Sumatriptan iontophoretic transdermal system

A novel approach to migraine-specific therapy

Jerome Goldstein, MD

Summary

The sumatriptan iontophoretic transdermal system (TDS) (Zecuity, NuPathe, Malvern, PA), a novel approach to the acute treatment of migraine, circumvents the gastrointestinal tract by using low-level electrical energy to transport sumatriptan across the skin. In clinical trials, sumatriptan TDS has provided consistent drug delivery; rapid relief of migraine headache pain and migraine-related nausea; and an excellent safety profile, with a low incidence of triptan-sensation adverse events. Ease of use/application of sumatriptan TDS by migraineurs during an attack is rated highly. Sumatriptan TDS will provide a convenient, acute migraine-specific therapeutic option to the significant subset of patients for whom oral formulations are suboptimal, particularly those with migraine-related nausea (MRN).

More than 28 million people in the United States have migraine,¹ a chronic neurologic disorder characterized by attacks of head pain accompanied by photophobia, phonophobia, nausea, and vomiting.² Patients with migraine typically experience a combination of head pain and associated symptoms during attacks, with gastrointestinal disturbances among the most common nonheadache symptoms; about half (49.5%) of patients have migraine-related nausea (MRN) with at least half of their attacks.³ Migraineurs with frequent MRN have a more pronounced symptom burden, are more likely to be occupationally disabled or on medical leave from work, and have greater medication-related impairment than patients in whom MRN is absent or less frequent.⁴ Satisfaction with acute treatment decreases as the frequency of MRN increases.³

Patients with migraine can be treated with a variety of medications, including analgesics (e.g., acetylsalicylic acid), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen), and migraine-specific medications (e.g., sumatriptan). Many migraineurs are given the oral formulations of these medications, but for some patients—particularly the high proportion with MRN—their clinical utility is limited. Orally administered acute migraine therapies can lead to delays or avoidance of treatment in nauseated patients,⁵ and up to 20% of patients experience treatment-emergent nausea after taking oral triptans.⁶ Accordingly, current treatment guidelines recommend nonoral formulations for patients with MRN,⁷ despite the challenges of using intranasal sumatriptan (nausea/vomiting, low bioavailability, bad/unusual taste) or

San Francisco Clinical Research Center, CA.

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Correspondence to: sfhaclin@aol.com

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subcutaneous sumatriptan (injection site reactions, atypical/unpleasant sensations). We review the sumatriptan iontophoretic transdermal system (TDS) (Zecuity, Teva, North Wales, PA), a novel, nonoral medication developed to provide the benefits of migraine-specific therapy to migraineurs for whom oral formulations are suboptimal.

Sumatriptan iontophoretic TDS

Sumatriptan TDS, which circumvents the gastrointestinal tract by using low-level electrical energy to transport sumatriptan across the skin (figure e-1 at Neurology.org/cp),⁸ is indicated for the acute treatment of migraine with or without aura in adults.

Pharmacokinetics

In a single-center, open-label, crossover study ($n = 25$) comparing the pharmacokinetics of sumatriptan TDS with the oral (100 mg), intranasal (20 mg), and subcutaneous (6 mg) formulations over 12 hours (table e-1), sumatriptan TDS achieved sustained, predictable target drug levels and had a lower risk of triptan-related sensations than the subcutaneous formulation.⁸ Sumatriptan was detected in plasma within 15 minutes, reaching plasma concentrations of 10 ng/mL in about 30 minutes, and concentrations of approximately 20 ng/mL were maintained until 4 hours postactivation. When drug delivery was completed, steady declines in serum concentration for sumatriptan matched the gradual reductions seen with the oral and intranasal formulations.⁸ Separate studies evaluating the pharmacology of sumatriptan TDS during a migraine attack and during a nonmigraine period, in elderly subjects, and with and without the addition of heat indicate that drug exposure will remain predictable and consistent across a variety of patients and clinical situations⁹ (details in appendix e-1).

Efficacy and safety

In a randomized, parallel-group, double-blind, placebo-controlled trial in 530 adult migraineurs, sumatriptan TDS (18%) outperformed placebo (9%) for headache pain-free at 2 hours after patch activation ($p = 0.009$) and maintained superiority through 12 hours after patch activation ($p \leq 0.0357$).¹⁰ For headache pain relief, sumatriptan TDS (52.9%) was better than placebo (28.6%) at 2 hours postdose ($p < 0.0001$), as well as from 1 hour through 12 hours after patch activation ($p \leq 0.0135$; figure, A).¹⁰ Within 1 hour of patch activation, 71% of patients in the sumatriptan TDS group were nausea-free compared with 58% in the placebo group, and by 2 hours after patch activation, 84% of patients who were treated with sumatriptan TDS were nausea-free compared with 63% who received placebo ($p \leq 0.0251$; figure, B).¹⁰ For all subsequent time points—up to and including 12 hours after patch activation—sumatriptan TDS was superior to placebo for freedom from nausea ($p \leq 0.01$). Compared with placebo-treated patients, a greater proportion of patients treated with sumatriptan TDS were photophobia- and phonophobia-free by 2 hours after patch activation ($p \leq 0.0028$ for all comparisons), differences that were maintained for all subsequent time points up to and including 12 hours ($p \leq 0.0095$).¹⁰

No treatment-emergent serious adverse effects (AEs) were attributed to the sumatriptan iontophoretic TDS. Treatment-emergent AEs were reported by 50% of patients who received the sumatriptan TDS and 44% of patients who received placebo. As expected, most AEs with the

Supplemental Data

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Figure (A, B) Percentages of patients reporting headache pain relief and freedom from nausea¹⁰ * $p \leq 0.05$ vs placebo** $p \leq 0.0001$ vs placebo*** $p \leq 0.01$ vs placebo

sumatriptan TDS were application site reactions (table e-2) that resolved within 2 days.¹⁰ Triptan-sensation AEs were experienced by 1.7% of the subjects both for atypical sensations and pain and pressure sensations vs 0% (atypical sensations) and 0.4% (pain and pressure sensations) for placebo.¹⁰

Use in clinical practice

Once the decision to prescribe sumatriptan TDS has been made, patients should be directed to the Patient Instructions for Use (figure e-2, provided with prescribing information and available at www.zecuity.com). Patients apply the sumatriptan TDS to the upper arm or thigh, and active medication is delivered into the bloodstream at a controlled rate over 4 hours. In clinical practice, it is reasonable to expect that the vast majority of patients will use the device correctly. A study involving 16 health care professionals and 48 patients reported that 100%

Compared with placebo-treated patients, a significantly greater proportion of patients treated with sumatriptan TDS were photophobia- and phonophobia-free by 2 hours after patch activation.

of subjects were successful in assembling, applying, and activating the sumatriptan TDS. In this study, the sumatriptan TDS received very high ratings (6.8 out of 7.0) for ease of use/application.⁹

To maximize the benefits of sumatriptan TDS, it is useful to understand its therapeutic limitations. Patients should avoid bathing or swimming during the 4 hours of patch operation, and it is unknown if drug delivery or tolerability will be affected by dermal irregularities (e.g., scars, tattoos). Even though rates are relatively low (7.7% over 12 months⁹), a small proportion of patients could develop allergic contact dermatitis, which requires discontinuation of therapy. There are no data from studies in children; therefore, sumatriptan TDS is not indicated in children. Access will be a central issue outside the United States, where sumatriptan TDS is not yet available.

REFERENCES

1. Lipton RB, Diamond S, Reed M, Diamond M, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. *Headache* 2001;41:638–645.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004;24(suppl 1):9–160.
3. Lipton RB, Reed ML, Fanning KM, Buse DC. Relationship between high frequency nausea and treatment satisfaction in episodic migraine. *Headache* 2011;51:32.
4. Lipton RB, Buse DC, Saiers J, Fanning KM, Serrano D, Reed ML. Frequency and burden of headache-related nausea: results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache* 2013;53:93–103.
5. Pryse-Phillips W, Aubé M, Bailey P, et al. A clinical study of migraine evolution. *Headache* 2006;46:1480–1486.
6. Lipton RB, Pascual J, Goadsby P. Effect of rizatriptan and other triptans on the nausea symptom of migraine: a post hoc analysis. *Headache* 2001;41:754–763.
7. US Headache Consortium. US Headache Consortium guidelines: Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. Available at: <http://tools.aan.com/professionals/practice/pdfs/gl0087.pdf>. Accessed September 2014.
8. Pierce M, Marbury T, O'Neill C, et al. Zelrix: a novel transdermal formulation of sumatriptan. *Headache* 2009;49:817–825.
9. Pierce M, O'Neill C, Felker F, Sebree T. Sumatriptan iontophoretic transdermal system: history, study results, and use in clinical practice. *Headache* 2013;53:34–42.
10. Goldstein J, Smith TR, Pugach N, Griesser J, Sebree T, Pierce M. A sumatriptan iontophoretic transdermal system for the acute treatment of migraine. *Headache* 2012;52:1402–1410.

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