application of this updated information from clinical trials, migraine impact on productivity, quality of life, and suffering will certainly be diminished. We hope that these achievements will create a stable path of management to benefit our patients, without interruption, into the foreseeable future.

Introduction

Migraine, a chronic, painful, disabling, and potentially progressive condition with an enormous social and economic impact, has been researched emphatically in the past 10 years. Clearer guidelines for performing clinical studies and large trial programs mostly carried out with the neuromodulators divalproate and topiramate have set new standards for treatment strategies guided by evidence-based medicine [1•]. In addition, description of how the drugs fit in migraine pathophysiology and their mechanisms of action has shed more light on a previous, partially blinded, strategy of treatments [2•].

Strategies for migraine prevention are being reassessed, including for many patients who would benefit from prophylaxis but are not receiving it. Additionally, certain subsets of migraineurs are recognized as potential benefactors from earlier and more aggressive preventive approaches. The evolution of clinical management incorporating behavioral headache management and optimized drug prevention with new acute treatment modalities is a changing paradigm for success with migraine sufferers [3].

Moreover, knowledge of the involvement of the imbalance between glutamate-mediated excitation and γ-aminobutyric acid (GABA)–mediated inhibition, along with the potential crucial role of T- and L-type calcium ion channel activity, directed paths for better understanding of migraine prevention through modulation of the biochemical phenomenon of cortical excitation and modulation of the nociceptive system [4].

The role of cortical excitability as a crucial mechanism involved in migraine has been evident for many years. The carbon dioxide hyperreactivity of cerebral blood vessels, phosphene studies, electrophysiologic studies, and even the assessment of markers for oxidative stress suggest that selected neurons in the migraine brain are more excitable. These phenomena, which are not fully understood yet, may be related to the imbalance between glutamatergic and GABAergic functions, perhaps mediated by a genetic defect [2•,5,6]. The defect in the FHM1 gene, which results in excessive gain of function in calcium channels, may release more glutamate into the postsynaptic cleft. Dysfunction of glutamate uptake or lack of its clearance

may be responsible for causing postsynaptic receptor stimulation and neuronal depolarization [2•,5]. Additionally, the effects of the FHM1 gene mutation on the calcium PQ channel, which is located presynaptically and has a regulatory role in neurotransmitter release and a postsynaptic role in neuronal excitability, may also be related to the transmission of nociceptive mechanisms [6–8]. Through different channelopathies both the FHM2 and FHM3 genes also result in excessive availability of excitatory glutamate, leading to neuronal excitability and nociception.

Indeed, approaches aiming at nociceptive mechanisms have been the focus of pharmacotherapy for migraine prevention. Recent trials demonstrate that pain is not only discriminated, but rather perceived, memorized, and expressed through multiple pathways at multiple levels of the nervous system. Modulation occurs at different levels of the cerebral cortex or at descending levels from the hypothalamus down into the trigeminal nucleus caudalis. In addition, modulating nociceptive pathways may exert effect by acting on receptors from various neurotransmitter systems such as the 5-hydroxytryptamine, dopaminergic, noradrenergic, glutamatergic, and GABAergic, with the emerging potential role of the cannabinoid, cholecystokinin, and adenosine receptor systems [2•].

In this article, we describe the possible relationship between data from trials involving preventive pharmacotherapy, behavioral headache prevention management, and optimized rational acute cotherapy as well as early intervention and their influence on daily clinical practice for migraine and, when available, tension-type headache.

Discussion

The myriad of information emerging on the underlying biochemical mechanisms of migraine, mostly discovered in trials with preventive pharmacologic agents, shows considerable promise for the treatment of migraine and other severe forms of primary headache. Both prophylaxis and acute therapy are optimized through better understanding of potential and actual targets for drug action, as are other treatments. In addition, the combined use of different pharmacologic agents, aiming at different mechanisms or perhaps performing synergistic effects on multiple pathways, has certainly improved the outcome parameters related to migraine treatment strategies. Additionally, combined use of preventive drugs and behavioral headache therapies has also yielded better results than the separate use of either treatment alone [9].

Despite current knowledge on pathophysiologic mechanisms involved in migraineurs' brains, the clinician must combine evidence-based therapies and common sense experience to deal with each patient, as patients react quite differently to the same strategies given the individual's psychosocial milieu. It is clear that universal endpoints demonstrated in clinical trials will not always translate in clinical practice to individual patient outcomes despite migraineurs' common shared pain mechanisms and known migraine targets and pathways. This result is related to varying degrees of clinical effects, patients' different beliefs and expectations, different desires of treating physicians and treated patients, and compliance issues as well as pharmacogenomic implications [2•].

Nonetheless, although most trials involving migraineurs are performed "under the wings" of heavy funding from drug makers, patients and practitioners benefit from research on acute treatment and prevention. Information obtained from recent trials and practitioners' indomitable desire to help patients is leading to optimized headache treatments, although clinicians in certain countries are tied to regulatory approaches that limit prescription of drugs that clinical trials and experience have shown or suggested to be effective in most patients.

The imperative to improve acute headache treatment efficacy led to nonfunded trials that revealed that combining the most promising class of neurovascular-specific acute treatment (a triptan) with a traditional inexpensive NSAID could improve outcomes [10–13]. Until just a few years ago, who would have thought that rational cotherapy based on nociceptive mechanisms represented the possibility for optimizing acute oral migraine therapy? Combining a triptan plus an NSAID reduces recurrence (return of the headache within 24 hours of becoming mild or absent after it was treated as moderate or severe) in clinical practice, and it is more efficacious in terms of pain-free measures and outcome, as well as for relief of nausea and photophobia. In addition, sustained pain-free measures in acute migraine are also more improved with the combination of these pharmacologic agents; there is no increase in side effects or modification of the tolerability of either drug alone [14,15•]. Moreover, centrally and peripherally acting prokinetic drugs (trimebutine and metoclopramide) might optimize the oral treatment of migraine attacks simply by promoting better triptan absorption, which may be an interesting pilot opportunity to address the well-known but neglected problem of reduced gastrointestinal motility during acute attacks. This concept depends on confirmation from larger studies but may suggest a new acute treatment strategy for improving migraine sufferers' clinical outcomes [16,17].

Although paradigms support optimizing preventative strategies, many headache clinicians, according to common statements made during various headache meetings, do not prescribe preventive monotherapy. Is this because clinicians who are really motivated to improve their patients' outcomes use combinations of preventive agents instead? Is this treatment strategy due to the discovery of potential new underlying migraine mechanisms? Or is polypharmacy practiced due to the practical reality that migraine is a multifaceted biopsychosocial disease and the psychosocial aspects are too difficult to otherwise address behaviorally? If migraine must be treated as a multi-target disease, and because the predominant mechanisms that need inhibition are cortical hyperexcitability and nociceptive dysmodula-

tion, and drugs are the treatment modality, perhaps we need to bend the rule of monotherapy [18]? Why has so little attention been devoted to evaluating the outcome of strategies combining drug and nondrug, especially behavioral, treatments [9]? Is it possible that trials using preventive pharmacologic agents demonstrate that a better approach is the use of different drugs to act on multiple neurotransmitter systems simultaneously [19,20•]? Or are treatments more effective using the combination of a proven beneficial tricyclic antidepressant plus physical or cognitive-behavioral therapy, as evidenced by studies conducted with subsets of difficult patients [21,22]? Perhaps these combined-approach studies will direct a changing paradigm of treatment in clinical practice, especially for patients with unremitting primary headaches or primary headaches associated with comorbid mood or anxiety disorders [23]. As Holroyd and colleagues [22] emphasized, patients with chronic tension-type headache are difficult to manage with the single options of behavioral or pharmacologic treatment, both of which are usually only modestly effective. Because data on combined effects for these two treatments are lacking, it is appropriate to carry out studies aimed at evaluating the combination of drug and nondrug treatments. Indeed, Holroyd et al. [22] demonstrated that combining up to 100 mg/day of amitriptyline (or up to 75 mg/day of nortriptyline) and stress management (eg, relaxation, cognitive coping) was significantly more effective ($P = 0.006$ and 0.003) than the use of the medications or the nondrug therapies alone, indicating that the clinical approach with this combination improves outcome relative to monotherapy.

Conclusions

New strategies for managing migraine are emerging because of the recently released studies suggesting possible new underlying mechanisms of migraine, the better understanding of the migraineur's brain, and the results of trials demonstrating more improved efficacy measures when combinations of drugs or drugs and nondrug therapies are used. These approaches are corroborated by statements from numerous clinicians who routinely do not use monotherapy for the prevention or treatment of acute attacks. In addition, it is suggested that certain patient subsets must be more aggressively managed, including an earlier submission to drug prevention. Interestingly, these revised paradigms, mostly regarding combination of drugs or drug and nondrug therapies, are progressively being incorporated into the currently available routines of practice. More work is needed until physician and patient expectations in daily clinical practice exceed the efficacy parameters obtained with the available trials, which evaluate prevention and acute treatment with ceiling effects of 60% to 70% [20•,24,25]. The particulars of each patient must be considered and combined with the conclusions of controlled trials in order to promote better outcomes for real-world treatment. This is what we all anxiously expect.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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