BMC Neurology

BioMed Central

Debate

Acute treatment of migraine. Breaking the paradigm of monotherapy

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Published: 28 January 2004

BMC Neurology 2004, **4**:4

Received: 27 November 2003

Accepted: 28 January 2004

This article is available from: http://www.biomedcentral.com/1471-2377/4/4

Abstract

Background: Migraine is a highly prevalent disorder. The disability provoked by its attacks results in suffering as well as considerable economic and social losses. The objective of migraine acute treatment is to restore the patient to normal function as quickly and consistently as possible. There are numerous drugs available for this purpose and despite recent advances in the understanding of the mechanisms and different biological systems involved in migraine attacks, with the development of specific 5-HT agonists known as triptans, current options for acute migraine still stand below the ideal.

Discussion: Monotherapeutic approaches are the rule but up to one third of all patients discontinue their medications due to lack of efficacy, headache recurrence, cost and/or side effects. In addition, a rationale has been suggested for the development of polytherapeutic approaches, simultaneously aiming at some of the biological systems involved. This paper reviews the fundamentals for this changing approach as well as the evidence of its better efficacy.

Conclusion: As a conclusion, most of the patients with a past history of not responding (no pain-free at 2 hours and/or no sustained pain-free at 24 hours) in at least 5 previous attacks should undergo a combination therapy suiting to their individual profile, which must include analgesics or non-steroidal anti-inflammatory agents plus a triptan or a gastro kinetic drug. The three-drug regimen may also be considered. In addition, changing the right moment to take it and the choice for formulations other than oral has also to be determined individually and clearly posted to the patient.

Background

Migraine is a highly prevalent disorder which manifests clinically as moderate to severe or severe headache attacks with frequent frontotemporal unilateral location and associated symptoms [1-3]. The pain is pulsating and/or pressure-type, usually associated with nausea, photophobia, phonophobia and osmophobia. Its attacks promote disability and generally worsen with physical activities. The duration may last from 4 to 72 hours when not treated or treated ineffectively [3]. The headache frequency is variable and some patients may present it on a weekly basis while others will have it less than once a

month [4]. The disability of migraine results in considerable economic and social losses [5].

Migraine attacks may present with four distinct phases: (1) prodromic phase with premonitory symptoms, (2) aura phase with transient neurological symptoms and signs, (3) headache phase with associated features and (4) recovery or postdromic phase frequently associated with resting and sleeping. Only the headache phase can be treated and despite the advances in understanding migraine, considerable uncertainty surrounding an effective and definitive way of treating the attacks remains [6,7].

The objective of acute migraine therapy is to restore the patient to normal function by rapidly and consistently alleviating the head pain and the associated symptoms of nausea, vomiting and sensory phobias without side effects and recurrence of the attack within 24 hours [8]. Several drug options and different formulations are available to treat migraine acutely. The choice of a specific medication type depends on individual characteristics such as headache intensity, speed of onset of action, presence of associated symptoms, the degree of incapacitation, and the patient's response [9].

There are specific and non-specific treatments for migraine attacks. Non-specific treatments, such as aspirin, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and combination analgesics, are used to treat migraine and a wide range of pain disorders [10]. Specific treatments, including ergotamine, dihydroergotamine and the triptans are effective for treating the attacks of primary headaches with neurovascular mechanisms, such as migraine and cluster headache, but not for treating other types of headaches [11].

Discussion

Reasons for changing the approach

Clinicians know that some patients do respond well to simple analgesics in a monotherapeutic approach but despite the advent of newer, highly effective migraine acute therapies, most of the patients still want rapid onset of complete pain relief [12], which cannot be provided by most of the current individual options for migraine treatment [13]. Although the triptans represented a tremendous positive impact on patient care and clinical practice, they are still far away from the optimum. Monotherapy using these selective 5-HT1B/1D agonists, especially orally, does not result in rapid, consistent, and complete relief of migraine in all patients [14]. The response rates in numerous controlled trials vary considerably. The aura phase of patients with migraine with aura can't be effectively treated, side effects may occur in up to 89% of the patients and up to 31% of those taking sumatriptan discontinue its use due to lack of efficacy, headache recurrence, cost and/or side effects [15-18]. In addition, most of these studies were performed using the endpoint headache relief (from moderate or severe to mild or none) rather than the current standard of headache free at 2 hours [19]. Moreover, due to variable placebo response rates, one must have to pursue parameters of therapeutic gain instead of absolute response [20].

Subcutaneous sumatritpan for instance, still considered the most efficacious drug for a migraine attack, promotes headache relief with a therapeutic gain of 51–52% [20]. The other triptans and triptan formulations range from 10 to 47% with regard to therapeutic gain. On the other hand, ergotamine derivatives have been used for over 40 years but little evidence exists that it is significantly more effective than placebo [21]. Although largely used in some countries, its pharmacokinetic is totally unpredictable, with oral and rectal bioavailability of less than 5%, which do not provide consistency through all attacks within the same patient [22,23]. Other options for migraine attacks include analgesics alone or combined with caffeine and/or metoclopramide and NSAID. These compounds vary largely in characteristics but in regard to efficacy may demonstrate therapeutic gains similar to 100 mg sumatriptan (around 29–30%)[24]. Recurrence, the returning of the headache within 24 hours after it has become mild or absent, is also a problem with triptans and with other acute migraine treatments. The use of sumatriptan, for example, may bring up recurrence after 6–7 h with the nasal spray, after 17 h with the tablets and after 10 h with the subcutaneous formulation [25]. The recurrence may require re-dosing, which can cause excessive use and more dissatisfaction with available treatments [26].

In addition, recent evidence has demonstrated that once peripheral and central sensitization occurs and allodynia cutanea develops, the triptans and other acute therapies will not work efficiently in order to provide consistent relief [27]. Moreover, migraine seems to involve different pathophysiological mechanisms named as "low" serotonin, neurogenic inflammation and dopaminergic hypersensitivity which implies that addressing one of the involved biological systems will always stand bellow the ideal [14]. The consistent demonstration of changes in 5-HT levels during migraine has ever been found in all migraineurs but alterations in 5-HT levels in metabolism have been reported by many investigators [14,28]. The inflammation in migraine is crucial. Transient disturbances in cortical sensory functions release potassium and hydrogen ions in the vicinity of sensory fibers that innervate the dura, which could activate C-fiber meningeal nociceptors and secretion of calcitonin-gene-related-peptide, therefore initiating neurogenic inflammation

[29,30] with the introduction of histamine, serotonin, bradykinin, and prostaglandins into this environment.

Mechanical hypersensitivity develops in receptors located in the dura mediating the throbbing of the headache and it's worsening during coughing, bending, or other physical activities that increase intracranial pressure [31]. In addition, the inflammation activates and sensitizes dorsal horn neurons leading to cutaneous allodynia in the ipsilateral periorbital skin followed by the expanding of receptive fields to the contralateral periorbital areas as well [32]. Finally, dopaminergic hypersensitivity has been documented in migraine by data demonstrating that migraineurs are more sensitive to the effects of dopaminergic agonists than nonmigraineurs. It is corroborated by the observation that many components of a migraine attack such as yawning, nausea, hypotension, cerebral blood flow changes and headache are induced by doses of dopamine agonists that have no effect in nonmigraineurs [14,33-36]. All of these facts point to a path of combining drugs aiming at different mechanisms and systems involved in migraine, at least in certain subsets of patients not responsive to traditional approaches, with regard to pain-free and sustained pain-free endpoints. But, does the simultaneous action on various pathophysiological mechanisms really improve efficacy and outcome?

Evidence of better efficacy

Monotherapeutic approaches to each of the biological systems involved in migraine result in definite, but often suboptimal, relief of a migraine attack. Therefore, it follows logically that polytherapy targeting more than one of these systems should be more efficacious than addressing only a single mechanism involved in migraine pathophysiology [14]. In addition, drugs rapid achieving onset of action could be able to function before the central sensitization and the development of cutaneous allodynia, providing better consistency across multiple attacks. Even prior to the introduction of 5-HT agonists, it was demonstrated that combining therapies result in better outcome. Lance recommended metoclopramide to be given before the administration of an ergot derivative in order to allow a faster gastric absorption, which is impaired during a migraine attack [37]. Wilkinson reported that 61% of her patients had total or significant relief of migraine following a regimen that included a dopamine antagonist, a simple analgesic, and an attempt to sleep. In the remaining patients, an ergot preparation was added and resulted in a total efficacy rate of 91% [38]. The combination of dihydroergotamine (DHE) plus prochlorperazine administered intravenously revealed to be a highly effective emergency room scheme as proposed by Callaham and Raskin [39]. We have been demonstrating that the combination of sumatriptan plus a NSAID such as tolfenamic acid or naproxen sodium reduces recurrence in clinical practice. In our first study, 240 moderate or severe attacks were treated with 100 mg sumatriptan and 200 mg of tolfenamic acid resulting in a decreasing recurrence rate from 62,5% to 23,8%. However, this was an open retrospective study, therefore, limiting further conclusions [40].

On the other hand, the use of 100 mg sumatriptan and 550 mg naproxen sodium reduced recurrence from 59% to 25,5% ($p < 0.0003$) compared to the use of sumatriptan plus placebo [41]. Another 5-HT agonist, the Rizatriptan, was also studied in combination with a member of a new class of NSAID, known as COX-2 selective inhibitors, characterized by better tolerability in regard to gastrointestinal side effects. In this study we suggested that a fast acting triptan such as Rizatriptan 10 mg combined with a long plasma half-life COX-2 inhibitor such as Rofecoxib 25 mg reduced recurrence, provided better sustained pain-free rates and demonstrated a trend for better efficacy rates with regard to headache and nausea relief when compared to the single use of Rizatriptan [42]. Recently we have demonstrated that 10 mg Rizatriptan plus 50 mg rofecoxib was more efficient than rizatriptan alone and the combination of rizatriptan plus 200 mg tolfenamic acid with regard to pain-free rates at 2 hours ($p = 0.008$ and $p = 0.007$, respectively) and photophobia at 2- and 4-hour timepoints ($p = 0.010$ and $p = 0.023$, Rizatriptan + Rofecoxib vs. Rizatriptan; $p = 0.003$ and $p = 0.015$, Rizatriptan + Rofecoxib vs. Rizatriptan + Tolfenamic acid). Recurrence was also significantly reduced with both combinations in comparison to rizatriptan alone (50% vs. 15,4%, Rizatriptan vs. rizatriptan + Rofecoxib; 50% vs. 7,7%, Rizatriptan vs. Rizatriptan + Tolfenamic acid). In this study (submitted for publication), 33 patients treated 184 moderate or severe attacks in a randomized counterbalanced order with rizatriptan alone, rizatriptan plus rofecoxib and rizatriptan plus tolfenamic acid. Side effects didn't differ significantly between the attacks treated with the three options.

Summary

Although these evidences clearly suggest advantages with the combination of drugs acting on different mechanisms involved in migraine, there is still a lack of controlled studies to support it. Despite that, drug combinations in migraine treatment are common among specialists. Fortunately, significant recent scientific progress has led to the ability to develop rational polytherapeutic regimens in migraine [14]. We propose that the subset of patients not having achieved pain-free status in up to 2 hours or not presenting sustained pain-free for 24 hours in at least 5 previous migraine attacks with their current acute treatment options undergo combination therapy with simple analgesics or NSAID plus a triptan or a gastro kinetic drug such as 20 mg metoclopramide or 30 mg domperidone or

200 mg trimebutine. The simultaneous use of these three classes of substances must be considered for those still remaining unresponsive to the proposed treatment objectives. In addition, changing the strategy of utilization for the chosen drugs may also improve efficacy and outcome. For those patients rapid developing severe headache, a combination of 6 mg injectable sumatriptan plus 100 mg rectal indometacin seems to be very effective. If nausea is a critical issue for that specific patient the use rectal metoclopramide or the administration of oral domperidone at the first sign of the attack may be useful as well. Patients have to be clearly informed with regard to the drug usage frequency limitations (up to two times a week, not negotiable!) since it is not desirable that the potential gained with the drug combination translates into a higher potential for drug overuse. As we break the current paradigm of treating all patients with monotherapy and the clinical experience expands in the future, the perspectives of identifying rapid, consistent and complete polytherapy for migraineurs will develop and certainly solidify and allow maximum efficacy with minimum side effects.

Competing Interests

None declared.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2377/4/4/prepub