

# The use of combination therapies in the acute management of migraine

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**Background and objectives:** Migraine is a highly prevalent neurological disorder with multiple peripheral and central mechanisms. Targeting a single mechanism for treating individual attacks as well as for performing the prophylaxis has been shown to be only partially effective. Recently, the role of combining agents for acute migraine treatment has gained attention and the combination of a triptan plus a non-steroidal anti-inflammatory drug (NSAID) has demonstrated better efficacy. This review focuses on the fundamentals of treating migraine attacks with two or more agents, and emphasizes the characteristics of the recently approved fixed combination sumatriptan–naproxen.

**Methods:** A PubMed search using the terms “migraine”, “treatment”, “acute”, “triptans”, “non-steroidal anti-inflammatory drugs”, “sumatriptan”, “naproxen”, and “combination” was used. In addition, abstracts presented in the major meetings of the American Headache and the International Headache Societies along with the American Academy of Neurology were also evaluated.

**Results:** Although most of the few studies encountered were not controlled, there is a clear trend for better efficacy in combining triptans with NSAID. Additionally, the results of two recent large and controlled studies using fixed combinations of sumatriptan (50 mg and 85 mg) with 500 mg naproxen sodium confirm the initial observations of the clear superiority of this combination over the use of each agent alone. The differences in the endpoints 24-hour pain-relief response as well as pain-free and pain-relief parameters at 2-hour time-point are the most noticeable efficacy measures. Tolerability was not different between studied drugs.

**Conclusions:** Combining triptans with NSAID and other agents for the acute treatment of migraine suggests better outcome efficacy measures than the use of single agents. The fixed combination of sumatriptan and naproxen sodium offers improved 2-hour and 24-hour benefits over monotherapy with each one these options. Recently issued FDA approval for marketing the combination (sumatriptan 50 mg–naproxen 500 mg) emphasizes the usefulness and safety of this new treatment for migraine attacks.

**Keywords:** migraine, acute treatment, sumatriptan, naproxen, combination

## Introduction and background

Migraine is a highly prevalent disorder manifesting clinically as headache attacks of moderate to severe or severe intensity. Migraine attacks generally induce a great deal of disability among its sufferers, resulting in considerable economic and social losses (Stewart et al 1994, 1996; Rasmussen 1995; Lipton and Stewart 1997; ICHD-II 2004).

The pathophysiology of migraine is multifaceted and complex. It is a primary headache disorder with a clear genetic basis, but during the intermittent attacks of headache, primary neural events result in the dilatation of meningeal blood vessels, which in turn results in pain, further nerve activation, and inflammation (Lipton and Stewart 1997). Migraine is currently considered a neurovascular headache, where the pain is interpreted as a combination of altered perception (due to peripheral or central sensitization) of stimuli that are usually not painful, as well as the activation

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of a neurovascular dilator mechanism in the first (ophthalmic) and second divisions of the trigeminal nerve. These events are probably initiated by the phenomenon of cortical spreading depression, at least in migraine with aura, but it may also occur in migraine without aura. It is important to emphasize that the pathophysiology of migraine involves multiple compartments of the nervous system, as well as multiple neurotransmitters (Goadsby et al 2002).

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 (Tfelt-Hansen and Welch 2000). 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 (Tfelt-Hansen and Lipton 1993; Dodick 2001). In addition, the preference of the patients as well as the treating physicians is to achieve rapid pain-free status (Lipton et al 2002). Unfortunately, the current acute treatment for migraine is not effective in all patients. Using available options, despite the selectivity for the serotonergic system obtained with the triptans, a probable ceiling effect of around 70% probably exists. Monotherapy, especially orally, does not result in rapid, consistent, and complete relief of migraine in all patients (Peroutka 1998). Additionally, the aura phase of patients with migraine with aura cannot be effectively treated, side-effects may occur in up to 89% of the patients, and up to 31% of those taking sumatriptan, for example, discontinue use due to lack of efficacy, headache recurrence, cost, and/or side-effects (Bates et al 1994; Dahlof 1995; Visser et al 1996a, 1996b). We have noticed this in clinical practice during the first half of the 1990s. At that time, dealing exclusively with headache patients, we have seen many patients who took the recently launched sumatriptan (in Brazil, it was released during the end of 1992) who were dissatisfied with the results and the costs of the new medication. Most have tried the subcutaneous formulation and repeatedly complained about recurrence and side-effects. With the oral formulations, the lack of a pain-free status was the frequently reported limitation. From the end of 1994, we started to combine sumatriptan with a non-steroidal anti-inflammatory medication in order to observe the behavior of the headache with regard to efficacy and sustained pain relief. Surprisingly, the commercially driven

aim of others patenting our idea has impeded further studies completely. The aim of this review is to discuss the progressively changing approach of treating migraine attacks with combination therapy in addition to recent evidence of the superiority presented by the fixed combination sumatriptan-naproxen over the use of each of both agents alone.

## Search methodology

A bibliographic search was conducted of manuscripts indexed on PubMed, written in English or with an abstract in English that allowed abstraction of relevant data. The keywords we chose were "migraine", "treatment", "acute", "triptans", "non-steroidal anti-inflammatory drugs", "sumatriptan", "naproxen", and "combination". We used an exploded search strategy for combining the keywords. Letters to the editor were excluded but abstracts presented on major meetings carried out by the American Headache Society and the International Headache Society during the last 5 years were used for evaluation. Data presented on the American Academy of Neurology meetings were also reviewed. We screened the results to find clinical trials on fixed drug combinations for the acute treatment of migraine.

## Results

The experience supporting the role of the synergistic effect of drug combinations in the acute treatment of migraine is not new. Lance (1981) recommended the administration of metoclopramide before the intake of an ergot derivative in order to allow a faster gastric absorption, which is impaired during a migraine attack. Wilkinson (1983) 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%.

Triptans have been compared with combinations of non-specific agents for migraine. Two studies demonstrated the effectiveness of combination therapy for migraine attacks (OSAM 1992; Tfelt-Hansen et al 1995). In one randomized controlled study, 100 mg sumatriptan was compared with 900 mg acetyl salicylic acid (ASA) plus 10 mg metoclopramide (MCP). Patients were instructed to wait until moderate to severe pain to treat, and then treat three attacks. The primary endpoint was pain relief (also called headache response or headache relief; moderate severe pain reduced to mild or no pain at 2 hours after treating moderate

to severe pain) at 2 hours. For the first attack, headache relief occurred in 45% of the patients taking ASA/MCP compared with 56% of those taking sumatriptan (not statistically significant). In the second and third attacks, sumatriptan 100 mg was superior to ASA/MCP. Recurrence over 48 hours was higher with sumatriptan than ASA/MCP (42% vs 33%). No information on 4-hour relief or pain-free results were published, but 6-hour complete relief (migraine free) was higher for sumatriptan in all three attacks (OSAM 1992). The second study was a comparison of lysine acetylsalicylic acid 900 mg (LASA) plus 10 mg MCP vs sumatriptan 100 mg over two attacks. The primary endpoint was headache relief at 2 hours after treating moderate to severe pain in the first attack. There was no significant difference between the LASA/MCP and the sumatriptan, this time for either attack. Migraine free at 2 hours and recurrence over 24 hours were statistically the same for LASA/MCP and sumatriptan (Tfelt-Hansen et al 1995). These studies emphasize that a combination of two different non-specific pharmacological classes may be as effective as the use of specific selective agents for migraine treatment.

There have been demonstrations that combining a triptan plus a non-steroidal anti-inflammatory drug (NSAID) reduces recurrence in clinical practice and may be more efficacious. In an open study, 240 moderate or severe migraine attacks were treated with 100 mg sumatriptan and 200 mg of tolfenamic acid or sumatriptan alone. Recurrence of any pain (primary endpoint – even mild pain was considered) was 62.5% for sumatriptan and 23.8% for combination (Krymchantowski et al 1999). In another study with a placebo-controlled design, the combination of 100 mg sumatriptan and 550 mg naproxen sodium significantly reduced recurrence from 59% (sumatriptan and placebo) to 25.5% (sumatriptan plus naproxen) (Krymchantowski 2000).

The efficacy and tolerability of the combination sumatriptan 50 mg (encapsulated) and naproxen sodium 500 mg administered concurrently was also evaluated in a recent multicenter, randomized, double-blind, double-dummy, placebo-controlled, four-arm study (Smith et al 2005). In this study, 972 patients treated a single moderate or severe migraine attack with placebo, naproxen sodium 500 mg, sumatriptan 50 mg, or a combination of both active drugs. Twenty-four-hour pain relief response was the primary endpoint, which was achieved by 46% of the combination-treated group compared with 26% of the sumatriptan-treated patients, 25% of the naproxen-treated patients, and 17% of the placebo-treated patients ( $p < 0.001$

for all comparators). The other endpoints, 2-hour headache response, 2-hour pain free response, and the improvement of associated symptoms at 2 hours also favored the combination of sumatriptan and naproxen sodium significantly ( $p < 0.001$ ). For 2-hour headache response the combination group revealed favorable response 65%, whereas 49%, 46%, and 27% of the sumatriptan-, naproxen sodium-, and placebo-treated patients, respectively, were better. However, tolerability was similar among all groups, which emphasizes the better efficacy of this combination without higher occurrence of adverse events.

The results of two identical randomized, double-blind, placebo-controlled and parallel-group studies carried out in various centers treating a single moderate-severe migraine attack with sumatriptan (85 mg) plus naproxen sodium (500 mg), sumatriptan 85 mg, naproxen sodium 500 mg, or placebo were recently reported (Brandes et al 2005). In the first study, 1470 patients were enrolled and the combination revealed significant superiority over placebo in pain-free and pain-relief rates at 2 hours ( $p < 0.001$ ). For sustained pain-free response, the combination of sumatriptan and naproxen sodium was also superior to sumatriptan, naproxen sodium, and placebo ( $p < 0.001$ ). The adverse events were similar among treated groups but no further details were presented. The second study is underway and enrolled 1441 patients.

Rizatriptan was also studied in combination with rofecoxib in two trials (Krymchantowski and Barbosa 2002; Krymchantowski et al 2004). In the first trial, absence of headache at 1 hour was seen in 25% of patients for rizatriptan vs 42% for combination ( $p = 0.082$ ); at 2 hours the figures were 60% and 76% (not significant). Recurrence of any pain was observed in 53% of subjects receiving rizatriptan vs 20% in the combination of group (Krymchantowski and Barbosa 2002).

Recently, a prospective, randomized, open study with regular patients of a tertiary center assessed randomized subjects to treat six consecutive attacks with rizatriptan (RI), rizatriptan and tolfenamic acid (RI+TA), or rizatriptan plus rofecoxib (RI+RO) in counterbalanced order (Krymchantowski et al 2004). A total of 184 attacks was treated. The pain-free rates at 1 hour were: RI: 15.5%; RI+RO: 22.6%; RI+TA: 20.3% (not significant). Pain-free rates at 2 hours were: RI: 37.9%; RI+RO: 62.9%, and RI+TA: 40.6% ( $p = 0.008$  for RI vs RI+RO;  $p = 0.007$  for RI+RO vs RI+TA, not significant for RI vs RI+TA). At 4 hours, pain-free rates were: RI: 69%; RI+RO: 82.3%; RI+TA: 78.1% (not significant for all comparisons). The

combination of RI+RO was superior to RI and to RI+TA for the absence of nausea and photophobia at 4 hours. Recurrence (after being pain-free at 2 hours) was observed in 50% of patients treated with RI, in 15.4% of those treated with RI+RO, and in 7.7% of those treated with RI+TA (Krymchantowski et al 2004).

Migraine attacks already with developed cutaneous allodynia may also benefit from combination therapy. Burstein et al (2005) tested sumatriptan injection and the COX1/COX2 inhibitor ketorolac to block ongoing sensitization in 23 patients who were treated with 6 mg SC sumatriptan 4 hours after the onset of migraine and with ketorolac 2 hours later (two IV boluses, 15 mg each, 10 minutes apart) (Burstein et al 2005). The patients remained allodynic after the sumatriptan injection but the administration of ketorolac 2 hours later rendered 74% of the patients both allodynia-free and pain-free within 1 hour. The authors suggested the possibility that the therapeutic action of COX1/COX2 inhibition was facilitated, to a certain degree, by the preceding action of sumatriptan (Burstein et al 2005).

The combination of a triptan (rizatriptan) and the peripheral opioid agonist trimebutine maleate was also superior than rizatriptan alone. The addition of this exclusive opioid receptor agonist acting at the Meissner and Auerbach mioenteric plexus to 10 mg of rizatriptan rendered 70.1% of pain-free status compared with 29.9% of the attacks treated with rizatriptan ( $p < 0.0001$ ) in the same patients through a randomized, cross-over, placebo-controlled trial. In this study, nausea and photophobia were also significantly better with the combination at 1- and 2-hour timepoints compared with rizatriptan alone (Krymchantowski et al 2005).

## Conclusions

Several areas of the central nervous system and vascular system, together with different mediators, are involved in migraine. As current treatments are not effective in a sizeable portion of the migraine sufferers, combining different classes of pharmacological agents is an attractive strategy for some patients. Additionally, most headache specialists consistently mention the fact that some of their patients use two, three, or eventually more pharmacological agents either to achieve reduction in headache frequency as well as to treat more effectively the intermittent attacks. This has also been our experience over the years in treating headache patients, mostly in tertiary centers. However, as described above, only a few studies deal with this issue, mostly uncontrolled and

therefore unreliable, although clear trends for better efficacy and 24-hour outcome measures are suggested.

On the other hand, the specific combination of sumatriptan and naproxen sodium was studied in randomized, controlled trials with proven efficacy and superiority over the use of each substance alone in various dosages. Initially we have demonstrated that two groups of 13 patients, who were recruited from a regular population under treatment in a tertiary center, had treated 39 moderate–severe attacks combining sumatriptan (100 mg) with placebo or with naproxen sodium (550 mg) in a double-blind design. The recurrence rate was significantly lower in the combination group compared with the placebo group (25.5% vs 59%,  $p < 0.001$ ). These patients had treated migraine attacks before with sumatriptan and with sumatriptan plus naproxen in an open-label fashion, revealing the clear trend for recurrence reduction with the combination. The recent studies with more appropriate methodology and larger populations of subjects confirmed our initial observations demonstrating that the combined use of sumatriptan (either 50 mg or 85 mg) and naproxen sodium (500 mg) do provide superior sustained response rates without increasing adverse events. Perhaps the use of other triptans with different NSAID or gastrokinetic drugs, as suggested in the studies described, do also provide better sustained response measures (sustained pain-free, sustained headache response, incidence of recurrence) and 2-hour pain-free or pain-relief measures. It is reasonable to suggest that since monotherapy with triptans or with NSAID commonly provide 2-hour response rates between 50% and 80%, and only half of such patients achieve a sustained response by 24 hours, the use of acute treatments with longer durations of efficacy are needed (Ferrari et al 2002; Goadsby et al 2002; Smith et al 2005). We all hope that future studies will provide better evidence of the advantages of using combination therapies in all parameters related to the treatment outcome, therefore promoting better efficacy, good tolerability, and less suffering, as hoped for by millions of migraineurs.

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