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Research Paper

A Unique Iontophoretic Patch for Optimal Transdermal Delivery of Sumatriptan

Steven J. Siegel,[1,5] Carol O'Neill,[2] Louise M. Dubé,[2] Peter Kaldeway,[3] Russell Morris,[4] David Jackson,[2] and Terri Sebree[2]

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Purpose. Migraines affect approximately 10% of the adult population worldwide. The purpose of this study was to assess the pharmacokinetic and safety profile of a novel iontophoretic sumatriptan delivery system, NP101, which uses an electrical current to propel sumatriptan across intact skin and into underlying tissue. Four unique prototype iontophoretic sumatriptan patch conditions were compared to a 6 mg subcutaneous injection and an oral 50 mg tablet of sumatriptan succinate.
Materials and Methods. This was a randomized, single-center, single-dose, six-period Phase I study.
Results. Patches were well tolerated with fewer adverse events than the subcutaneous injection. Adverse events that were more prevalent for NP101 than other formulations included localized sensations and reactions at the patch site. A linear relationship was observed between total applied current and sumatriptan delivery. Patches delivering 6 and 12 mA per h yielded favorable sumatriptan systemic profiles, delivering drug at a rate that maintained plasma levels above the target level (≥10 ng/ml) for greater than 7 h.
Conclusions. This study met the initial objective to define the dose–current relationship in humans as well as delimiting specific current and current density targets for a well tolerated patch design that can deliver therapeutic drug levels for longer periods than currently possible.

KEY WORDS: clinical trial; iontophoresis; migraine; phase I; sumatriptan.

INTRODUCTION

Migraine is a condition that affects approximately 10% of the adult population worldwide, yielding approximately 600 million people with about 28 million in the USA alone (1–3). In addition to headache pain, migraine can be associated with a variety of other symptoms, including diarrhea, cold extremities, facial pallor, nausea, vomiting and sensitivity to external stimuli such as light, sounds or odors. Such migraines typically last for up to 24 h, but can range from 4 to 72 h and patients often experience migraine attacks one to two times per month. Pharmacologic interventions constitute the mainstay of treatment for migraines and are available for both acute treatment (abortive) and prevention (prophylactic). Mild migraine can often be effectively treated with over-the-counter medications including aspirin, acetaminophen, NSAIDs, and combination products that include caffeine. Triptans are the mainstay of treatment for acute migraine of moderate to severe intensity (4). When these agents are used early in the course of an attack, triptans abort more than 80% of migraines within 2 h (5). However, several different triptan products are available with variation in the efficacy and tolerability of different medications in this class. Triptans are also available in a variety of formulations (oral, dissolvable tablet, nasal spray and injectable). Non-oral formulations are typically used for patients with gastrointestinal symptoms of nausea or vomiting and/or when a more rapid onset of action is desired.

Triptans are thought to work by activating serotonin (5-HT) receptors on trigeminovascular nerve endings, inhibiting the release of neurotransmitters that cause painful cranial vasodilatation. Furthermore, triptans produce active vasoconstriction and may relieve symptoms of migraine by stimulating 5-HT receptors on cranial vessels (6). Sumatriptan is the most widely prescribed triptan, comprising roughly half of all triptan prescriptions between 2002 and 2004. The three currently marketed sumatriptan formulations each have advantages and disadvantages. The injection and intranasal formulations offer rapid onset of action and may reduce further gastrointestinal discomfort. The injection also provides a good response in most patients, but yields a higher maximum concentration that may contribute to a higher side effect burden. However, many patients do not like the

[1] Division of Neuropsychiatry, University of Pennsylvania, Translational Research Laboratories, 125 S. 31st St. Rm. 2223, Philadelphia, Pennsylvania 19104, USA.
[2] NuPathe Inc., 375 E. Elm Street, Suite 110, Conshohocken, Pennsylvania 19428, USA.
[3] Kendle International Clinical Pharmacology Unit, Bolognalaan 40, Utrecht, 3584 CJ, The Netherlands.
[4] Travanti Pharma Inc., 2520 Pilot Knob Rd., Suite 100, Mendota Heights, Minnesota 55120, USA.
[5] To whom correspondence should be addressed. (e-mail: siegels@mail.med.upenn.edu)

discomfort and inconvenience of the injection and the bitter taste of the intranasal formulation. The oral formulation offers convenience and ease of use but produces unreliable blood levels and inconsistent response. Recurrence (rebound) occurs with all three sumatriptan formulations (7). This common problem with recurrence is likely due to persistence of the original event with a time course exceeding the duration of action from the currently available formulations. This is particularly so because sumatriptan has a serum elimination half-life of only 2 h and most of the active drug is eliminated within 4–6 h in the majority of patients. Thus, an optimal product would seek to provide the advantages of rapid, systemic sumatriptan administration found in the injection without the need for an injection and with a consistent duration of action which exceeds the time course of the patient's migraine. These goals could be accomplished, in theory, with sustained delivery systems such as a patch.

This study assesses the pharmacokinetic and safety profile of a novel iontophoretic sumatriptan delivery system (NP101) in order to bridge the unmet needs in migraine treatment. Iontophoresis is a process which utilizes bipolar electrical fields to propel charged molecules across intact skin and into underlying tissue (8, 9). Using this technology, sumatriptan is delivered through a thin, disposable, single-use device with a self-contained galvanic power battery source and small, wafer-thin lithium battery. The sumatriptan patch is attached to the skin with adhesive and is designed for systemic delivery of a fixed amount of sumatriptan, controlled by the design of the electrodes. Active (electronic) transdermal drug delivery can provide significant advantages relative to traditional passive transdermal drug delivery. These include greater rate and control of delivery. This system is intended to provide rapid and consistent therapeutic blood levels without an injection over several hours with the goal of preventing recurrent headaches. Thus, iontophoretic patch delivery is designed to be a significantly superior method of delivering sumatriptan compared to any currently available oral formulation and more tolerable and convenient than the injection or intranasal preparations. The iontophoretic delivery also offers the advantage of circumventing first-pass metabolism following oral administration of sumatriptan.

NP101. NP101 employed Wearable Electronic Disposable Drug delivery technology (WEDD®), which utilizes a proprietary power and control circuitry that has been custom designed for the application. With WEDD, the rate that medications are delivered is regulated by applied voltage between delivery and return electrode pads, the duration of action is regulated by a fixed and known content of sacrificial electrode materials, and current control is regulated by integrated resistance and/or transistors incorporated into each patch. The WEDD design is simple, and amenable to creating wearable, disposable iontophoretic patches. Based on results of *in vitro* studies, the amount of drug delivered by the iontophoretic patch is expected to be directly proportional to the current applied and to maintain a zero-order delivery rate over time (i.e. 1 mAmp should deliver 1 mg/h). *In vitro* studies were performed by using a Side-By-Side two-chamber glass diffusion cell system (Permegear or equivalent). A 1,000 nominal molecular weight limit biosynthetic millipore ultrafiltration membrane, which acted to simulate the stratum corneum of the skin, separated the two chambers of the cell. Various drug concentrations of sumatriptan succinate were added to the 1 cc donor chamber with a zinc delivery anode in place and 0.9% NaCl solution (Sigma) was added to the 3 cc receiver chamber with a silver/silver chloride cathode in place. Active delivery (with current) and passive delivery (with no current) were run concurrently at various time periods with passive delivery acting as a control. UV-Vis spectrophotometry (Cecil CE 2041 UV-Vis Spectrophotometer) was used to measure sample absorbance at 284 nm. *In vitro* data indicated a delivery efficiency (as function of mg mA^{-1} min^{-1}) of 0.017 mg mA^{-1} min^{-1}. In these studies, 1 mA of current delivered about 1 mg of drug per hour, whereas 2 mA of current delivered about 2 mg of drug per hour.

MATERIALS AND METHODS

Patch Design. The NP101 systems used in this study were prototype systems designed for the transdermal iontophoretic delivery of sumatriptan. For this clinical study, the drug formulation was approximately 1 cc of an aqueous solution of sumatriptan succinate (4% by weight). The solution was prepared at the clinical site, within 24 h of the time of use. The ionized drug was delivered iontophoretically, across the stratum corneum by the second component of the system, an iontophoretic drug delivery device designed to deliver current at either 0.5 or 1.0 mA for 1.5, 3.0 or 6.0 h as detailed below. The device uses a current regulating transistor and up to four 3 V button cell batteries attached to a Zn anode and an AgCl cathode. The drug solution is dispensed onto an absorbent pad in contact with the anode. Normal saline is placed on the absorbent pad in contact with the cathode. Current flow and drug delivery is initiated when the loaded patch, secured with a perimeter adhesive, is applied against the skin. Delivery stops when the patch is removed at the time identified in the protocol. All patches for the current study were designed to deliver a theoretical dose of 1 mg of drug per mA/h based on previous *in vitro* models (unpublished observation).

Study Design. This is a randomized, single-center, single-dose, six-period, pilot study of the pharmacokinetics of a prototype iontophoretic patch of sumatriptan compared to the pharmacokinetics of 6 mg subcutaneous injection and an oral 50 mg tablet of sumatriptan (base) as the succinate salt. The objectives of this Phase I study were to evaluate the pharmacokinetic profile of four prototypes patches of sumatriptan compared to 6 mg subcutaneous injection and 50 mg oral tablet. The subjects received all treatments at 10:00 A.M. ±1 h after an overnight fast. Subjects ate breakfast 3 h pre-dosing, lunch 2.5 h post-dosing, dinner 7.5 h post-dosing and had snacks at 6.5 and 12 h post-dosing. NP101 patches were placed on a clean, relatively hair-free region of the subject's upper back. For conditions in which two patches were placed simultaneously, one was placed on each side of the subject's back.

Subjects. Eight healthy adult subjects (four males and four females) between 18 and 50 years of age were selected to participate in this study. The subjects received no other medication (prescription or over-the-counter) for 2 weeks prior to study entry. The study was conducted in six confinement periods, each lasting approximately 2 days. All subjects began confinement the morning of day -1 and remained confined until

approximately 24 h after dosing for each dosing period. There was a minimum of 3 days between each of the dosing periods. The demographic variables for the subjects are listed in Table I.

Treatments. There were six formulations tested to allow comparison of all formulations in the same subjects. Treatment conditions included:

Treatment 1: Sumatriptan 50 mg (as the succinate salt) fast disintegrating oral tablet (Imigran Ftab® 50)
Treatment 2: Sumatriptan 6 mg (as the succinate salt) subcutaneous injection
Treatment 3: – 1.0 mA patch, 10 cm^2 reservoir, 1.5 h—theoretical dose of 1.5 mg of sumatriptan
Treatment 4: – 0.5 mA patch, 10 cm^2 reservoir, 3.0 h—theoretical dose of 1.5 mg of sumatriptan
Treatment 5: – two 1.0 mA patches, 10 cm^2 reservoir each, 3.0 h—theoretical dose of 6.0 mg of sumatriptan
Treatment 6: – two 1.0 mA patches, 10 cm^2 reservoir each, 6.0 h—theoretical dose of 12.0 mg of sumatriptan

Safety measures. The following variables were included as safety endpoints: adverse events mapped to body system and preferred term using the MedDRA dictionary, skin erythema, vital signs, ECG and clinical laboratory tests including hematology and clinical chemistry. Clinical laboratory tests were drawn at screening (no more than 28 days prior to the first dosing) and on day 1 of each dosing period including HBsAg, HCV-Ab, HIV-Ab 1+2, Pregnancy Test (females only), ethanol breath test and drug screen (except HBsAg, HCV-Ab, HIV-Ab 1+2, which was done at screening only). Vital signs including blood pressure, heart rate, and temperature were also assessed pre-dosing, 30 min, 1, 2, 6 and 12 h and 24 h post-dosing. Because of the possibility of local skin reaction to the patch from adhesive, current or drug, a skin erythema scale was also assessed at patch removal and at 24 h after removal (Table II). The skin irritation assessment used a five-point scoring system to quantify the degree of erythema present at the patch application site. This score is consistent with respect to the nominal categories used for the five-point ordinal scale recommended by the Environmental Protection Agency (EPA) in their Health Effect Test Guidelines on acute dermal irritation. A complete physical examination was performed at screening. Vital signs were assessed at screening, at admission on day 1 and pre-dosing, 30 min, 1, 2, 6, 12 and 24 h post-dosing for each of the six dosing periods. Additionally, an electrocardiogram was performed at screening and day 2 for each of periods 4 and 6. Vital signs were assessed at screening, at admission on day 1 and pre-dosing, 30 min, 1, 2, 6, 12 and 24 h post-dosing for each of the four dosing periods.

Table I. Descriptive Statistics for Subject Demographic Variables

Subject	Sex	Age	Weight (Kg)
1	Male	34	87.2
2	Male	28	79.1
3	Male	38	75.6
4	Male	50	75.3
5	Female	18	59.0
6	female	37	64.4
7	female	28	73.3
8	female	22	62.8

Table II. Erythema Scale Utilized to Rate the Degree of Skin Irritation from Patches

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharply defined borders
3	Intense erythema with or without oedema
4	Intense erythema with oedema and blistering/erosion

Pharmacokinetic measures. Blood samples were collected after drug administration to determine plasma sumatriptan concentrations. Plasma samples were analyzed using a validated HPLC-MS/MS method (PPD, Middleton, VA). The pharmacokinetic profile of each formulation was assessed including calculation of area under the drug concentration-time curve from time zero to 24 h. ($AUC_{0–24}$), area under the drug concentration-time curve up to the last measurable concentration extrapolated to infinity (AUC_{∞}), time of maximum drug concentration (T_{max}), maximum observed drug concentration (C_{max}), total body clearance (CL) and terminal elimination half-life ($T_{1/2}$). Pharmacokinetic parameters were calculated from non-compartmental analysis using WinNonlin version 4.1. Clearance obtained from the 6 mg sc injection was used to calculate the dose delivered during iontophoretic delivery based on the assumptions of linear pharmacokinetics and same CL between the two administrations. The dose delivered during iontophoretic application was calculated using the equation: $F * Dose\ delivered = AUC_{0-\infty}\ \text{iontophoretic} \times \text{Clearance}_{sc}$ with F equal to the fraction of dose absorbed into systemic circulation. Sixteen blood samples were collected at 0, 15, 30 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 h post-dosing for each of the six dosing periods. The reference therapies included 6 mg of sumatriptan subcutaneous injection and 50 mg of oral sumatriptan delivered as a single 50 mg tablet. Doses are expressed as sumatriptan-free base for subcutaneous and oral formulations.

RESULTS

Subjects. A total of eight subjects received study medication and eight subjects completed the study as per protocol. All study subjects were of Caucasian race with the mean age being 32.3 years.

Pharmacokinetics. All pharmacokinetic parameters including $AUC_{(0\text{-}inf)}$ (ng h ml^{-1}), $AUC_{(0–24)}$ (ng h ml^{-1}), CL (l/hr), C_{max} (ng/ml), T_{max} (h), $T_{1/2}$ (h) for each preparation are listed in Table III. We first compared 50 mg oral formulations (Treatment 1) and the 6 mg sumatriptan injection (Treatment 2) with NP101 patches delivering 0.5 mA for 3 h (Treatment 3) or 1 mA for 1.5 h (Treatment 4). The amount of drug delivered for the 1 mA patch for 1.5 h and the 0.5 mA patch for 3 h was 1.45 mg, compared to a theoretical dose of 1.5 mg. These data showed that the mean $AUC_{0–24}$ and C_{max} for both patch conditions were

Table III. Pharmacokinetic Results for NP101 Patches as Compared with Oral and Injectable Formulations are Presented

	Comparators		NP101 Patches				
Treatment	1	2	3	4	5	6	
Theoretical dose (mg)			1.5	1.5	6.0	12.0	
Dose delivered (mg)	50.0	6.0	1.45	1.45	7.4	15.7	
PK Parameter	50 mg tablet (n=8)	Sub-q injection (n=8)	NP101 patch 1.5 h 1 mA (n=8)	NP101 patch 3.0 h 0.5 mA (n=8)	NP101 patch 3.0 h 2 mA (n=8)	NP101 patch 6.0 h 2 mA (n=7)[a]	
$AUC_{(0\text{-inf})}$ (ng h ml^{-1})	103.50 (34.06)	73.45 (14.77)	19.68 (25.28)	19.58 (51.27)	89.15 (53.93)	188.60 (27.51)	
$AUC_{(0-24)}$ (ng h ml^{-1})	100.99 (34.54)	72.96 (15.00)	19.16 (25.71)	19.00 (53.33)	88.87 (54.22)	189.11 (27.50)	
CL (l/h)	532.03 (32.50)	83.07 (13.05)	78.03 (25.80)	93.58 (56.49)	123.89 (94.83)	89.51 (30.72)	
Weight normalized CL (l h^{-1} kg^{-1})	7.33 (27.8)	1.16 (11.3)	1.09 (22.9)	1.25 (44.1)	1.65 (77.9)	1.23 (29.3)	
C_{max} (ng/ml)	26.41 (26.71)	58.42 (24.48)	8.29 (27.09)	5.21 (49.10)	28.66 (65.86)	34.63 (34.68)	
T_{max} (h)	1.31 (83.80)	0.28 (31.43)	1.50 (0.00)	2.30 (30.29)	2.22 (34.83)	4.14 (45.00)	
$T_{1/2}$ (h)	5.93 (33.31)	2.02 (11.04)	1.88 (14.53)	2.05 (24.88)	2.05 (13.67)	2.11 (7.01)	

Sumatriptan pharmacokinetic data arithmetic means (CV%)
[a] Subject 8 was excluded from pK analyses in Treatment 6 due to early removal of her patch.

significantly lower than either oral or injection. The AUC_{0-24} for both NP101 preparations in this part of the study were approximately 19% of the oral and 26% of the injection. C_{max} was 31% of oral and 14% of injection for Treatment 3 and 20% of oral and 9% of injection for Treatment 4 (Table III). Following the favorable safety profile and minimal skin irritation from patch Treatments 3 and 4, two additional treatments were tested. Treatment 5 delivered a total of 2 mA for 3 h from a pair of 1 mA NP101 patches and Treatment 6 delivered 2 mA for 6 h from a pair of 1 mA NP101 patches. Treatment 5 (3 h 2 mA patches) yielded an AUC_{0-24} value which was approximately 88% of the 50 mg oral preparation and 122% of the 6 mg injection. Treatment 6 (6 h, 2 mA patches) yielded an AUC that was approximately 187% of the 50 mg oral preparation and 259% of the 6 mg injection. C_{max} was 109% of oral and 49% of injection for Treatment 5 and 131% of oral and 59% of the injection for Treatment 6.

Trends. AUC for the patches increased proportionally as a function of current-time intervals and C_{max} were proportional to current. Apparent T_{max} for NP101 ranged from 1.5 to 4.1 h in proportion to the length of time the patch was administered. Because of the sustained plateau for sumatriptan level with NP101, the T_{max} is not a peak as noted for both oral and injectable preparations. Rather, maximum serum concentration is reached in approximately 1.5 h for all patch formulations and is maintained at that level

Fig. 1. Sumatriptan plasma concentration profiles (Mean+SEM). **a** Data are displayed on a linear scale. **b** Data displayed using a semi-log scale. Symbols: *triangles*-Treatment 1 (sumatriptan 50 mg oral tablet); *squares*—Treatment 2 (sumatriptan 6 mg subcutaneous injection); *open squares*—Treatment 3 (1.0 mA patch, 1.5 h); *closed circles*—Treatment 4 (0.5 mA patch, 3.0 h); *stars*—Treatment 5 (two 1.0 mA patches, 3.0 h); *diamonds*—Treatment 6 (two 1.0 mA patches, 6.0 h)

Table IV. Summary of Treatment Emergent Adverse Events

AE category	Treatment 1 (*n*=8; %) 50 mg Tablet	Treatment 2 (*n*=8; %) 6 mg Sub-q injection	Treatment 3 (*n*=8; %) 1.5 h 1 mA NP101 Patch	Treatment 4 (*n*=8; %) 3.0 h 0.5 mA NP101 Patch	Treatment 5 (*n*=8; %) 3.0 h 2 mA NP101 Patches	Treatment 6 (*n*=8; %) 6 .0 h 2 mA NP101 Patches
Gastrointestinal disorder						
Abdominal discomfort			1 (12.5)			
Nausea		2 (25)				
General disorders/administration site disorders						
Burning sensation at patch site				1 (12.5)		
Itching at patch site				1 (12.5)		
Tingling at patch site					3 (37.5)	3 (37.5)
Pain at patch site						1 (12.5)
Pain at injection site		1 (12.5)				
Injection site reaction		1 (12.5)				
Excoriation patch site						1 (12.5)
Neurological disorders						
Somnolence		2 (25)				
Headache		2 (25)	1 (12.5)		1 (12.5)	1 (12.5)
Emotional		1 (12.5)				
Visual flashes		1 (12.5)				
Blurred vision						1 (12.5)
Dizziness	2 (25)	3 (37.5)				
Fatigue						1 (12.5)
Chills		1 (12.5)				
Ear, nose and throat disorders						
Throat discomfort (globus feeling)		1 (12.5)				
Paresthesias on nose		1 (12.5)				
Cardiovascular disorders						
Chest pain		1 (12.5)				
Burning sensation head, face, chest		1 (12.5)				
Musculoskeletal and connective tissue disorders						
Weakness		1 (12.5)				
Other						
Cannula site reaction (blood draw)	1 (12.5)	2 (25)				

All but the cannula site reactions for obtaining blood samples were defined as related (possible or probable) to treatment by the principal investigator. There were no serious adverse events.

until patch removal. The 3 and 6 h 2 mA patches maintained sumatriptan levels above 10 ng/ml for 4 and 7 h, respectively, as compared to approximately 3 h for oral and 1.5 h for injectable (Fig. 1). Thus, NP101 was capable of maintaining proposed therapeutic sumatriptan levels for four times longer than the 6.0 mg injection and twice as long as the 50 mg oral preparation, offering substantially longer duration of treatment than either preparation. The elimination half-life for the subcutaneous formulation was approximately 2 h. The elimination half-life after removing the patch was also 2 h and was similar across all different treatments.

Safety. NP101 was generally well tolerated with fewer adverse events than the 6 mg subcutaneous injection (Table IV). Adverse events that were more prevalent for NP101 than other formulations were notable only for localized sensations and reactions at the patch site.

Skin Erythema. Skin erythema scores are noted in Table V. For Treatment 6, one subject requested the 6.0 h two 1 mA patches be removed 34 min prior to the scheduled time due to discomfort at the patch site. For Treatment 6, the drug and saline solutions appeared to leak in three subjects. Solution leakage from the patches may have resulted in uneven current density in the patch with areas of increased current density which resulted in some irritation. The investigator concluded that leaking of fluid was likely to have caused the score of intense erythema for subject three.

Vital signs, clinical laboratories and ECG. In this study, no abnormal findings were reported as an adverse event from the physical examination, electrocardiogram, clinical laboratories, or vital sign measurements.

DISCUSSION

The current study demonstrates pharmacokinetic data and safety profile for a novel iontophoretic patch delivery system for the anti-migraine medication sumatriptan. This system has the potential to fill an unmet need in migraine care by providing a less invasive systemic delivery of the most widely prescribed and preferred triptan. Because this is a transdermal formulation, it circumvents concerns about taking an oral medication during an attack that may have nausea and vomiting, often associated with gastroparesis, among the prominent or presenting symptoms. Additionally, the iontophoretic patch system can deliver steady state, therapeutic drug levels for significantly longer periods of time than are achievable from subcutaneous injections or nasal preparations. This is particularly important in helping patients avoid recurrence that is likely due to the rapid metabolism of bolus injections that result from the short half-life of sumatriptan. Improved drug delivery systems represent a logical, cost effective and expedient alternative to trying to develop an equally efficacious medication with longer half-life. (10, 11) It also obviates the need for painful injections with the subcutaneous preparation or the severely unpleasant taste that is commonly reported from nasal preparations. Additional advantages for patches include lower C_{max} with comparable AUC, yielding a safer delivery profile with less severe and fewer side effects. The latter was evident in the current study with less adverse events among the patch conditions than the injectable formulation.

NP101 Patches demonstrated a linear relationship between current and sumatriptan delivery as predicted, validating previous *in vitro* models during development. (12–14) Initial trials with 1.5 mA-hr patches (1 mA for 1.5 hr or 0.5 mA for 3 hr) yielded very good tolerability. However, these patches yielded low sumatriptan plasma levels as expected for these current-time intervals. Based on the high tolerability with initial patch design, subsequent patches were tested at higher current-time intervals. Patches delivering 6 and 12 mA h yielded more favorable sumatriptan systemic profiles, with the 2 mA-6 hr design delivering drug at a rate that maintained the target level of 10 ng/mL for greater than 7 hr, supporting the hypothesis that the iontophoretic sumatriptan patch may be able to maintain therapeutically appropriate steady state drug levels for longer intervals than currently possible with either 50 mg oral or 6 mg injectable formulations. Several previous studies have examined the incidence and timing of headache recurrence following successful treatment of a migraine attack. These studies indicate that a second administration of sumatriptan is equally effective as the first in

Table V. Erythema Scores for All Periods, n=8 for All Conditions

Subject no.	Treatment 3		Treatment 4		Treatment 5				Treatment 6			
	1.5 h 1 mA Patch		3.0 h 0.5 mA Patch		3.0 h 2 mA Patches				6.0 h 2 mA Patches			
					Removal		24 h		Removal		24 h	
	Removal	24 h	Removal	24 h	Left	Right	Left	Right	Left	Right	Left	Right
1	1	1	1	0	1	1	1	0	2	2	2	2
2	1	0	1	0	1	1	1	1	2	2	1	1
3	1	1	1	0	1	1	1	1	1	2	1	4
4	1	1	1	1	1	1	1	1	2	2	1	1
5	1	0	1	1	1	1	1	0	1	1	1	1
6	1	1	1	1	1	1	1	1	1	1	1	1
7	1	1	1	1	1	2	1	1	1	1	2	1
8	2	1	1	0	1	1	1	1	2	1	1	1

Treatment 3 and 4 had a single patch application. Treatments 5 and 6 utilized two patches each to create a larger surface area with reduced current density as planned for future design modifications based on the results of these studies.

reducing migraine pain (15–17). Additionally, administration of oral sumatriptan four h after the initial treatment with a 6 mg s.c. injection has been shown to yield significantly longer pain -free interval than injection alone (15.6 versus 10.3 h) (18). Therefore, we hypothesize that sustained delivery of sumatriptan from an NP101 iontophoretic patch could achieve a similar degree of sustained pain -free interval as repeated dosing. However, future efficacy trials will be needed to determine if this hypothesis is true in practice.

Pharmacokinetic data in the current study are largely consistent with previous studies using the WEDD technology for other active pharmaceutical agents. For example, delivery of dexamethasone sodium phosphate with WEDD has been described with human volunteer patients, regarding total dosage delivered and depth of penetration as well as amount of drug delivered for a given current and duration (13, 19). WEDD technology has also been used for the delivery of fentanyl in human volunteers, where it was demonstrated that minimum effective concentrations of fentanyl were found after a 30 min application. More recently, pharmacokinetic studies reported the delivery of granisetron and calcitonin using hairless rats with WEDD technology (19, 20). These studies suggested that approximately 1 mg of drug is delivered for each mA hour of charge. As noted in Table III, NP101 delivered slightly less than predicted for treatments 3 and 4 (each 3% less than predicted) and more than predicted for treatments 5 and 6 (23 and 31% greater than predicted, respectively). This discrepancy with previous data, only at the higher charge values of 360 mA min for treatment 5 and 720 mA min for treatment 6, may have occurred because these values exceed the previously tested amounts of charge delivered with the WEDD device. Therefore, current data suggest that there may be greater efficiency of drug delivery at higher charge values than would have been anticipated from previous studies using lower charge.

It should be noted that the oral formulation in the current study yielded a longer terminal elimination half-life than anticipated. Additionally, the terminal half-life may have appeared greater than previously reported because of the high sensitivity of the LCMS method used (limit of quantification=0.20 ng/ml), resulting in quantification of clinically insignificant levels and possibly reflecting the presence of a deep compartment (6, 21). Also, the apparent T_{max} for NP101 ranged from 1.5 h for the 1.5 h preparation to 4.5 h for the 6 h preparation. This range reflects the lengthening of apparent T_{max} with increased duration of sustained administration of sumatriptan. Although some authors have proposed that shorter T_{max} may be associated with improved rates of response, these comparisons have been in the context of comparing oral preparations of different agents rather than accounting for a sustained delivery mechanism employed in the present study (6). As such, the ability to assess the relative role of T_{max} as a relevant parameter may be of less utility in this context. There were several limitations to the current design and formulation. Three of 48 patches (6%) malfunctioned resulting in fluid leakage and increased skin irritation, likely from uneven contact and increased current density. Patch failures are currently being addressed for subsequent studies. Future design modifications will also incorporate increased pad area to reduce current density, which we hypothesize will result in less irritation based on results obtained with our 0.5 mA patch. Additionally, future studies will position patches on the subjects' upper arm to facilitate ease of self-application. In summary, studies met the initial objectives to define the dose–current relationship for iontophoretic delivery of sumatriptan in humans as well as delimiting specific current and current density targets for a well tolerated patch design that can deliver therapeutic drug levels for longer intervals than currently possible.

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