



Sumatriptan and Naproxen for Treatment of Migraine in Adolescents

Marcia L. Buck, PharmD, FCCP, FPPAG

It is estimated that 8 to 23% of adults and adolescents 11 years of age and older suffer from migraines.^{1,2} Over the past decade, the serotonin 5-HT_{1B,1D} receptor agonists (triptans) have become a mainstay in the acute management of migraines in adults. While often used off-label in adolescents and older children, several randomized placebo-controlled clinical trials have failed to demonstrate significant benefit in relieving migraine symptoms.³⁻⁶ Analysis of these trials identified a high placebo-response rate in this population, with 30-50% of placebo-treated adolescents citing pain relief within 2 hours. Nonrandomization techniques have been used in more recent studies to identify early placebo responders, help to reduce the placebo response rate to expected values (5-10%) and providing for a more accurate interpretation of the effect of treatment.⁴

Until this year, only two drugs in this class had been approved by the Food and Drug Administration (FDA) for pediatric patients. The first, almotriptan received an indication in 2009 for acute management of migraine in children 12 to 17 years of age and older. The second, rizatriptan, was given an expanded indication in 2011 to include treatment of migraine in children 6 to 17 years of age. On May 15, 2015, the FDA announced an extension of the original 2008 approval of the combination of sumatriptan and naproxen sodium (Treximet[®]) to include acute management of migraines in children 12 years of age and older, giving prescribers a third option.^{7,8}

Mechanism of Action

Sumatriptan, 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate, is a selective 5-HT_{1B,1D} receptor subtype agonist. It has been proposed that the 5-HT₁ agonists, the triptans, as well as ergotamine, dihydroergotamine, and methysergide, have four mechanisms of action. Stimulation of the 5-HT_{1B} receptor on cranial vascular smooth muscle may produce vasoconstriction, counteracting the pulse synchronic activation of stretch receptors that are

the possible cause for the throbbing sensation. Stimulation of 5-HT_{1D} receptors on the trigeminal nerve terminals of the meningeal blood vessels may block the release of neuropeptides that cause pain and inflammation. In addition, stimulation of central 5-HT_{1B/1D/1F} receptors in the trigeminal nucleus caudalis may inhibit transmission of afferent signaling from the first-order to second-order trigeminal sensory neurons, preventing wind-up in trigeminal sensory processing and the pain hypersensitivity that comes with long-lasting central sensitization. Lastly, 5-HT₁ agonists may produce stimulation of 5-HT_{1B/1D} receptors in the ventroposteromedial thalamus, inhibiting the processing of nociceptive input from the second-order to the third-order trigeminal sensory neurons in that area.

Naproxen sodium, (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid, is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). While the mechanism of action of the NSAIDs in the treatment of migraines is not well understood, these agents are known to inhibit cyclooxygenase (COX) enzymes COX-1 and COX-2, blocking prostaglandin synthetase and reducing production of inflammatory mediators. It has been suggested that the combination of sumatriptan and naproxen sodium may act synergistically to prevent the development of sensitization of the trigeminal ganglion as well as provide sustained analgesic and anti-inflammatory effects for up to 24 hours.⁸⁻¹¹

Pharmacokinetics

The bioavailability of sumatriptan in adults is only 15%, the result of both incomplete absorption and significant first-pass metabolism.⁸ Naproxen is nearly completely absorbed after oral administration, with a bioavailability of 95%. Food has no significant effect on the absorption of either drug. The maximum concentration (C_{max}) of sumatriptan with the combination product is similar to that of

sumatriptan tablets, but with a slightly longer time to achieve the maximum (T_{max} 0.3-4 hrs versus 1.5 hrs). In contrast, the C_{max} of naproxen with the combination product is approximately 30-40% lower than that achieved when the drug is given alone and the T_{max} is delayed (0.3-12 hrs versus 4 hrs). The values for the area under the concentration-time curves (AUC) for both drugs in the combination, however, are similar to those achieved when given singly.

Sumatriptan is 14-21% bound to plasma proteins and has a volume of distribution of 2.7 L/kg in adults. It is extensively metabolized via monoamine oxidase (MAO), primarily isozyme A, and has an elimination half-life of 2 hours. Both primary metabolites are inactive. Naproxen is highly bound (99%) to albumin and has a volume of distribution of only 0.16 L/kg. It is metabolized to 6-O-desmethyl naproxen, with a half-life of approximately 19 hours.

In a manufacturer-sponsored pharmacokinetic study comparing 24 children 12-17 years of age to 26 adults, the sumatriptan C_{max} and AUC of the children were 50-60% higher following a single dose of the combination tablet containing 10 mg sumatriptan and 60 mg naproxen sodium than when the drugs were given separately.^{8,12} Maximum concentration and AUC were 6-26% higher following a dose of the 30 mg sumatriptan and 180 mg naproxen sodium or the 85 mg sumatriptan and 500 mg naproxen sodium tablets compared to the individual drugs. Pharmacokinetic parameters were similar between the pediatric and adult subjects.

Clinical Trials

In 2011, McDonald and colleagues described the results of an open-label safety study of the 85 mg sumatriptan and 500 mg naproxen sodium combination in adolescents.¹³ This 12-month multicenter trial enrolled 656 patients between 12 and 17 years of age with an average of 2-8 migraines per month lasting more than 2 hours. Patients were instructed to take the combination tablet as soon as possible when symptomatic and to wait 2 hours before taking a rescue medication (an NSAID, acetaminophen, or an antiemetic). A second dose of the combination tablet was not to be taken within a 24-hour period. At study completion, a total of 12,927 doses had been taken, with an average of 2.5 tablets taken per month per subject. The most common adverse effects were nausea (7%), dizziness (3%), muscle tightness (3%), and chest discomfort (3%). None of the patients had serious adverse events considered by the investigators to be drug-related. Seven percent of patients withdrew because of adverse effects; 5% withdrew because of lack of efficacy. Although not a primary outcome, patients were pain-free within 2 hours

of 42% of the doses taken. Patients also reported an improvement in quality of life and were generally satisfied with the efficacy of the combination.

The safety and efficacy of the combination also were studied in two randomized placebo-controlled trials. In the June 2012 issue of *Pediatrics*, Derosier and colleagues published the results of a randomized, parallel group study of the combination in 589 adolescents between 12 and 17 years of age.¹⁴ Patients had to have experienced 2 to 8 migraines per month for at least 6 months. All subjects entered a 12-week run-in phase in which patients received a blinded placebo as treatment for one migraine. Those with an early positive response (relief of pain within 2 hours) were excluded from further study. The remaining subjects were entered into the 12-week double-blind phase. Patients were randomly assigned to receive placebo or sumatriptan and naproxen sodium in one of three dose combinations: 10 mg sumatriptan and 60 mg naproxen, 30 mg sumatriptan and 180 mg naproxen, or 85 mg sumatriptan and 500 mg naproxen. The primary endpoint was the number of patients who were pain-free at 2 hours.

The 2-hour pain-free rates were significantly higher for all treatment arms compared to placebo: 29% for the 10 mg sumatriptan and 60 mg naproxen dose, 27% for the 30 mg sumatriptan and 180 mg naproxen dose, and 24% for the 85 mg sumatriptan and 500 mg naproxen dose, compared to 10% for placebo (all $p = 0.003$). Posthoc analysis revealed no significant differences in response among the three doses and no correlation between patient age and response. A statistically significant difference was noted in the number of patients who remained pain-free from 2 to 24 hours between the 85 mg sumatriptan and 500 mg naproxen sodium dose and placebo (23% versus 9%) and in the number of patients who were photophobia-free and phonophobia-free at 2 hours (59% versus 41% and 60% versus 42%, respectively, each comparison $p = 0.008$).

Although not statistically significant, there was a trend towards less use of other rescue medication with treatment. Thirty-two percent of patients given placebo required rescue medication, compared to 15%, 16%, and 14% of the groups given the low, mid-range, and high-dose treatments. The number of patients who were nausea-free at 2 hours was not different among the groups with 70% of patients in the placebo group and 82%, 77%, and 70% with the three doses, respectively.

Adverse effects reported in 2% or more of study subjects included nasopharyngitis (1%), hot

flushes (1-2%), and muscle tightness in the neck or jaw (1-2%). There were no serious adverse effects reported, and none of the subjects withdrew from the study because of an adverse effect. The authors concluded that all three doses of the combination product were well tolerated and provided similar efficacy in treating migraine pain in adolescents. They suggested that the combination of 10 mg sumatriptan and 60 mg naproxen may be more suitable for younger adolescents and those with migraines of shorter duration, while the 85 mg sumatriptan and 500 mg naproxen dose may be more useful in older adolescents or those with frequent recurrence.

Earlier this year, Winner and colleagues reported the results of a multicenter placebo-controlled, cross-over study of the combination 85 mg sumatriptan and 500 mg naproxen sodium in adolescents with migraines.¹⁵ Ninety-four subjects between 12 and 17 years of age were enrolled, with a total of 347 migraines treated. Patients were instructed to take their study medication within 1 hour of pain onset, even if mild. Sumatriptan and naproxen sodium produced a significantly higher percentage of patients who were pain-free at 2 hours (37% compared to 18% in the placebo group, $p < 0.004$). The percentage of patients who were pain-free at 24 hours was higher in the treated patients (86% versus 78%), but the results were not significant. Adverse effects were considered mild and were similar between the two groups.

Contraindications

The combination of sumatriptan and naproxen sodium is considered contraindicated in patients with a history of coronary artery disease, arrhythmias associated with cardiac accessory conduction pathways, peripheral vascular disease, uncontrolled hypertension, stroke, transient ischemic attacks, or a history of hemiplegic or basilar migraines due to the increase risk of stroke in these patients.⁸ It is also contraindicated in patients with ischemic bowel disease, asthma, severe hepatic impairment, third-trimester pregnancy, or any history of hypersensitive reactions to either component.

Warnings and Precautions

Sumatriptan and naproxen sodium should be used only in patients with an established diagnosis of migraines.⁸ It is not indicated for migraine prophylaxis or the treatment of cluster headaches. Sumatriptan has been associated with serious adverse cardiovascular effects, including myocardial infarction, within hours of administration, as well as cerebrovascular events. It has also been associated with vasospastic reactions involving the peripheral vasculature

and gastrointestinal vasculature, resulting in infarction or Raynaud's syndrome.

Nonsteroidal anti-inflammatory drugs (NSAIDs) also have been associated with an increased risk for cardiovascular and cerebrovascular events (hypertension, heart failure, myocardial infarction, thrombotic events, and stroke) as well as gastrointestinal bleeding, ulceration, or perforation and renal or hepatic toxicity.⁸ Serious skin reactions, including Stevens Johnson syndrome, and anemia have also been reported with NSAID use. Both sumatriptan and naproxen sodium have been associated with hypersensitivity reactions, including anaphylaxis.

Adverse Effects

In a recent placebo-controlled trial of adolescents 12-17 years of age, the combination of sumatriptan and naproxen sodium produced an adverse reaction profile similar to that of the placebo group.⁸ None of the patients had a serious adverse event requiring discontinuation of treatment. Reactions occurring in $\geq 2\%$ of patients, and more frequently than in patients given placebo, included flushing with pyrexia (hot flashes) and transient muscle tightness. Similar adverse effects have been observed in clinical trials in adults.

Drug Interactions

Sumatriptan is contraindicated in patients who have received ergotamine-containing drugs, such as dihydroergotamine or methysergide, or another triptan within the previous 24 hours.⁸ It is also contraindicated in patients who have received a monoamine oxidase (MAO)-A inhibitor within the previous 2 weeks. Administration of serotonin 5-HT₁ receptor agonists with tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or MAO inhibitors may place patients at risk for serotonin syndrome.⁸ This syndrome, with altered mental status, autonomic instability, and hyperreflexia or tremors, may occur within minutes to hours of receiving a new drug or an increase in dose.

Concomitant administration of NSAIDs and methotrexate or lithium may delay the clearance of these drugs and increase the risk for toxicity.⁸ The use of NSAIDs with aspirin may reduce the protein binding of aspirin and increase the risk for bleeding. Use with diuretics, angiotensin-converting enzyme inhibitors, or beta-adrenergic blocking agents may decrease their effectiveness. Administration of NSAIDs with warfarin may lead to a greater risk for gastrointestinal bleeding. The clearance of naproxen may be reduced when given with probenecid.

Administration

Treximet® is available in bottles of nine tablets containing either 85 mg sumatriptan and 500 mg naproxen sodium (85/500 mg) or 10 mg sumatriptan and 60 mg naproxen sodium (10/60 mg).⁸ The recommended dose for adults is one 85/500 mg tablet. The dose may be repeated after 2 hours, but no more than two doses should be taken within a 24-hr period. The recommended initial dose for patients 12-17 years of age is one 10/60 mg tablet, with a maximum dose of one 85/500 mg tablet. Doses may be taken with or without food, but should not be split, crushed, or chewed.

The safety of more than five doses in adults or two doses in children over a 30-day period has not been studied. In patients with mild to moderate hepatic dysfunction, a maximum dose of 10/60 mg is recommended.⁸ Use of sumatriptan and naproxen sodium is not recommended in patients with severe hepatic or renal impairment.

Summary

The selective serotonin 5-HT₁ receptor agonists have become a common treatment for acute migraines in adults and are increasingly being used in the adolescent patient population. With changes in study design, newer research has been able to establish the efficacy and safety of these drugs in children and adolescents. The approval of the combination of sumatriptan and naproxen sodium last month adds a third triptan with an indication for use in pediatrics.

The editors would like to thank Dr. Howard P. Goodkin for serving as our guest editor for this issue of the newsletter.

References

1. Smitherman TA, Burch A, Sheikh H, et al. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. *Headache* 2013;53:427-36.
2. Wöber-Bingöl C. Pharmacological treatment of acute migraine in adolescents and children. *Paediatr Drugs* 2013;15:235-46.
3. Evers S. The efficacy of triptans in childhood and adolescence migraine. *Curr Pain Headache Rep* 2013;17:342.
4. Sun H, Bastings E, Temeck J, et al. Migraine therapeutics in adolescents: a systematic analysis and historic perspectives of triptan trials in adolescents. *JAMA Pediatr* 2013;167:243-9.
5. Fujita M, Sato K, Nishioka H, et al. Oral sumatriptan for migraine in children and adolescents: a randomized, multicenter, placebo-controlled, parallel group study. *Cephalalgia* 2014;34:365-75.
6. Hämmäläinen M. Oral sumatriptan for the acute treatment of migraine in children and adolescents: yet another failed study [editorial]. *Cephalalgia* 2014;34:325-6.
7. Anon. FDA approves Treximet for migraine in teens. *Drugs.com*. May 15, 2015. Available at: <http://www.drugs.com/newdrugs/fda-approves-treximet-sumatriptan-naproxen-sodium-migraine-pediatric-patients-4214.html> (accessed 6/5/15).
8. Treximet® prescribing information. Pernix Ireland Limited. May 2015. Available at:

<http://www.treximet.com/Areas/Patient/Contents/pdf/prescribing-information.pdf> (accessed 6/4/15).

9. Dahlöf C, Van Den Brink AM. Dihydroergotamine, ergotamine, methysergide and sumatriptan – basic science in relation to migraine treatment. *Headache* 2012;52:707-14.
10. Blumenfeld A, Gennings C, Cady R. Pharmacological synergy: the next frontier on therapeutic advancement for migraine. *Headache* 2012;52:636-47.
11. Khoury CK, Couch JR. Sumatriptan-naproxen fixed combination for acute management of migraine: a critical appraisal. *Drug Design Devel Ther* 2010;4:9-17.
12. Walls CM, Berges AC, Dalton ZX, et al. Pharmacokinetics of sumatriptan and naproxen following the administration of a single combination tablet at three doses to adolescent subjects with migraine and healthy adult subjects [abstract]. *Headache* 2010;50(S1):8-9.
13. McDonald SA, Hershey AD, Pearlman E, et al. Long-term evaluation of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescents. *Headache* 2011;51:1374-87.
14. Derosier JF, Lewis D, Hershey AD, et al. Randomized trial of sumatriptan and naproxen sodium combination in adolescent medicine. *Pediatrics* 2012;129:e1411-e1420.
15. Winner P, Linder S, Hershey AD. Consistency of response to sumatriptan/naproxen sodium in a randomized placebo-controlled, cross-over study for the acute treatment of migraine in adolescence. *Headache* 2015;55:519-28.

In Memoriam

With much sadness, we wish to mark the passing of Dr. J. Owen Hendley, who over the years served as our most frequent Guest Editor. Owen was an avid reader of the newsletter and provided a consistent voice for keeping our focus on new therapies of use to pediatric health care providers in primary care. He encouraged us to write articles that not only summarized the literature, but also provided the reader with a clear opinion on the role of each drug or vaccine in practice. Above all, he wanted there to be no hesitation when addressing controversial issues, whether overuse of antibiotics or suboptimal vaccination rates. We will greatly miss his great wealth of clinical experience, but even more his humor and generous spirit.

*Contributing Editor: Marcia Buck, PharmD
Editorial Board: Kristi N. Hofer, PharmD
Clara Jane Snipes, RPh
Susan B. Cogut, PharmD*

Pediatric Pharmacotherapy is available on the University of Virginia School of Medicine website at <http://www.medicine.virginia.edu/clinical/departments/pediatrics/education/pharm-news/home.html>. For comments or suggestions for future issues, please contact us at mlb3u@virginia.edu.