JPP Journal of Pharmacy and Pharmacology

JPP 2009, 61: 1219–1228

Received March 27, 2009
Accepted June 23, 2009
DOI 10.1211/jpp/61.09.0012
ISSN 0022-3573

Research Paper

Rapid absorption of sumatriptan powder and effects on glyceryl trinitrate model of headache following intranasal delivery using a novel bi-directional device

Remy Luthringer[a], Per G. Djupesland[b], Colin D. Sheldrake[c], Anthony Flint[c], Peter Boeijinga[a], Philippe Danjou[a], Agnès Demazières[a] and Graeme Hewson[c]

[a]Forenap FRP, Rouffach, France, [b]OptiNose AS, Oslo, Norway and [c]OptiNose UK Ltd, Swindon, UK

Abstract

Objectives The aim was to investigate the pharmacokinetics of intranasal sumatriptan (administered using a novel bi-directional powder delivery device) and study its effects on quantitative electroencephalography in patients with migraine. The safety profiles of the two formulations were also compared.

Methods The pharmacokinetics of intranasal sumatriptan (10 mg and 20 mg) administered using a novel breath-actuated bi-directional powder delivery device were compared with subcutaneous sumatriptan (6 mg), along with an investigation of their effects on the electroencephalogram (EEG) following glyceryl trinitrate (GTN) challenge in 12 patients with migraine using a randomized, three-way cross-over design.

Key findings Following intranasal delivery, median t_{max} was 20 min with both doses compared with 10 min after the subcutaneous dose. Mean ± SD values for C_{max} were 96 ± 25, 11 ± 7 and 16 ± 6 ng/ml for subcutaneous, intranasal 10 mg and intranasal 20 mg formulations, respectively. Values for area under the curve were also lower with the intranasal doses. Intranasal and subcutaneous sumatriptan induced similar EEG changes characterized by reduced theta-power and increased beta-power. The majority of study participants were free of pain according to the headache severity score with all treatments from 15 min through to 8 h post-dose. All treatments were well tolerated and there were no reports of bitter aftertaste after intranasal delivery. Sumatriptan was rapidly absorbed after intranasal administration using the new device. Using the GTN challenge, sumatriptan powder delivered intranasally at a dose of 20 mg by the new device had effects similar to those of subcutaneous sumatriptan on EEG and reported headache pain, despite much lower systemic exposure.

Conclusions Administration of sumatriptan intranasally at doses of 10 mg and 20 mg by the breath actuated bi-directional powder delivery device results in rapid absorption. Delivery to target sites beyond the nasal valve induced a similar EEG profile to subcutaneous sumatriptan 6 mg and prevented migraine attacks in patients following GTN challenge. Intranasal administration of sumatriptan powder with the breath actuated bi-directional powder delivery device was well tolerated.

Keywords EEG; glyceryl trinitrate challenge; intranasal sumatriptan; migraine; pharmacokinetics

Introduction

Migraine is a common, costly and disabling condition characterised by recurrent headache attacks of moderate to severe intensity lasting 4–72 h, associated with gastrointestinal, neurological and autonomic symptoms.[1] In the USA, the prevalence of migraine is about 18% in women and 6% in men.[2,3]

Sumatriptan, a highly selective ligand for the 5-$HT_{1B/1D}$ serotonin receptors, was the first registered triptan and remains widely used as an effective anti-migraine drug. This class of compounds alleviate migraine attacks by blocking neurogenic inflammation and the release of nociceptive neuropeptides, including calcitonin gene-related peptide (CGRP), in addition to producing contraction of cerebral vessels.[4] Sumatriptan is

Correspondence: Dr Remy Luthringer, Forenap FRP, 27 rue du 4ème RSM, B.P. 27, 68250 Rouffach, France. E-mail: remy.luthringer@forenap.com

available as oral tablets, subcutaneous injection, intranasal spray and suppository. All these formulations have been found to be effective in relieving headache and associated symptoms of migraine in placebo-controlled studies in patients.[5,6] Because of delayed gastric emptying during a migraine attack, non-oral formulations may offer benefits in terms of speed of onset of effect. Subcutaneous sumatriptan appears to have the fastest onset of action and the therapeutic gain with intranasal and oral formulations is small or lacking during the first 30 min. It is, however, important to stress that the intranasal spray appears to induce less adverse events and is a good option in patients with needle phobia.[7] However, the narrow nasal valve renders existing nasal delivery devices suboptimal for efficient delivery to the highly vascularised respiratory mucosa beyond the valve where absorption is expected to occur faster.[8,9] Furthermore, sniffing during actuation will cause additional narrowing of the elastic tissues of the valve and suck a large part of the dose rapidly through the nose to the mouth, to be lost to swallowing. To overcome this problem, OptiNose has developed a breath actuated bi-directional delivery system that delivers significantly more drug beyond the nasal valve to the posterior part of the nasal cavity.[8] The device consists of a sealing nosepiece inserted into one nostril and a mouthpiece into which the patient blows.

Human models of migraine have been developed to study drug effects under standardised conditions. The glyceryl trinitrate (GTN) model, which uses systemic or sublingual administration of GTN, is the most commonly used to induce neurovascular headaches (cluster headache and migraine) and is considered as safe, reproducible and reliable.[10–15] Sublingual administration of GTN is easier and this modality has been shown to reproduce the main features of spontaneous headache attacks experienced by patients with migraine without aura and cluster headaches.[13] Headache manifestations onset rapidly after sublingual GTN administration, with a peak between 8 and 18 min and a duration between 30 and 60 min.[11]

The value of the GTN model in migraine drug development has been demonstrated by studies showing that a subcutaneous administration of sumatriptan followed by GTN administration significantly decreased the subsequent GTN-induced headache response in healthy subjects.[12] In this study, the pharmacokinetics of intranasal sumatriptan (10 mg and 20 mg) administered using a novel bi-directional powder delivery device were compared with subcutaneous sumatriptan (Imigrane 6 mg) along with an investigation of their effects on quantitative electroencephalography (qEEG) in patients with migraine during the migraine-free phase using the GTN-induced migraine model. The safety profiles of the two formulations were also compared.

Methods

Subjects and study design

This open-label, randomized, active treatment-controlled, three-way crossover study took place in a single centre (Forenap-Pharma, France) after approval by an independent ethics committee (CCPPRB of Strasbourg, France). The study was conducted in accordance with the Declaration of Helsinki and current Good Clinical Practice guidelines. All participants gave their written informed consent before selection and received financial compensation for participation.

Twelve people with a history of migraine without aura of moderate or severe intensity for at least one year participated in the study. Migraine was defined according to the International Headache Society criteria. Except for migraine, the study participants were in good health according to the various assessments performed at the screening visit, including a standard EEG, a physical examination, medical history, vital signs, a 12-lead electrocardiogram (ECG), serology and laboratory tests. Women were required to use an effective contraceptive method. Individuals were excluded from the study if they showed evidence of any condition likely to interfere with the use of the intranasal device (e.g. nasal obstruction or velum insufficiency). They were also excluded if they showed evidence of any significant disease (particularly vascular diseases, nasal obstruction) or used medications that could lead to misinterpretation of the study results (e.g. drugs for migraine prophylaxis in the previous month) or contraindicated medicines (e.g. antidepressants of the SSRI and MAOI classes). History or any evidence of substance abuse or addiction to alcohol, tobacco (>5 cigarettes per day) or xanthine-containing beverages were also reasons for exclusion from the study.

The study participants underwent three inpatient periods of 2.5 days each (from day −1 to the morning of day 2) with a minimum washout of five days. Subjects could not be admitted to a period if they had experienced a migraine attack less than 48 h before the study visit. In each period, the patients received a single dose of intranasal sumatriptan (10 or 20 mg) or subcutaneous sumatriptan (6 mg) as active comparator around 0830 h after overnight fasting according to their randomly assigned treatment sequence. The intranasal administrations of sumatriptan were performed by the patients themselves using the breath-actuated bi-directional powder delivery device (OptiNose). The capsules were filled with 15 mg sumatriptan succinate in powder form, which is equivalent to 10 mg sumatriptan base. For the 10 mg intranasal dose the delivery was through one nostril using a single powder delivery device, whereas for the 20 mg dose the delivery was achieved by an administration to each nostril using two powder delivery devices. Each person taking part in the study was instructed in the use of the breath-actuated bi-directional powder delivery device on initial screening and at the enrollment visit before treatment administration using an empty device. Sumatriptan (6 mg) was injected subcutaneously into the arm of the patient by the study staff using a pre-filled syringe (Imigrane, GSK).

A sublingual administration of 0.9 mg GTN was given 15 min after sumatriptan administration. Thus, we were studying the efficacy of sumatriptan formulations in preventing the occurrence of a GTN-induced migraine. The participants stayed in a supine position for 8 h following the GTN challenge.

Blood samples (5 ml) to determine sumatriptan plasma concentrations were drawn immediately before dosing, every 10 min, plus at 5 min and 15 min, during the first 90 min

following sumatriptan administration and at 2 h, 4 h, 6 h, 8 h and 12 h post-dose. When pharmacokinetic and pharmacodynamic evaluations were to be performed at the same time, the blood sample was collected before qEEG, and subjective evaluations were performed last.

Spontaneous EEG was recorded in resting condition (relaxed with eyes closed) from a 28-lead system (including four artefact channels) before drug administration (double baseline) and then continuously during the first 1.5 h post-dosing. Additional 10-min EEG measures were recorded 2, 4, 6 and 8 h post-dose.

The severity of the migraine attacks, the presence of accompanying symptoms (nausea, vomiting, phonophobia, photophobia) and functional disability were self-estimated by a questionnaire and a visual analogue scale (VAS) to measure pain severity 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h post-dose. The VAS scale was between 0 (no headache) and 100 (extreme pain).

Adverse events and concomitant therapies were monitored throughout the study. Vital signs, ECG, physical examination, laboratory tests, urine drug screen, blood pregnancy test and alcohol test were checked on admission at each period. Vital signs were also assessed before, and at regular times after, sumatriptan administration up to 24 h post-dose. ECG was monitored continuously for 8 h after sumatriptan administration in addition to the punctual ECG performed before administration, as well as 2 h and 24 h post-dose. All the safety parameters (except urine drug screen and alcohol test) were checked again at the end of study visit, which took place 7–10 days after the last study period.

Sumatriptan analysis

Blood samples were collected into lithium heparin tubes, immediately refrigerated on ice and centrifuged within 15 min of collection. Plasma was separated and stored at –20°C until analysis. After addition of the internal standard (sumatriptan-d6 hemisuccinate), plasma samples were extracted using solid-phase extraction with an OASIS HLB 30 mg/1ml cartridge. Before adding the sample the cartridge was conditioned with methanol and water. Following addition of the sample the cartridge was washed first with 1 ml water, then with 1 ml methanol–deionised water (3 : 7). Samples were eluted with 2×500 μl 3% acetic acid in methanol and dried at 40°C under nitrogen. Before transfer to an LC vial for injection into the column, samples were reconstituted in 0.1% formic acid. Plasma concentrations of sumatriptan were measured by a validated high-performance liquid chromatography method with tandem mass spectrometry detection (LC/MS/MS) utilising positive APCI at Gen-Probe Life Sciences Ltd (Livingstone, UK). The column used was an ACE 3 CN 50×2.1 mm, with an ACE 3 CN guard column. The calibration curves were all linear ($r > 0.99$) over the range 0.2 (lower limit of quantitation) to 80 ng/ml (upper limit of quantitation). The inter-assay precision (expressed as percentage of coefficient of variation) and the inter-assay accuracy (expressed as percentage of bias) were in the ranges of 5.3–7.8 and 0.3–10.9 for sumatriptan concentrations between 0.6 and 400 ng/ml, respectively.

Pharmacokinetic and statistical analysis

A standard non-compartmental method (WinNonlin V1.1 software) was used to calculate the following pharmacokinetic parameters of sumatriptan: maximal concentrations (C_{max}) and the times at which they occurred (t_{max}) were directly derived from the observed data. Area under the plasma concentration–time curves from pre-dose to infinity ($AUC_{0-\infty}$) were calculated by the linear trapezoidal rule. The terminal plasma elimination half-life (t½) was derived from the logarithmic concentration–time curves. Mean parameters ± standard deviations (SD) were calculated and plots of mean concentration ± standard error of the mean (SEM) over time were constructed. Comparisons of all parameters, except t_{max}, between the intranasal and subcutaneous formulation of sumatriptan were analysed using an analysis of variance model for crossover design after log transformation. Comparisons of t_{max} between treatments were performed with the non-parametric Wilcoxon signed rank test. For all parameters, except t_{max}, the ratio of intranasal to subcutaneous sumatriptan was given with the corresponding 90% confidence interval (CI). No differences between the routes of administration were established if the 90% CI for C_{max} and $AUC_{0-\infty}$ fell within the conventional 80–125% interval.

For EEG data, filter settings of 0.5–70 Hz (12 dB/octave) and sampling frequency of 256 Hz were used. After having visually removed the artifacts, 2-s EEG epochs were subjected to the fast Fourier transformation algorithm yielding contributions for each 0.5 Hz frequency bins. These were averaged for consecutive recording sessions for each period for computation of absolute (square-root of power in μV) and relative (%) energy or power estimates in the following frequency bands: delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz), beta (13–32 Hz). Alpha slow wave index (ASI = alpha/(delta + theta)), an index of cortical arousal, was also calculated. For qEEG analyses, power in the different frequency bands was subjected to the statistical decision tree (SDT) analysis, an electrode-by-electrode procedure based on Wilcoxon signed-rank tests.[16] This method allows comparison between the intranasal and subcutaneous formulations of sumatriptan at different post-dosing time points on an electrode-by-electrode basis. The statistical maps resulting from the SDT analysis are coded according to the level of statistical trend ($P < 0.1$) or significance ($P < 0.05$ or $P < 0.01$). To avoid false positives or type I error related to multiple testing, a grouping procedure was applied (i.e. having similar readouts on at least 5 contiguous electrodes).

Subjective evaluations of headache pain, nausea and vomiting, with frequency tables given for pain severity (mild, moderate, severe), and safety data were analysed descriptively.

Results

The majority of study participants (11/12) were female. The mean (range) age was 31 years (21–43), weight 61.6 kg (51.5–69.5) and body mass index 21.5 kg/m^2 (18–24.4).

The results presented below are based upon all 12 patients, except for the 20 mg intranasal sumatriptan group where one patient received only 10 mg, due to the drug capsule not being punctured in one device. This person was

excluded from the pharmacokinetic and pharmacodynamic analyses, but included in the safety analysis.

Pharmacokinetics

Sumatriptan plasma concentration–time profiles after administration of 10 mg intranasally, 20 mg intranasally and 6 mg subcutaneously show a much lower delivery of sumatriptan following intranasal administration compared with subcutaneous injection (Figure 1). The profiles for the two intranasal doses show a dose-related delivery. Pharmacokinetic parameter values are summarized for each formulation in Table 1. Median t_{max} was at 20 min with the two intranasal doses compared with 10 min for the subcutaneous dose but with wide inter-subject variability, mainly with the intranasal doses, as indicated by the large range of values (see Table 1). The highest t_{max} values were due to a delayed peak observed in two patients (360 min and 240 min) but a distinct early peak within the first 30 min was also present in these two subjects. There was no significant difference in median t_{max} for either of the intranasal doses compared with the subcutaneous dose using the Wilcoxon signed-rank test. Mean C_{max} and $AUC_{0-\infty}$ values increased with dose following intranasal administration. These parameters were much lower following intranasal administration than values for 6 mg subcutaneous sumatriptan, and the 90% CI for the ratio between intranasal and subcutaneous treatments did not meet the equivalence criteria for any of the parameters (Table 2). The elimination t½ of sumatriptan was longer for both intranasal doses compared with the subcutaneous administration.

Quantitative EEG

Only results for relative powers are presented since the effects were qualitatively similar, but less pronounced for absolute powers. In terms of relative energy, the effects of sumatriptan 10 mg and 20 mg intranasally were broadly similar to the reference 6 mg subcutaneous dose with sustained theta-power reduction for the first 40 min accompanied by increased beta power (Figure 2a). A reduction of relative delta-power was observed only at late time points (6 h, 8 h) for the intranasal administrations, but also within the first hour after the reference. The percentage of alpha activity was unchanged by any formulation except for a slight increase with the reference.

Although EEG changes in different frequency bands are qualitatively similar, statistical differences were detected between the intranasal doses of sumatriptan and the reference formulation (Figure 2b). Most of these differences were observed with the lower intranasal dose. A significant higher level of theta activity in the interval 10–30 min accompanied by a lower percentage of alpha power at time 20 min were reported when comparing the 10 mg intranasal dose with the 6 mg subcutaneous dose. On the other hand, when comparing the 20 mg intranasal dose with the reference, theta activity did not differ and the main treatment effect was a significant lower alpha activity (first 20 min, 40 min, 2 h and 8 h post dosing). Significantly higher delta activity was also observed but only for the first 10 min (before the GTN challenge). As a consequence of higher delta or theta power and lower alpha power, ASI was also significantly lower with the two intranasal doses compared with subcutaneous sumatriptan (see Figure 2b).

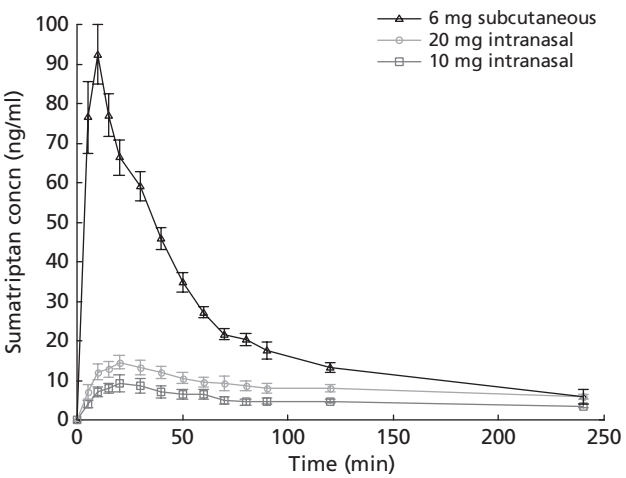


Figure 1 Plasma concentration–time curves up to 240 min post-dose following the administration of 10 mg intranasal, 20 mg intranasal and 6 mg subcutaneous sumatriptan to migraine sufferers. Data are means ± SEM for $n = 12$ study participants, except 20 mg intranasal sumatriptan where $n = 11$ (one subject only received 10 mg sumatriptan in error and was excluded from analysis).

Subjective migraine assessment

Most of the study participants reported no pain at any time of headache assessment, irrespective of the administered dose form of sumatriptan (Table 3). No more than three reported mild pain within 30 min after sumatriptan, likely due to the combined GTN challenge after 15 min (see below), whatever the route and dose. Moderate pain was reported in a maximum of two patients after 10 mg intranasal sumatriptan, in one after 20 mg intranasal sumatriptan and no subjects after 6 mg subcutaneous sumatriptan. Similarly, mean headache pain scores measured by VAS were low throughout for each treatment (<10 on a scale of 0–100).

No participant suffered from nausea or vomiting whatever the treatment administered. Two cases of photophobia were reported 30 min after the two intranasal sumatriptan doses. One person complained of functional disability 15 min and 30 min after 10 mg intranasal sumatriptan administration. A total of 5 (41%), 1 (9%) and 1 (9%) patients received rescue analgesics in the intranasal 10 mg, intranasal 20 mg and subcutaneous 6 mg dosing conditions, respectively.

Tolerability

All adverse effects were of mild or moderate severity, were generally transient in nature (resolved within one day) and recovered spontaneously. Treatment-emergent adverse events and treatment-related adverse events are summarised in Table 4. The majority of treatment-emergent adverse events were associated with GTN administration (e.g. hypotension and headache). No treatment-related adverse events were reported for the low intranasal dose (10 mg). Treatment-related adverse events consisted of two cases of mild epistaxis following administration of the 20 mg intranasal dose and single episodes of chest pain, paraesthesia and hot flushes in

Table 1 Sumatriptan pharmacokinetic parameters

Parameter	Statistic	Intranasal sumatriptan		Subcutaneous sumatriptan
		10 mg (n = 12)	20 mg (n = 11)	6 mg (n = 12)
C_{max} (ng/ml)	Mean ± SD	11 ± 7	16 ± 6	96 ± 25
	Min–Max	3–31	4–26	68–143
t_{max} (min)	Median	20	20	10
	Min–Max	10–360	5–240	5–30
$AUC_{0-\infty}$ (ng min/ml)	Mean ± SD	2220 ± 1605	2940 ± 975	6400 ± 1824
	Min–Max	452–6385	1144–4307	4290–11239
t½ (min)	Mean ± SD	178 ± 124	149 ± 29	106 ± 31
	Min–Max	58–508	120–209	76–172

C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; $AUC_{0-\infty}$, area under plasma concentration–time curve from time 0 to infinity; t½, terminal half-life.

Table 2 Results of the analysis of variance of sumatriptan pharmacokinetic parameters

Parameter	Least squares means		Point estimate for test/reference ratio	90% CI
	Intranasal 10 mg/20 mg (Test)	Subcutaneous 6 mg (Reference)		
Test = 10 mg intranasal				
C_{max} (ng/ml)	2.22	4.54	9.9	6.5–14.9
$AUC_{0-\infty}$ (ng min/ml)	7.49	8.73	28.7	19.3–42.8
Test = 20 mg intranasal				
C_{max} (ng/ml)	2.61	4.54	14.6	11.4–18.6
$AUC_{0-\infty}$ (ng min/ml)	7.91	8.73	44.0	37.7–51.3

CI, confidence interval, C_{max}, maximum plasma concentration; $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 to infinity.

two patients treated with 6 mg subcutaneous sumatriptan. No bitter aftertaste following intranasal sumatriptan was reported. There were no clinically significant alterations of cardiovascular or laboratory parameters related to sumatriptan administration.

Discussion

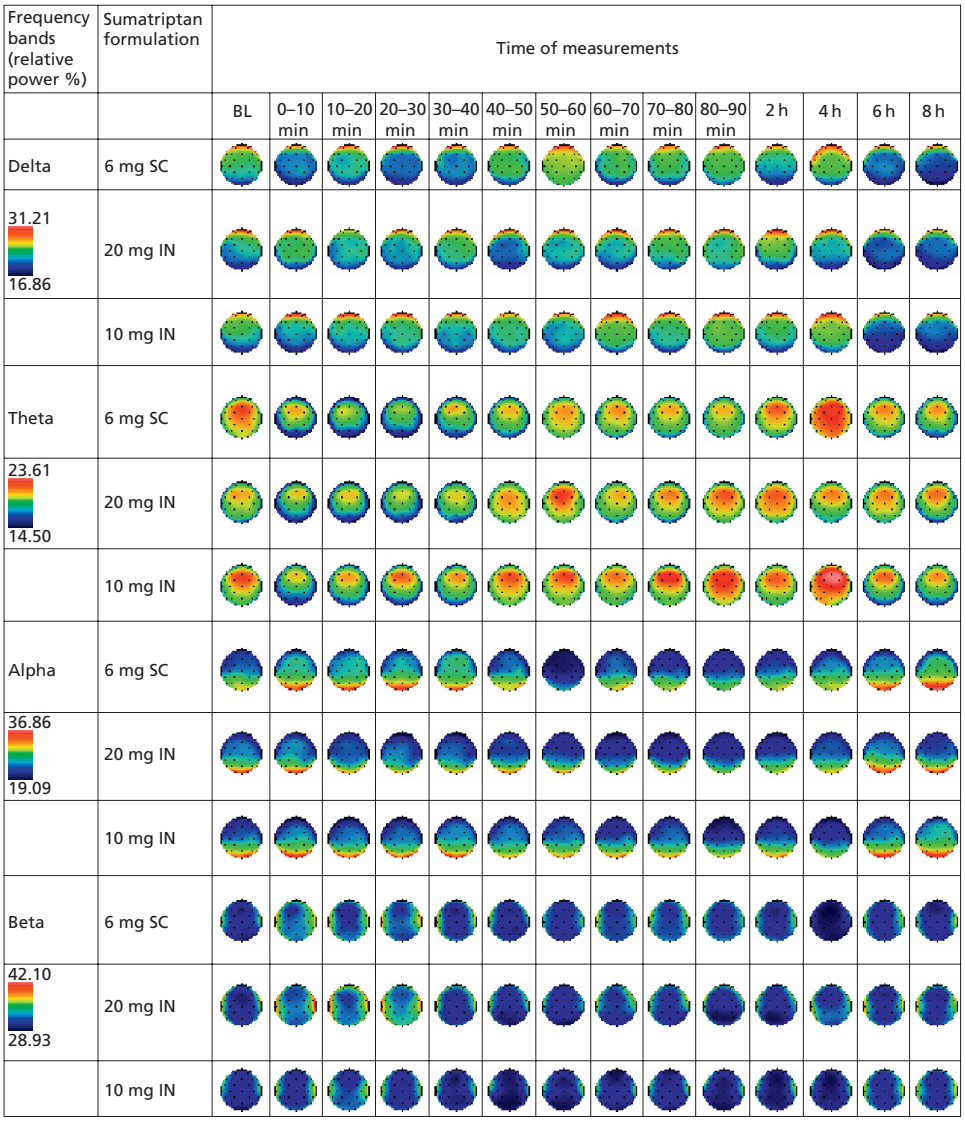
The most striking result from this study is the rapid absorption of 10 mg and 20 mg sumatriptan administered intranasally by the breath-actuated bi-directional powder delivery device. The intranasal administration of 10 mg and 20 mg sumatriptan induced a similar EEG profile to that of 6 mg injected subcutaneously and prevented migraine attacks in migraine suffers following GTN challenge despite a much lower systemic exposure. When interpreting the results, the potential bias of the open-label design without a placebo-control must be taken into account. Although drug expectancy may influence subjective measures of pain, it is unlikely to affect objective qEEG measures and pharmacokinetic data.

Rate and extent of absorption

Sumatriptan at doses of 10 mg or 20 mg was efficiently delivered intranasally by the powder delivery device and was rapidly absorbed. Several authors have pointed out that a rapid initial rate of absorption seems to be essential for the onset of the clinical effects of triptans in migraine.[17,18] Despite a high between-subject variability, the median t_{max} of 20 min found for both the 10 mg and 20 mg intranasal administrations was considerably shorter than the 1.5–2 h reported for the conventional nasal spray[18,19] and closer to the 10 min reported in this study, and in a previous one,[19] for subcutaneous sumatriptan.

Both the mean C_{max} and $AUC_{0-\infty}$ data for intranasal sumatriptan show that plasma concentrations were related to the dose administered, with higher concentrations observed with the 20 mg dose than with the 10 mg dose. Due to high inter-subject variability and small sample size, however, it is not possible to draw definitive conclusions regarding dose-proportionality with the two doses of intranasal sumatriptan. The mean C_{max} and $AUC_{0-\infty}$ values of sumatriptan delivered with the intranasal powder delivery device were substantially lower than for the 6 mg subcutaneous administration. Such differences with 6 mg subcutaneous sumatriptan have been previously reported after the administration of 20 mg sumatriptan liquid by conventional nasal spray where the mean C_{max} was 12.9 ng/ml compared with 69.5 ng/ml following 6 mg subcutaneous sumatriptan.[19] Moreover, C_{max} and $AUC_{0-\infty}$ values (see Table 1) for sumatriptan delivered with the powder delivery device are comparable with those for sumatriptan delivered with a conventional

(a)



(b)

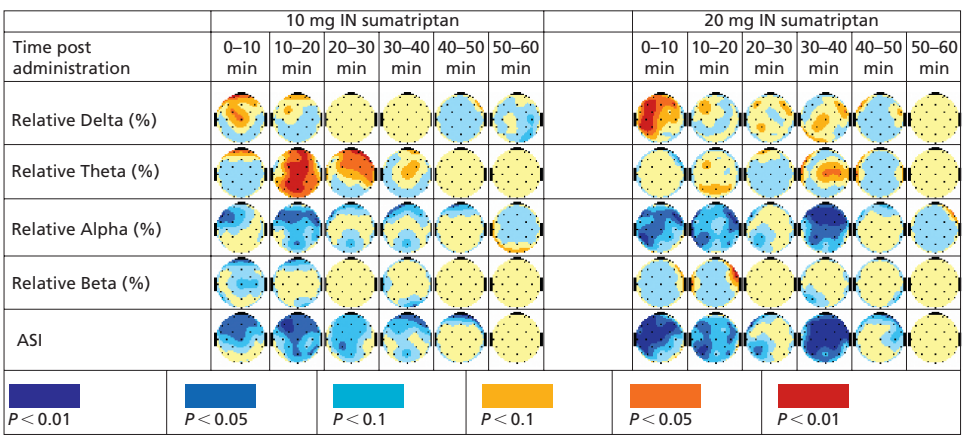


Figure 2 (a) EEG mapping of relative spectral energy and (b) statistical interkinetic maps of EEG changes in the first 60 minutes following acute administration of intranasal sumatriptan (10 mg and 20 mg) or subcutaneous sumatriptan (6 mg) to migraine sufferers. SC, subcutaneous; IN, intranasal; BL, baseline; ASI, alpha slow wave index (alpha/delta + theta); blue scale lower relative power compared with SC sumatriptan; red scale higher relative power compared with SC sumatriptan. n = 12 for 6 mg SC and 10 mg IN, n = 11 for 20 mg IN.

Table 3 Headache severity score

Time	Category	Intranasal sumatriptan		Subcutaneous sumatriptan
		10 mg (n = 12)	20 mg (n = 11)	6 mg (n = 12)
15 min	Mild pain	1 (8.3%)	0 (0.0%)	3 (25.0%)
	Moderate pain	2 (16.7%)	0 (0.0%)	0 (0.0%)
	No pain	9 (75.0%)	11 (100%)	9 (75.0%)
30 min	Mild pain	3 (25.0%)	3 (27.3%)	2 (16.7%)
	Moderate pain	1 (8.3%)	1 (9.1%)	0 (0.0%)
	No pain	8 (66.7%)	7 (63.6%)	10 (83.3%)
1 h	Mild pain	2 (16.7%)	0 (0.0%)	1 (8.3%)
	Moderate pain	0 (0.0%)	1 (9.1%)	0 (0.0%)
	No pain	10 (83.3%)	10 (90.9%)	11 (91.7%)
2 h	Mild pain	1 (8.3%)	0 (0.0%)	0 (0.0%)
	Moderate pain	0 (0.0%)	1 (9.1%)	0 (0.0%)
	No pain	11 (91.7%)	10 (90.9%)	12 (100%)
4 h	Mild pain	1 (8.3%)	0 (0.0%)	0 (0.0%)
	Moderate pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No pain	11 (91.7%)	11 (100%)	12 (100%)
6 h	Mild pain	1 (8.3%)	1 (9.1%)	1 (8.3%)
	Moderate pain	0 (0.0%)	1 (9.1%)	0 (0.0%)
	No pain	11 (91.7%)	9 (81.8%)	11 (91.7%)
8 h	Mild pain	1 (8.3%)	1 (9.1%)	1 (8.3%)
	Moderate pain	0 (0.0%)	1 (9.1%)	0 (0.0%)
	No pain	11 (91.7%)	9 (81.8%)	11 (91.7%)

Values are n (%).

Table 4 Overview of treatment-emergent adverse events

	Intranasal sumatriptan		Subcutaneous sumatriptan
	10 mg (n = 12)	20 mg (n = 12)	6 mg (n = 12)
No. of adverse events			
All adverse events	11	15	15
Treatment-related adverse events	0	2	3
No. of subjects reporting adverse events			
All adverse events	8	8	10
Treatment-related adverse events	0	2	2

liquid nasal spray.[18] It must be noted, however, that the 10 mg and 20 mg sumatriptan powder doses refer to nominal doses of base corresponding to actual delivered doses of approximately 7.5 and 15 mg (OptiNose data on file), whereas the conventional spray doses refer to emitted doses of 10 and 20 mg (vials are filled with 23% extra to compensate for residuals in the single-dose Pfeiffer device[20]). For equivalent delivered doses the C_{max} and $AUC_{0-\infty}$ for the sumatriptan nasal powder administered using the powder delivery device would therefore be expected to be higher than the values for the conventional nasal spray.

It has been suggested that the rate of drug absorption correlates better to the therapeutic onset than the extent of absorption, explaining the similar clinical efficacy of a 20 mg conventional nasal spray to that of 100 mg oral tables despite significant differences in plasma levels.[17] The early rapid absorption of intranasal sumatriptan powder resulting in a short t_{max} close to that of subcutaneous administration suggests that a significant fraction of the drug is absorbed from the nose to the blood with potential impact on the clinical effect. It is, however, possible that other mechanisms may be involved in the clinical effectiveness of nasal triptans, in particular the improved nasal deposition pattern of bi-directional delivery coupled with the potential for nose-to-brain delivery as discussed below under Impact of nasal deposition pattern.

Hybrid absorption pattern

A small early peak believed to represent the fraction absorbed nasally has been observed in the pharmacokinetic profile for sumatriptan administered with a conventional nasal spray[19] as well as zolmitriptan nasal spray.[21] It has been estimated that only about 10% of the sumatriptan delivered with the conventional nasal spray is absorbed from the nose, the rest being absorbed from the gastrointestinal tract, giving a 'hybrid' absorption pattern resulting in a bioavailability only slightly higher that the figure of 14% reported for oral sumatriptan formulations, which is low due to first-pass metabolism.[22] A similar pattern is observed for zolmitriptan where the oral bioavailability is 40% and the fraction absorbed nasally is about 30%. Interestingly, the $AUC_{0-\infty}$ for nasal zolmitriptan is not increased compared with tablets.[21] The initial peak of the hybrid absorption

pattern is much more pronounced for sumatriptan nasal powder compared with both zolmitriptan and sumatriptan administered by conventional nasal spray, suggesting both a faster rate and greater extent of nasal absorption (estimated to be 30% nasal absorption with the new powder device compared with 10% for the standard nasal spray).[22] The hybrid pharmacokinetic profile, with the early high peak due to fast nasal absorption and a delayed gastrointestinal absorption phase, may actually provide a favourable combination for early onset and sustained effect.[21]

Impact of nasal deposition pattern

Bi-directional delivery significantly improves deposition beyond the nasal valve compared with conventional spray pumps largely depositing the drug on the non-ciliated anterior epithelial segment.[8,9] Despite a faster clearance rate beyond the valve, it is possible that a small molecule like sumatriptan is more readily absorbed through the highly vascularized single-layer respiratory mucosa than through the anterior third lined by squamous epithelium.[23] Fast initial nasal absorption into the systemic circulation with subsequent penetration of the blood–brain barrier may optimize binding to receptors in the cerebral vasculature involved in the pathogenesis of migraine and explain why the effects of sumatriptan administered from the powder delivery device on the qEEG are similar to subcutaneous administration despite a much lower C_{max} and AUC. More direct effects via the sphenopalatine ganglion of the trigeminal nerve innervating both the cerebral vessels and the nasal cavity could also play a role. However, administration of sumatriptan using a conventional nasal spray to the side of the migraine has not shown any benefit over delivery to the contralateral side.[5] Local absorption from the nose to the central nervous system (CNS) through other routes has also been suggested as a possible explanation. Several recent rat studies have demonstrated increased delivery of a number of triptans and other drugs directly to the brain via olfactory pathways following intranasal delivery.[24–28] A study with radiolabelled nasal zolmitriptan, together with charcoal to prevent gastrointestinal absorption, has failed to document direct nose-to-brain transport in man, but the spray device used is unlikely to delivery significant quantities to the upper posterior segments of the nose and the sensitivity of the method may be insufficient to detect small quantities in the brain.[29] In a recent study in rats, enhanced deposition to the olfactory region demonstrated a significant improved nose-to-brain transport and reduced systemic absorption as compared with delivery to the lower and more anterior segments of the nose.[27] It therefore remains a possibility that the greater delivery to the posterior part of the nasal cavity beyond the nasal valve using the new bi-directional powder device may result in a direct action on the sphenopalatine ganglion or nose-to-brain transport, which in turn may offer an explanation for a comparable effect to subcutaneous injection in the GTN model of migraine.

Quantitative EEG effects

The aim of this study was to compare the effects of intranasal sumatriptan with the reference subcutaneous formulation and no placebo arm was used to avoid unnecessary exposure of study participants to an additional GTN challenge. Consequently, this study does not allow direct determination of the GTN challenge-induced qEEG changes. However, the latter has been characterized in previous studies with increase in relative slow-wave activity described as the main effects in migraine sufferers during GTN-induced headache whereas decrease in alpha and beta activity was not significant.[30,31] A similar pattern of EEG slowing appears to characterize migraine sufferers compared with controls.[32–34]

In this study, among the different frequency bands tested, the most sensitive potential marker encountered was the theta band. The percentage of activity in this frequency band was consistently decreased with the three treatments before GTN challenge and maintained for at least 15 min following the GTN challenge. These results are in accordance with previous findings reporting a decreased percentage of slow frequency activity with 6 mg subcutaneous sumatriptan and are opposite to the EEG changes induced by the GTN challenge (excess of theta activity by more than 15%, delta only a few percent).[30] In our hands the drug in addition increased beta EEG activity. Noteworthy, in the study by Thomaides *et al.*,[30] the subcutaneous injection of sumatriptan was given after the GTN challenge whereas in our study, sumatriptan was given preventively. Relative alpha power and ASI (data not shown) were stable throughout the study for all treatments except for a late significant increase (6–8 h) with the subcutaneous formulation.

When given via the intranasal route of administration, 10 and 20 mg of sumatriptan powder induced a similar EEG profile to the active comparator. Even when using inferential statistics with high sensitivity and resolution, differences in beta EEG activity were practically non-existent between the intranasal and subcutaneous routes of administration.

For other frequency bands, intranasal drug administration yielded only subtle differences within the first 30–40 min. This concerns theta EEG activity values and, less importantly, a lack of the trend for alpha increases as seen for the reference drug.

Overall, EEG values with the 10 mg intranasal dose deviated more from the reference subcutaneous treatment than those obtained with the 20 mg intranasal dose, demonstrating some dose-dependency in the CNS compartment.

Limitations

Definite conclusions about pharmacokinetic differences between the breath actuated bi-directional powder delivery device and the conventional nasal spray cannot be drawn from this study and further investigation is needed. However, the pharmacokinetic (t_{max}) and pharmacodynamic, as well as the efficacy, results suggest that the effects of the new intranasal formulation (especially the 20 mg dose) is close to the effects of a 6 mg subcutaneous

administration. Another limitation is the fact that the study was performed in a model of migraine consisting of provoking neurovascular headache by administration of GTN. Although this model has been well-validated, one may wonder if our efficacy results can be generalized to spontaneously occurring migraine attacks. In this regard, a double-blind placebo-controlled study performed in 109 migraine patients[35] corroborates the efficacy results of our study and further highlights the predictive validity of the GTN model in the development of novel anti-migraine drugs.

Conclusions

Administration of sumatriptan intranasally at doses of 10 mg and 20 mg by the breath actuated bi-directional powder delivery device results in rapid absorption. Delivery to target sites beyond the nasal valve induced a similar EEG profile to 6 mg subcutaneous sumatriptan and prevented migraine attacks in migraine sufferers following GTN challenge. Intranasal administration of sumatriptan powder with the breath actuated bi-directional powder delivery device was well tolerated.

Declarations

Conflict of interest

P. Djupesland, C. Sheldrake and A. Flint are employed by OptiNose; G. Hewson is a consultant for OptiNose UK Ltd. R. Luthringer, P. Boeijinga, P. Danjou and A. Demazières are employed by Forenap, who conducted the study under contract to OptiNose UK Ltd. R. Luthringer is now a member of the OptiNose board, but at the time of the conduct of the study had no relationship with OptiNose other than conducting the study as part of the Forenap team.

Funding

The study was funded by OptiNose UK Ltd.

References

1. Headache classification subcommittee of the International Headache Society. The international classification of headache disorders (2nd edition). *Cephalalgia* 2004; 24: 8–160.
2. Lipton RB *et al*. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001; 41: 646–657.
3. Diamond S *et al*. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American migraine prevalence and prevention study. *Headache* 2007; 47: 355–363.
4. Ferrari MD, Saxena PR. Clinical effects and mechanism of action of sumatriptan in migraine. *Clin Neurol Neurosurg* 1992; 94: S73–S77.
5. Dalhöf C. Sumatriptan nasal spray in the acute treatment of migraine: a review of clinical studies. *Cephalalgia* 1999; 19: 769–778.
6. Dalhöf C. Sumatriptan: pharmacological basis and clinical results. *Curr Med Res Opin* 2001; 17: S35–S45.
7. Tfelt-Hansen P. Efficacy and adverse events of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment: a systematic review based on number needed to treat. *Cephalalgia* 1998; 18: 532–538.
8. Djupesland PG *et al*. Breath actuated device improves delivery to target sites beyond the nasal valve. *Laryngoscope* 2006; 116: 466–472.
9. Aggarwal R *et al*. The assessment of topical nasal drug distribution. *Clin Otolaryngol* 2004; 29: 201–205.
10. Afridi SK *et al*. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. *Pain* 2004; 110: 675–680.
11. Costa A *et al*. Nitrite oxide pathway and response to nitroglycerine in cluster headache patients: plasma nitrite and citrulline levels. *Cephalalgia* 2003; 23: 407–413.
12. Iversen HK. Human migraine models. *Cephalalgia* 2001; 21: 781–785.
13. Sances G *et al*. Reliability of the nitroglycerin provocative test in the diagnosis of neurovascular headaches. *Cephalalgia* 2004; 24: 110–119.
14. Tvedskov JF *et al*. The prophylactic effect of valproate on glyceryltrinitrate-induced migraine. *Cephalalgia* 2004; 24: 576–585.
15. Tvedskov JF *et al*. The effect of propranolol on glyceryltrinitrate-induced migraine. *Cephalalgia* 2004; 24: 1067–1087.
16. Dago KT *et al.* Statistical decision tree: a tool for studying pharmaco-EEG effects of CNS-active drugs. *Neuropsychobiology* 1994; 29: 91–96.
17. Fox AW. Onset of effect of 5-$HT_{1B/1D}$ agonists: a model with pharmacokinetic validation. *Headache* 2004; 44: 142–147.
18. Moore KH *et al*. Safety, tolerability, and pharmacokinetics of sumatriptan in healthy subjects following ascending single intranasal doses and multiple intranasal doses. *Cephalalgia* 1997; 17: 541–550.
19. Duquesnoy C *et al*. Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. *Eur J Pharm Sci* 1998; 6: 99–104.
20. Rudy AC *et al.* Accuracy of intranasal (IN) butorphanol tartrate (BT) delivery in 2 nasal spray pumps used in clinical study. Presented at 2000 AAPS Annual Meeting. *AAPS PharmSci* 2000; 2: Abstract 913.
21. Goadsby PJ, Yates R. Zolmitriptan intranasal: a review of the pharmacokinetics and clinical efficacy. *Headache* 2006; 46: 138–149.
22. Fuseau E *et al*. Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet* 2002; 41: 801–811.
23. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. *Adv Drug Deliv Rev* 1998; 29: 3–12.
24. Vyas TK *et al*. Preliminary brain-targeting studies on intranasal mucoadhesive microemulsions of sumatriptan. *AAPS PharmSciTech* 2006; 7; Article 8 (http://www.aapspharmscitech.org).
25. Wang C *et al*. Uptake and biodistribution of rizatriptan to blood and brain following different routes of administration in rats. *Int J Pharm* 2007; 337: 155–160.
26. Westin UE *et al*. Direct nose-to-brain transfer of morphine after nasal administration to rats. *Pharm Res* 2006; 23: 565–572.
27. Charlton ST *et al*. Nasal administration of an angiotensin antagonist in the rat model: effect of bioadhesive formulations on the distribution of drug to the systemic and central nervous systems. *Int J Pharm* 2007; 338: 94–103.
28. Charlton ST *et al*. Evaluation of direct transport pathways of glycine receptor antagonists and an angiotensin antagonist from the nasal cavity to the central nervous system in the rat model. *Pharm Res* 2008; 25: 1531–1543.

29. Bergström M *et al*. Blood-brain barrier penetration of zolmitriptan – modeling of positron emission tomography data. *J Pharmacokin Pharmacodyn* 2006; 33: 75–91.
30. Thomaides T *et al*. EEG and topographic frequency analysis in migraine attack before and after sumatriptan infusion. *Headache* 1996; 36: 111–114.
31. Thomaides T *et al*. Intravenous valproate aborts glyceryl trinitrate-induced migraine attacks: a clinical and quantitative EEG study. *Cephalalgia* 2008; 28: 250–256.
32. Tan HJ *et al*. The electroencephalogram changes in migraineurs. *Med J Malaysia* 2007; 62: 56–58.
33. De Tommaso M *et al*. EEG spectral analysis in migraine without aura attacks. *Cephalalgia* 1998; 18: 324–328.
34. Lia C *et al*. Computerized EEG analysis in migraine patients. *Ital J Neurol Sci* 1995; 16: 249–254.
35. Djupesland PG *et al*. Nasal delivery of sumatriptan powder with a novel bi-directional device is highly effective in treating a single migraine attack. *Headache* 2008; 48: LB S70.