Efficacy And Safety Of Sumatriptan Plus Naproxen Sodium In The Acute Treatment Of Migraine: Systematic Review And Meta-Analysis Of Randomized Controlled Trials

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Citation

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Abstract

To assess the efficacy and safety of combined sumatriptan and naproxen sodium compared with sumatriptan monotherapy in the acute treatment of migraine. Clinical trials were identified through electronic searches (MEDLINE, CINALH, EBM review and the Cochrane Library) up to February 2011 and historical searches of relevant articles. Studies were included in the meta-analysis if they were 1) double-blind, randomized, controlled trials that evaluated sumatriptan plus naproxen sodium against sumatriptan in moderate or severe migraine in adult patients, and 2) reporting the efficacy in terms of headache relief, pain-free, relief of migraine-associated symptoms, sustained headache relief, sustained pain-free, or headache recurrence. Two authors independently extracted data and assessed study quality. Disagreements were resolved by a third investigator. Treatment effects and adverse effects were expressed as risk ratio (RR). Three trials involving a total of 1952 patients were included in the meta-analysis. Sumatriptan plus naproxen sodium was more effective than sumatriptan alone in providing headache relief and pain-free within 2 hours (pooled RR 1.20; 95%CI 1.11-1.30, $p < 0.00001$, and 1.42; 95%CI 1.23-1.65, $p < 0.00001$, respectively). It was also superior to sumatriptan monotherapy in achieving headache relief at 4 hours, relief of migraine-associated symptoms, sustained headache relief, and sustained pain-free responses. The risk of headache recurrence reduced significantly with sumatriptan plus naproxen sodium (pooled RR 0.64, 95% CI 0.51-0.80, $p = 0.0001$). Combined therapy of sumatriptan and naproxen sodium was as well tolerated as sumatriptan monotherapy. Its effectiveness relative to currently available treatments has yet to be further defined by appropriate head-to-head clinical trials.

INTRODUCTION

Migraine is a chronic neurovascular disorder characterized by recurrent attacks of headache accompanied by gastro-intestinal and neurological symptoms that typically last from 4 to 72 hours[1]. The prevalence in adult populations ranges from 0.7% to 22%, with the highest prevalence in both men and women between the ages of 25 and 55 years[2]. Migraine also poses a significant burden on the health care system in terms of the cost of prescription drugs and care in inpatient, outpatient and emergency settings[3]. Approaches to treating migraine include nonpharmacologic and pharmacologic treatments for acute migraine and for its prophylaxis. Pharmacologic treatment of migraine attacks primarily aims at alleviating head pain and symptoms accompanying migraine, avoiding headache recurrence, restoring patient's ability to function, and minimizing the use of rescue medications[4]. These goals are normally achieved with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), opioids, ergotamines, and triptans. New strategies in acute treatment have recently been investigated, for example, calcitonin gene-related peptide (CGRP) receptor antagonists and serotonin 5-HT_{1F} receptor agonists[5].

Sumatriptan, the first available triptan, is a selective agonist for 5-HT_{1B} and 5-HT_{1D} receptors. The anti-migraine effect results from three main mechanisms of action, i.e. cranial vasoconstriction, peripheral trigeminal inhibition, and inhibition of transmission through second order neurons of the trigeminocervical complex[6]. In moderate to severe migraine, sumatriptan 100 mg has been reported to have similar efficacy to zolmitriptan 5 mg[7] and almotriptan 12.5 mg and 25 mg[8] and be superior to naratriptan 2.5 mg[9]. A 50 mg dose has been shown to be as effective as effervescent aspirin 1000 mg but associated with higher incidence of adverse events[10].

Naproxen is an effective nonselective inhibitor of cyclo-

oxygenase (COX), resulting in the inhibition of prostaglandin synthesis mediated via both COX-1 and COX-2. Naproxen sodium improved the solubility of naproxen, achieving fast absorption and rapid onset of action. The recent meta-analysis has demonstrated that naproxen sodium is effective in reducing headache intensity, rendering patients pain-free within 2 hours, improving nausea, photophobia, and phonophobia, and sustaining headache relief and pain-free from 2 hours through 24 hours after dosing[11].

As both sumatriptan and naproxen sodium have been reported to be effective in treating migraine attack through different mechanisms of action, combining sumatriptan and naproxen sodium may offer more favourable clinical benefits over monotherapy with either agent. In April, 2008, the US Food and Drug Administration approved sumatriptan-naproxen fixed combination tablet developed specifically to target multiple migraine mechanisms. We therefore undertook a systematic review and meta-analysis of the available evidence to evaluate the efficacy and safety of sumatriptan plus naproxen sodium compared with sumatriptan alone in an attempt to determine its therapeutic benefit in the treatment of migraine attacks.

METHODS

IDENTIFICATION OF STUDIES

Reports of randomized controlled trials of combination therapy of sumatriptan and naproxen sodium were identified through a systematic search of MEDLINE, CINAHL, EBM review, and the Cochrane Library. The bibliographic databases were searched from their respective inception to February 2011. The MeSH search terms used were "sumatriptan", "naproxen", "migraine disorders", "headache disorders", "vascular headaches" and "randomized controlled trial". This was followed by keyword search using "naproxen sodium", "cephalalgia", and "cephalgia" as keywords. The reference lists of all retrieved articles, meta-analyses, systematic and narrative reviews were also scanned to identify possible published randomised controlled trials. No language restriction was imposed.

STUDY SELECTION

Two reviewers independently screened abstracts in accordance with the inclusion criteria. Any discrepancies were resolved by a third reviewer. Full-text articles were retrieved and reviewed. The studies were included in the meta-analysis if they were 1) double-blind, randomized controlled trials that evaluated oral sumatriptan combined with naproxen sodium against sumatriptan monotherapy in moderate or severe migraine attacks in adult patients, and 2) reporting the efficacy in terms of headache relief, pain-free, relief of migraine-associated symptoms, sustained headache relief, sustained pain-free, or headache recurrence.

DATA EXTRACTION AND QUALITY ASSESSMENT

Data extraction and study quality assessment were performed independently by two investigators using a standardized form. Disagreements were resolved by a third investigator. The data abstracted were the year of publication, study location, study design, patient characteristics, number of patients, treatment regimen, outcome measures. The incidence of any adverse effects was also recorded. The methodological quality of study was assessed using the scale developed by Jadad et al. which focuses exclusively on the control of bias in randomization, blinding, and patient attrition[12]. Out of the possible maximum score of 5 points, studies with a score of 2 points or less were classified as 'low quality', while those with a score of 3 points or more were of 'high quality'.

STATISTICAL ANALYSIS

Primary outcome was headache relief at 2 hours. Secondary outcomes included headache relief at 4 hours, pain-free at 2 hours, relief of migraine-associated symptoms at 2 hours, sustained headache relief, sustained pain-free, headache recurrence, and safety. Headache relief rate was defined as the proportion of patients in whom headache severity decreased from moderate or severe (grade 2, 3) to mild or no headache (grade 0, 1), according to the IHS criteria. Pain-free rate was defined as the proportion of patients whose headache severity reduced to no pain at 2 hours post dose. Sustained headache relief was estimated based on the proportion of patients whose headache of moderate or severe pain reduced to mild or none pain at 2 hours post dose with no return of moderate or severe pain within 24 after dosing. Sustained pain-free rate was the percentage of patients without any recurrence of headache within 24 hours of initial dose. Relief of accompanying migraine symptoms, namely nausea, photophobia, and phonophobia, was estimated based on the proportion of patients with such symptoms at the beginning of treatment reduced to none at 2 hours post-dose. Headache recurrence rate was the proportion of patients whose headache of moderate or severe pain reduced to mild or none at 2 hours, but subsequently recurred within 24

hours of initial dose. Safety was assessed based on the number of patients who experienced any adverse effects. The results of individual studies were analysed on an intention-to-treat basis. Treatment effects and adverse effects were expressed as risk ratio (RR), risk difference (RD), and number needed to treat (NNT) as well as 95% confidence interval. The inverse variance-weighted method was used for the pooling of RR, RD and the estimation of 95% confidence interval[13]. The number needed to treat was calculated as the inverse of the pooled risk difference. A random effects model was used when the Q-statistic for heterogeneity was significant at the level of 0.1[14], otherwise the fixed effects model was used[13]. The degree of heterogeneity was quantified using I-squared statistic which is the percentage of total variation across studies due to heterogeneity[15]. The statistical analysis was undertaken using RevMan version 5.0.25 (Cochrane Collaboration, Oxford, UK). P-value of less than 0.05 was considered to be statistically significant.

RESULTS

STUDY CHARACTERISTICS

Figure 1 summarizes the process of identifying eligible studies. We identified 9 published papers[16-23] reporting the results of 10 randomized controlled trials of sumatriptan plus naproxen sodium in the treatment of migraine. All were published in English. Of these, four trials compared sumatriptan-naproxen sodium against placebo [20-23] and one was also placebo-controlled and measured prostaglandin levels in the saliva of individuals during menstrual migraine[24]. These five trials were excluded. One trial each reported the number of recurrence in relation to the number of attacks treated[16] and function, productivity, and satisfaction outcomes[19]. They were then further excluded. The remaining two papers involving the results of 3 trials met our inclusion criteria for meta-analysis[17, 18]. It was noted that one paper[18] reported the results from two trials and, therefore, was treated as two separated studies. All the studies included in our systematic review were of high quality. Doses of sumatriptan were 50 mg[17] or 85 mg[18] and naproxen sodium 500 mg. Characteristics of the included trials are presented in the Table.

Figure 1

Fig 1 Study selection process

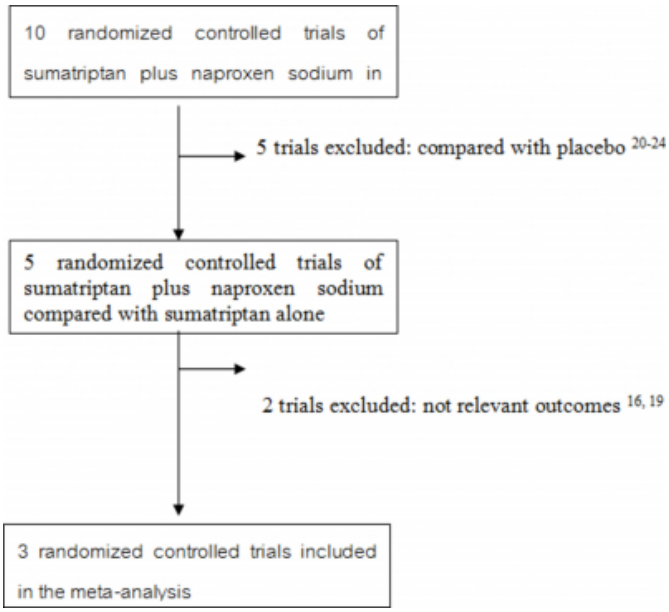


Figure 2

Table. Characteristics of randomized controlled trials of sumatriptan plus naproxen sodium in acute migraine treatment

Study	Quality score	Location	Intervention	N	Any adverse events
Smith et al. [17]	4	USA	ST 50 mg plus NPS 500 mg, or ST 50 mg, or NPS 500 mg or placebo for a single migraine attack	972 ST+NPS = 251 ST = 229 NPS = 250 Placebo = 242	ST+NPS 23% ST 24% NPS 17% Placebo 15%
Brandes et al. [18]	3	USA	ST 85 mg plus NPS 500 mg, ST 85 mg, NPS 500 mg, or placebo for a single migraine attack	1461 ST+NPS = 370 ST = 365 NPS = 361 Placebo = 365	ST+NPS 27% ST 24% NPS 13% Placebo 12%
Brandes et al. [18]	3	USA	ST 85 mg plus NPS 500 mg, ST 85 mg, NPS 500 mg, or placebo for a single migraine attack	1495 ST+NPS = 367 ST = 370 NPS = 371 Placebo = 387	ST+NPS 26% ST 28% NPS 14% Placebo 10%

NPS naproxen sodium, ST sumatriptan, IHS International Headache Society

EFFICACY

HEADACHE RELIEF

A total of 1952 patients were involved in the three trials of combination treatment of sumatriptan and naproxen sodium that reported the results in terms of the proportion of patients whose pain intensity reduced from severe or moderate to mild or none within 2 and 4 hours after treatment[17, 18]. There was no significant heterogeneity among study results. As

expected, sumatriptan plus naproxen sodium was more effective than sumatriptan alone. The pooled RRs were 1.20 (95% CI 1.11-1.30, p < 0.00001), and 1.20 (95% CI 1.13-1.28, p < 0.00001) at 2 and 4 hours postdose, respectively (Figure 2). The risk differences yielded the means numbers needed to treat of 10 (95% CI 7-17) and 8 (95% CI 6-12), respectively.

PAIN-FREE AT 2 HR

Patients receiving combined therapy were more likely to become pain-free at 2 hours compared with those treated with sumatriptan monotherapy. The pooled RR was 1.42 (95% CI 1.23-1.65, p < 0.00001). (Figure 2) On average, treating 10 (95% CI 8-17) patients with sumatriptan plus naproxen sodium would result in one patient who becomes pain-free within 2 hours.

RELIEF OF MIGRAINE-ASSOCIATED SYMPTOMS

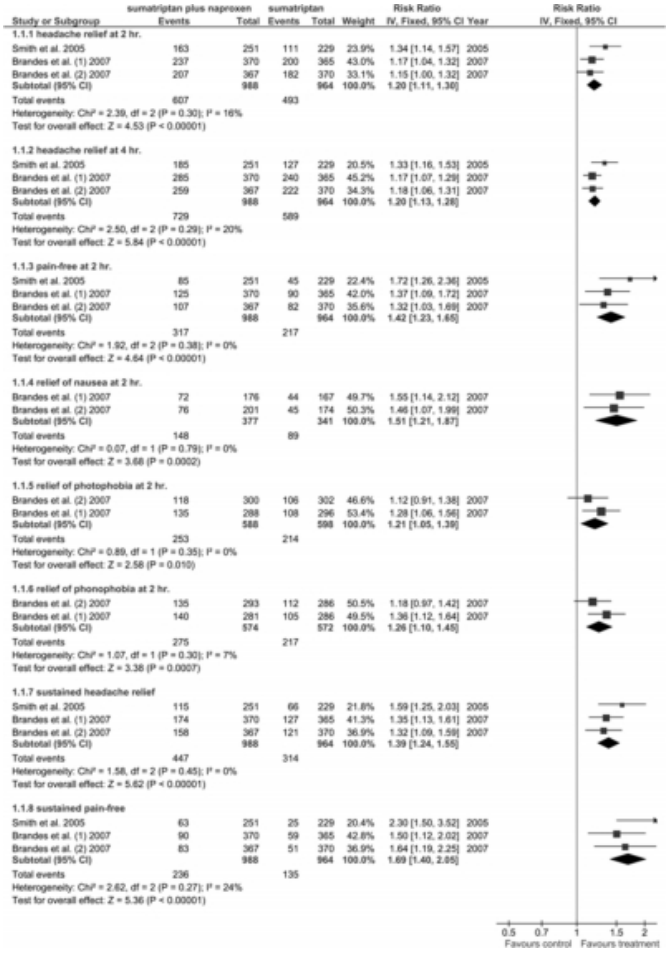
In patients who experienced nausea, photophobia, or phonophobia during migraine attacks, the relief of such symptoms at 2 hours was increased by 51% (95% CI 21%-87%, p = 0.0002), 21% (95% CI 5%-39%, p = 0.01), and 26% (95% CI 10%-45%, p = 0.0007), respectively, with the combination of sumatriptan and naproxen sodium compared with sumatriptan. The means number needed to treat for nausea, photophobia, and phonophobia were 8 (95% CI 5-17), 15 (95% CI 8-50), and 10 (95% CI 7-25), respectively.

SUSTAINED HEADACHE RELIEF

Headache relief from 2 hours through 24 hours after dosing was better with sumatriptan plus naproxen sodium than with sumatriptan alone. The pooled risk difference of 0.13 (95% CI 0.08-0.17) corresponded to the mean number needed to treat of 8 (95% CI 6-13).

Figure 3

Fig 2 Efficacy of sumatriptan plus naproxen sodium versus sumatriptan in acute migraine attack



SUSTAINED PAIN-FREE

Similarly, the risk of pain-free at 2 hours post-dose with no return of headache pain within 24 hours of the initial dose was increased with the combined therapy compared with sumatriptan. The pooled risk difference was 0.10 (95% CI 0.07-0.13, p < 0.00001), corresponding to the mean number needed to treat of 10 (95% CI 8-15).

HEADACHE RECURRENCE

Among those who experienced headache relief at 2 hours after initial dose, the risk of headache recurrence within 24 hours after dosing was reduced by 36% (95% CI 20%-49%) with the combination of sumatriptan and naproxen sodium compared with sumatriptan alone (pooled RR 0.64, 95% CI 0.51-0.80, p = 0.0001).

SAFETY

All three trials[17, 18] reported the number of patients who experienced at least one adverse event that could be

transformed to adverse events rate. The adverse event rates ranged from 23% to 28% in both groups. Surprisingly, the risk of any adverse events did not differ between sumatriptan plus naproxen sodium and sumatriptan monotherapy (pooled RR 1.00, 95% CI 0.86-1.16). The adverse events commonly reported among the two groups were somnolence, dizziness, paresthesia, and tinnitus.

DISCUSSION

A combination tablet containing sumatriptan 85 mg (as sumatriptan succinate) and naproxen sodium 500 mg has recently been approved by the US Food and Drug Administration for the acute treatment of migraine[18]. As triptans and NSAIDs target distinct aspects of the vascular and inflammatory processes hypothesized to underlie migraine headaches, it is not surprising that the combination therapy is more effective than sumatriptan monotherapy in the acute treatment of migraine as shown in our meta-analysis. Sumatriptan 50 or 85 mg plus naproxen sodium 500 mg was associated with more patients achieving headache relief, pain-free response, sustained headache relief, sustained pain-free response, and relief of migraine-associated symptoms. The risk of headache recurrence significantly reduced with combination therapy compared with sumatriptan monotherapy. The risk of adverse events did not differ between the two groups. The adverse events commonly reported were somnolence, dizziness, paresthesia, and tinnitus.

The International Headache Society (IHS) recommends that the proportion of patients with pain-free at 2 hours be used as a primary efficacy measure in clinical trials of drugs in migraine as it is clinically relevant and reflects patients' expectations[25]. Headache relief at 2 hours, sustained pain-free, and time to meaningful pain relief can be used as secondary efficacy measures. Despite the IHS recommendation and its limited clinical relevance, headache relief (or headache response) has been commonly used as the primary endpoint in many trials in migraine. As migraine is often related with associated symptoms namely nausea, photophobia, and phonophobia, it is also important that drugs used for migraine attack be effective against these symptoms[25]. The three trials included in our meta-analysis reported the primary efficacy measure in terms of headache relief at 2 hours postdose. We, therefore, used it as the primary outcome in this meta-analysis. The secondary efficacy measures comprised headache relief at 4 hours, pain-free at 2 hours, sustained headache relief, sustained pain-free, relief of migraine-associated symptoms at 2 hours, and headache recurrence. All these measures were included in our meta-analysis.

Migraine pathophysiology involves a combination of events, including the cortical spreading depression (CSD) and the release of inflammatory mediators such as prostaglandin E2 (PGE2) and nitric oxide which have direct effect on perivascular nociceptors. CSD also triggers the complex mechanisms of afferent and efferent trigeminal vascular events by stimulating the release of CGRP from the trigeminovascular system. PGE2 has also been shown to stimulate CGRP release from the primary cultures of adult rat trigeminal neurons[26]. The superiority of sumatriptan plus naproxen sodium over sumatriptan alone can be explained by dual mechanisms targeting both serotonergic dysmodulation and inflammation in migraine. Triptans and NSAIDs target different aspects of the vascular and inflammatory processes hypothesized to underlie migraine headaches. Triptans reduce CGRP-mediated vasodilation, inhibit the release of inflammatory mediators from trigeminal nerves, and decrease the transmission of pain impulses to the trigeminal nucleus caudalis[27, 28]. In particular, sumatriptan acts as 5-$HT_{1B/1D}$ receptor agonist. 5-HT_{1B} receptors are expressed mainly on cranial blood vessels whereas 5-HT_{1D} receptors are expressed on presynaptic trigeminal nerve. Stimulation of 5-HT_{1D} receptors by sumatriptan will inhibit CGRP and substance P release, thus decreasing neurogenic inflammation and preventing central sensitization. NSAIDs inhibit the synthesis of prostaglandins and may mitigate meningeal inflammation while preventing or mitigating central sensitization arising from activation of glial cells in the brain stem[29, 30]. Naproxen sodium is more water soluble and provides faster onset of action when compared with naproxen base. Naproxen sodium reversibly inhibits COX-1 and COX-2 enzymes and thereby inhibits prostaglandin synthesis. This mechanism would help reduce CGRP and substance P release from presynaptic trigeminal nerve. Therefore, the combination of sumatriptan and naproxen sodium has pharmacologic rationale since they have different mechanism of actions. Besides the favourable pharmacodynamic combination, the analgesic effects of naproxen which lasts for up to 7 hours would help prolong pain relief when used in combination with short half-life triptans[23]. Sumatriptan is short-acting drug, with plasma half-life of 2-2.5 hours, therefore the recurrence of headache is common[31].

Not all patients respond to sumatriptan. Response rates in terms of headache relief at 2 hours after treatment with oral sumatriptan has been reported to be approximately 60%[32]. Among the patients who do respond, about one in three experience headache recurrence within 24 hours[33]. As demonstrated in our meta-analysis, sumatriptan combined with naproxen sodium further reduced the risk of headache recurrence by 36% (95% CI 20%-49%) in comparison with sumatriptan alone. Sumatriptan plus naproxen sodium thus may offer an alternative option for migraineurs who failed to response adequately to sumatripan monotherapy. Although the risks of adverse events were similar between the two regimens, the use of combination therapy should be cautious as both triptans and NSAIDs have been reported to be associated with serious cardiovascular side-effects[5, 34].

Our meta-analysis was not without limitation. Only published trials were included and only three studies were pooled. This may introduce a bias in favor of combination therapy. A funnel plot and the method of Egger et al.[35] are normally performed to assess possible publication bias in meta-analysis. However, we did not conduct such test as the number of studies included was too small. Although the trials assessing different doses of sumatriptan (50 and 85 mg) were combined, no significant heterogeneity was observed. Given its overall efficacy and tolerability as demonstrated in our meta-analysis, sumatriptan plus naproxen sodium may offer an alternative in the treatment of migraine headache in migraineurs who do not respond adequately with either sumatriptan or naproxen sodium monotherapy. Nevertheless, further trials are needed for head-to-head comparison with other active agents currently available for the acute treatment of migraine in order to clearly establish its place in oral therapy of migraine headache.

CONCLUSIONS

The combination of sumatriptan and naproxen sodium offers more clinical benefits than sumatriptan monotherapy in the treatment of moderate to severe migraine attacks in adults. Sumatriptan 50 or 85 mg plus naproxen sodium 500 mg is consistently effective in alleviating headache, rendering patients pain-free within 2 hours, improving nausea, photophobia, and phonophobia, and sustaining headache relief and pain-free from 2 hours through 24 hours after dosing. It was well-tolerated and caused no more adverse events than sumatriptan monotherapy. Further high-quality, head-to-head trials comparing the combination therapy against other active comparators are warranted to better establish its place in oral therapy in the acute treatment of migraine.

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