Transdermal Delivery of Sumatriptan for the Treatment of Acute Migraine

Mark W. Pierce

NuPathe Inc., Conshohocken, Pennsylvania 19428

Summary: Migraine is a common, multisymptom disorder that can severely impact the daily activities of migraineurs. Triptans (primarily sumatriptan) are the most commonly prescribed treatment for migraine and are considered a relatively safe and effective initial therapy. Unfortunately, current sumatriptan formulations (i.e., oral, nasal, subcutaneous) may be associated with limitations that can result in patients' delaying or avoiding treatment. For oral formulations, these limitations include difficulty in taking an oral medication due to the nausea and vomiting that often accompany migraine, and inconsistent absorption, whereas nasal and subcutaneous formulations may be associated with low bioavailability and an undesirable rate of

adverse events, respectively. An alternative to current formulations is transdermal drug delivery, particularly iontophoresis. Transdermal delivery has several advantages over current formulations, including avoidance of the gastrointestinal tract, controlled and sustained delivery, and convenient administration. This article reviews the *in vitro*, *in vivo*, and preclinical data supporting the use of iontophoresis for the delivery of sumatriptan, as well as the recent clinical data for Zelrix (NuPathe Inc., Conshohocken, PA), an iontophoretic sumatriptan patch currently in phase III development for the treatment of migraine. **Key Words:** Iontophoresis, migraine, transdermal, sumatriptan, Zelrix.

INTRODUCTION

Migraine is a common condition affecting nearly 12% of the population within the United States, with approximately 93% of migraineurs reporting some level of impairment during an attack and more than half (54%) of those describing the impairment as severe.¹ For example, in a 3-month period, 25% of migraineurs missed at least 1 day of work or school, 28% reported that their work or school productivity was reduced by at least half, 48% could not do typical household work, and 29% missed a family or social function.¹ This is likely because migraine is a multi-symptom disorder that may include not only severe headache pain but also frequently nausea (e.g., reported in one survey to occur in a majority of episodes by 56% of respondents who have ever had nausea, in every episode by 32%, and at least once by 92%),² and also vomiting (32% reporting the occurrence in a majority of episodes, 13% in every episode, and 68% at least once),² among other symptoms.

The American Academy of Neurology guidelines indicate triptans as an effective and relatively safe initial treatment choice for patients with moderate to severe migraines.³ Among these are almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Triptans are believed to work by binding agonistically to serotonin receptors, primarily the 5-HT_{1B} and 5-HT_{1D} receptors.⁴ These are expressed in the smooth muscle cells of the intracranial blood vessels and the trigeminal nerve fibers, respectively, and their activation is believed to produce vasoconstriction and block cranial vasodilatation, thereby leading to pain relief.^{4,5}

Sumatriptan is the most frequently prescribed migraine therapy in the United States⁵ and is available in oral, nasal, and subcutaneous formulations. Unfortunately, each of these formulations may be associated with limitations that can result in patients' delaying or avoiding treatment. One of the primary issues with oral sumatriptan is related to nausea and vomiting associated with a migraine episode. Thirty-one percent of patients who previously experienced nausea and 42% of those who previously experienced vomiting stated that these symptoms interfered with taking oral migraine medication.² Furthermore, because of incomplete absorption and presystemic metabolism, oral sumatriptan is also

Address correspondence and reprint requests to: Mark W. Pierce, M.D., Ph.D., NuPathe Inc., 227 Washington St., Suite 200, Conshohocken, PA 19428. E-mail: mpierce@nupathe.com.

FIG. 1. Schematic of iontophoresis.

associated with low bioavailability ($\sim 15\%$).⁶ Not only does intranasal sumatriptan have a low bioavailability similar to oral sumatriptan ($\sim 17\%$), but as many as 1 in 4 users have reported a bad or unusual taste depending on the dose (25% of patients with 20-mg dose).⁷ Finally, although subcutaneous sumatriptan has a much higher bioavailability ($\sim 97\%$ ⁸), injections are often the least attractive option for patients and may be associated with an undesirable rate of adverse events (primarily injection site reactions [59% of patients] and atypical sensations [42% of patients]⁸).

An alternative to these methods is transdermal delivery, a well-established route of administration with benefits including avoidance of the gastrointestinal tract and first pass metabolism, sustained and controlled delivery, and convenient administration.⁹ This article will review the history of transdermal delivery of sumatriptan, with a particular focus on iontophoretic sumatriptan as an emerging option for migraineurs.

PASSIVE VERSUS ACTIVE TRANSDERMAL DELIVERY

Perhaps the most familiar means of transdermal drug delivery is through passive methods, such as ointments and passive patches (e.g., nicotine patches). The main restriction with passive delivery is the barrier property of the skin (stratum corneum), which typically limits delivery to low-molecular weight drugs that are lipophilic and effective at low doses.¹⁰ Although various attempts have been made to increase permeability (e.g., the inclusion of chemical enhancers), none of these options fundamentally change the properties of the skin, and therefore drug delivery is still limited.⁹

Active methods are those that engage an external energy source to help drive the drug across the skin, thereby facilitating delivery of smaller, lipophilic molecules, while also allowing larger charged and hydrophilic molecules to be transdermally delivered. Methods of active transdermal delivery include electrical (e.g., iontophoresis, electroporation) and mechanical (e.g., microneedle, abrasion), as well as others (e.g., ultrasound, magnetophoresis).⁹ Among the active methods, ionto-

phoresis has the most application, with several iontophoretic devices already Food and Drug Administration approved and marketed (e.g., fentanyl, lidocaine) or in clinical development (e.g., acyclovir).¹⁰ An iontophoretic device is worn on the skin and may consist of an anode electrode (+) in a reservoir containing positively charged drug in solution, a cathode electrode (−) in a reservoir containing a negatively charged salt solution, an electronic device to control a mild electrical current, and a power supply (FIG. 1). Once applied, the electrical current carries the positively charged drug molecules from the patch into the skin and across the stratum corneum, where it is rapidly absorbed and distributed systemically.

PASSIVE TRANSDERMAL DELIVERY OF SUMATRIPTAN: *IN VITRO* MODEL SYSTEMS

As previously mentioned, triptans are the most widely prescribed migraine therapies, and therefore the focus of the vast majority of published research on transdermal migraine therapy. Sumatriptan was the first triptan synthesized and is the primary triptan investigated for transdermal delivery. Initially, an *in vitro* standard diffusion model system was used to characterize the passive diffusion of sumatriptan and the effect of a variety of chemical enhancers.¹¹ The model system consisted of two chambers (one with sumatriptan solution in an isotonic buffer [donor chamber] and one with isotonic buffer only [receptor chamber]) separated by porcine skin. Passive transfer was assessed by measuring the amount of sumatriptan in the receptor chamber at regular intervals using a previously validated high-performance liquid chromatography method.^{11,12} Several chemical enhancers were investigated, including ethanol; polyethylene glycol 600 (PEG600); Span 20 (sorbitan monolaurate); oleic acid, (−)- α -bisabolol; 1,8-cineole (eucalyptol); and R-(+)-limonene. The results demonstrated that sumatriptan could permeate the skin when enhanced by treatment with ethanol; Span 20; PEG600; oleic acid; 1,8-cineole; and R-(+)-limonene. However, it was unclear if therapeutic concentrations could be achieved.

Once it was established that sumatriptan could be delivered transdermally, additional *in vitro* experiments investigated the use of a bioadhesive patch¹³ and various

patch substrates¹⁴ to assist with drug delivery. One of these studies examined the use of a patch made of polyvinyl alcohol (PVA), Plastoid E 35H (Rhom GmbH & Co. KG, Darmstadt, Germany), and sorbitol, with and without Transcutol (Gattefossé, Gennevilliers Cedex, France) or PEG600 to deliver sumatriptan.¹³ The patches were placed on a portion of rabbit ear skin and diffusion was assessed via high-performance liquid chromatography similar to the previously described study. The total amount of sumatriptan that diffused from the patch was similar to that of sumatriptan solution, but with a higher rate of diffusion (flux) in the first 5 h.¹³

The previously described patch consisted mainly of PVA (~60% dry).¹³ A subsequent study assessed a variety of other polymers for use in a transdermal sumatriptan system.¹⁴ Specifically, Balaguer-Fernández et al.¹⁴ examined methyl cellulose (MC), polyvinyl pyrrolidone (PVP), and a PVP-PVA mixture. The patches were developed and assessed in a fashion similar to the previous patch study,¹³ but with Azone (Netqem, Durham, NC) used as an enhancer. The amount of sumatriptan delivered was highest with the MC-Azone patch, with a significantly ($p < 0.05$) higher steady-state flux compared with PVP and PVP-PVA formulations.¹⁴ Based on their results, the authors concluded that to reach the plasma concentrations of sumatriptan observed with subcutaneous injection (maximum, 72 ng/mL), the minimum surface area of a passive transdermal patch using the most effective formulation (MC-Azone) would be at least 293 cm². Because this is not realistic, it was clear that delivery of therapeutic quantities of sumatriptan with these passive formulations would not be feasible.

IONTOPHORETIC DELIVERY OF SUMATRIPTAN: *IN VITRO* AND PRECLINICAL MODEL SYSTEMS

In the same study that assessed different possible patch polymers,¹⁴ the authors also investigated the application of iontophoretic technology to the MC-Azone patch and determined that based on the observed sumatriptan transdermal flux of 284.7 $\mu\text{g}/\text{cm}^2\text{h}$, an iontophoretic patch would require only a 17 cm² surface area.¹⁵ Two additional studies of iontophoretic patches were reported. The first was an *in vitro* study using porcine skin that assessed the effect of current density and ionic strength.¹⁶ A cathode buffer solution of 75 mM NaCl, plus 20 mM HEPES (*N*-[2-Hydroxyethyl]piperazine-*N'*-[2-ethanesulfonic acid]) (pH = 7.4) and an anode solution of 14.5 mM sumatriptan succinate in the same buffer (pH = 6.5) were placed in separate electrode chambers, each of which covered an area of 0.9 cm². High-performance liquid chromatography was then used to quantify the amount of sumatriptan delivered by both

a 0.25 mA/cm² and 0.50 mA/cm² current density; the 0.25 mA/cm² current density was also investigated using a lower ionic strength buffer solution of 25 mM NaCl. The results showed that a current density of 0.25 mA/cm² and a low ionic strength buffer solution (25 mM) provided the best conditions for transdermal delivery of sumatriptan, with transdermal flux of 1273 ± 83 nM/cm²h compared with a passive delivery control, a 385-fold increase.¹⁶

Based on results from a separate *in vitro* study, the second study examined the iontophoretic delivery of sumatriptan *in vivo*.¹⁷ A two-compartment iontophoretic patch containing 37 mg of sumatriptan at pH 7.0 was placed on each of three prepubescent female pigs. The cathode and anode surface areas were 8 cm² each, and a biphasic current protocol was used in which step 1 (from 0–180 min) had a current intensity of 0.45 mA/cm², and step 2 (from 181–360 min) had a current intensity of 0.2 mA/cm². Peak sumatriptan plasma concentrations of 90 to 100 ng/mL occurred between 90 and 180 minutes after initiation of iontophoresis.¹⁷

IONTOPHORETIC DELIVERY OF SUMATRIPTAN IN MAN

Recently, clinical studies of the safety, pharmacokinetics, and efficacy of sumatriptan delivery have been reported with NP101 (Zelrix [NuPathe Inc., Conshohocken, PA]), a single-use, disposable, transdermal patch that delivers sumatriptan via iontophoresis. A phase I randomized, single-center, single-dose, 6-period, crossover study evaluated the safety and pharmacokinetic profiles of four different prototype iontophoretic sumatriptan patches (NP101) compared with 6 mg of subcutaneous (treatment 1 [GlaxoSmithKline]) and 50 mg of oral sumatriptan (treatment 2, Imigran FTab [GlaxoSmithKline, United Kingdom]).⁵ The four prototypes included: 1) NP101.01 (1 mA for 1.5 hours [treatment 3]); 2) NP101.02 (0.5 mA for 3 hours [treatment 4]); 3) NP101.03 (2 mA for 3 hours [treatment 5]); and 4) NP101.04 (2 mA for 6 hours [treatment 6]). A total of eight normal subjects (aged 18–50 year) received each of the 6 treatments with a minimum of 3 days between each dosing period. Treatments 5 and 6 provided the most favorable sumatriptan profiles. Treatment 5 yielded an area under the curve from time 0 to 24 h (AUC_{0–24}) and maximum observed concentration (C_{max}) that were 88% and 109% of the oral formulation, respectively, and 122% and 49% of the subcutaneous formulation, respectively. Values for the AUC_{0–24} and C_{max} of treatment 6 were 187% and 131% of the oral formulation, respectively, and 259% and 59% of the subcutaneous formulation, respectively. In addition, the formulation of treatment 6 delivered sumatriptan at a rate that maintained a target sumatriptan plasma concentration of at least 10 ng/mL for greater

than 7 hours.⁵ NP101 treatments were generally well tolerated, with the most common adverse events being mild to moderate skin erythema at the site of patch application. This study demonstrated in man the feasibility of well-tolerated transdermal delivery of sumatriptan via iontophoresis in sufficient quantity to be potentially effective in the treatment of migraine.

A second phase I study examined the safety and pharmacokinetic profiles of two refined NP101 patches (Zelrix I, II) and compared them to subcutaneous, oral, and nasal sumatriptan.¹⁸ This study was a single-center, open-label, single-dose, crossover study in which 25 normal subjects (aged 21–57 years) received each of five treatments: 1) sumatriptan (100 mg oral), 2) sumatriptan (6 mg subcutaneous), 3) sumatriptan (20 mg nasal spray), 4) Zelrix I patch (3 g sumatriptan gel containing 120 mg of sumatriptan succinate delivered at 4 mA for 1 h followed by 2 mA for 3 h), and 5) Zelrix II patch (2.6 g sumatriptan gel containing 104 mg of sumatriptan succinate delivered at 4 mA for 1 h followed by 2 mA for 3 h). The mean drug delivery during the 4-h period was approximately 6.1 mg for both Zelrix patches, and the $C_{\max}$ values (24.8 ng/mL for Zelrix I and 23.1 ng/mL for Zelrix II) fell between those for the nasal (12.5 ng/mL) and oral (51.6 ng/mL) formulations. The Zelrix patch was well tolerated with no unexpected adverse events. Of note, there were no reported atypical sensations with Zelrix (a commonly reported adverse event associated with triptan use) compared with 61% of subjects reporting atypical sensations associated with the subcutaneous formulation. This may be due to the lower $C_{\max}$ associated with Zelrix relative to the subcutaneous formulation.¹⁸

FIG. 2. Zelrix patch (NuPathe Inc., Conshohocken, PA) as worn by a patient.

The results of a randomized, double-blind, placebo-controlled phase III study of Zelrix (FIG. 2) in the treatment of acute migraine have been recently reported.¹⁹ In this trial, 530 patients meeting International Classification of Headache Disorders diagnostic criteria of migraine headache were randomly assigned 1:1 to treat a single, moderate-to-severe migraine headache with either Zelrix or a matching placebo patch. The protocol defined primary endpoint was pain free, with key secondary endpoints of photophobia free, phonophobia free, and nausea free, all at 2 h postpatch activation. Compared with a placebo, significantly more Zelrix patients reported freedom from headache pain (18% Zelrix vs 9% placebo [$p = 0.009$]), photophobia (51% Zelrix vs 36 % placebo [$p = 0.0028$]), phonophobia (55% Zelrix vs 39% placebo [$p = 0.0002$]), and nausea (84% Zelrix vs 63% placebo [$p < 0.0001$]), whereas at the same time reporting no use of rescue medication (60% Zelrix vs 40% placebo [$p < 0.0001$]) and experiencing sustained headache pain relief for 2 to 24 h postpatch activation (34% Zelrix vs 21% placebo [$p = 0.002$]). A significantly higher proportion of patients treated with Zelrix experienced both pain relief and nausea-free endpoints at 1 h compared with placebo (Zelrix 29% vs placebo 19% for pain relief [$p = 0.0135$], and Zelrix 71% vs placebo 58% for nausea free [$p = 0.0251$]). Zelrix was well tolerated, with only 2% of patients who discontinued use due to adverse events, which was the same rate as the placebo. Treatment-emergent adverse events were reported by 51% of Zelrix patients and 45% of patients receiving a placebo. These events were predominantly transient application site events, with most classified as mild or moderate in intensity.

Overall, iontophoretic delivery of sumatriptan seems to have several benefits in comparison to traditional delivery methods; however, there are limitations that should be noted. Primarily, transdermal delivery may be associated with application site reactions. For example, in the previously discussed phase I and III studies of Zelrix, the most common adverse events were application site pruritus and application site pain.^{18,19} In both studies, these application site reactions were generally mild and resolved within 2 days. In addition, there are some limitations placed on the use of an iontophoretic patch, including restrictions on bathing and swimming once the patch is applied to the skin, and avoidance of scars, lesions, tattoos, etc, at the site of application.

TRANSDERMAL DELIVERY OF OTHER TRIPTANS

In addition to sumatriptan, transdermal delivery of rizatriptan and zolmitriptan has also been studied. The passive transdermal delivery of an elastic liposomal formulation of rizatriptan was evaluated in both *in vitro* and *in vivo* analyses.²⁰ Compared with a solution of

rizatriptan, the elastic liposome formulation allowed for a drug deposition that was 10-fold higher with a sustained release through 24 hours and a 3-fold increase in biologic activity, suggesting a possible future option for delivery of migraine therapy. Similar to the Zelix patch, the iontophoretic delivery of zolmitriptan is also currently under investigation.²¹ *In vitro* and *in vivo* analyses demonstrated that zolmitriptan may be well suited for use in an iontophoretic device.²¹

CONCLUSIONS

Transdermal drug delivery is an established route of administration that has several benefits in comparison to more traditional routes, including avoidance of the gastrointestinal tract, controlled and sustained delivery, and convenient administration.⁹ These benefits may be attractive to migraineurs as the current oral, nasal, and subcutaneous formulations are each associated with their own limitations. Sumatriptan is one of the more commonly prescribed migraine therapies, and current research suggests that new devices, such as the Zelix iontophoretic patch, may provide additional treatment options for migraineurs.

Acknowledgments: Editorial and medical writing support was provided by Michael Malia, PhD, at Complete Publication Solutions, LLC. This work was supported by funding from NuPathe, Inc.

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