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Intranasal absorption of rizatriptan – *in vivo* pharmacokinetics and bioavailability study in humans

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Rizatriptan nasal spray was developed to achieve fast a high effectiveness and to overcome limitations associated with oral formulation. The objective of this study was to investigate the pharmacokinetics and tolerability of a rizatriptan nasal spray compared with an oral formulation in a two treatments, two periods, randomized crossover design. At each phase, each subject received 5 mg rizatriptan as a nasal spray or an oral tablet. Plasma concentrations of rizatriptan were determined by HPLC. Rizatriptan was absorbed more rapidly following nasal spray with detectable plasma concentrations 5 min after dosing. There was no statistically significant difference for AUC or C_{max} values between the nasal spray and the oral tablet. The relative bioavailability of nasal formulation to oral formulation was 96% ± 16%. All the formulations were well tolerated and adverse events were generally of short duration and of mild intensity. Thus, rizatriptan nasal spray offers more rapidly absorption compared to the oral route, which may be particularly beneficial to those patients who have gastrointestinal disturbances during their migraine attack or who have difficulty in swallowing a tablet.

1. Introduction

Rizatriptan is a selective 5-$HT_{1B/1D}$ receptor agonist that directly and selectively constricts intracranial, extracerebial blood vessels and inhibits the release of sensory neuropeptides from perivascular nerves to prevent neurogenic vasodilation and extravasation in the dura matter (De-Hoon et al. 2000). In comparison to sumatriptan, the drug is rapidly absorbed (t_{max} 1.4 h versus 2.5 h) and shows a 3-fold greater oral bioavailability (40% versus 14%) (Lee et al. 1999). Rizatriptan has been shown to relieve migraine within 2 h in 67% to 77% of patients (Goldstein et al. 1998). Conventional oral tablets of rizatriptan (Maxalt^{TM}) are effective and convenient for many patients with migraine. However, oral administration of a conventional tablet may not be ideal for all patients. Swallowing a conventional tablet and water may exacerbate migraine-associated nausea and vomiting. Another limitation of oral treatment is that migraine-associated gastrointestinal disburdens (vomiting, inhibition of gastric motility, and delayed gastric emptying) may affect the absorption of orally administered drugs. (Tokola and Neuvonen 1984a, 1984b; Volans 1978). Development of a formulation that is rapidly absorbed and has fewer side effects may help to overcome these obstacles.

A nasal spray formulation of rizatriptan has been developed with the intention of accelerating absorption and reducing time to effective pain relief. This article describes the results of a clinical study to access the pharmacokinetics and tolerability of rizatriptan nasal spray and compare these properties with an oral tablet, each at a delivered dose of 5 mg.

2. Investigations and results

2.1. Pharmacokinetic study

The Fig. shows the mean plasma profiles versus time of rizatriptan after a single 5 mg dose applied as a nasal spray and as an oral tablet. Table 1 shows main pharmacokinetic parameters of rizatriptan after intranasal and oral administration. The observed values of the pharmacokinetic parameters of rizatriptan after oral administration were in good agreement with those reported previously (Vyas et al. 2000).

The pharmacokinetic parameters used to assess the bioequivalence of the nasal verse the oral formulation were $AUC_{0-\infty}$ and AUC_{0-t} for the extent of absorption and C_{max} and t_{max}

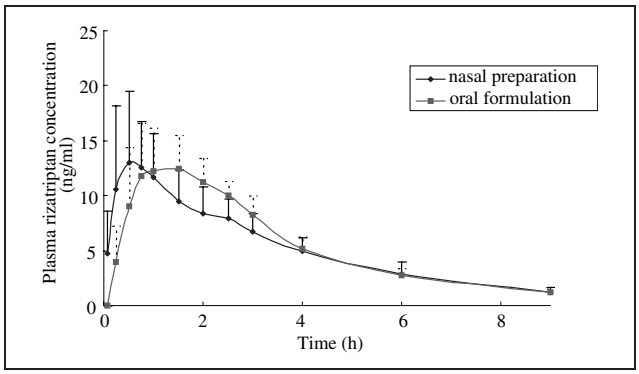

Fig.: Mean plasma profiles versus time of rizatriptan after single 5 mg dose as a nasal spray and as an oral tablet

Table 1: Pharmacokinetic parameters of rizatriptan after intranasal and oral

Parameter	Nasal formulation	Oral formulation
$AUC_{0-\infty}$ ($h \cdot ng\ ml^{-1}$)	52.40 ± 12.39	53.99 ± 10.56
AUC_{0-t} ($h \cdot ng\ ml^{-1}$)	47.94 ± 11.83	50.05 ± 9.43
C_{max} ($ng \cdot ml^{-1}$)	14.36 ± 5.50	14.26 ± 3.51
$t_{1/2}$ (h)	2.48 ± 0.40	2.22 ± 0.47
t_{max} (h)	0.53 ± 0.18	1.25 ± 0.62

for the rate of absorption. Table 2 show the results of the bioequivalence analysis of the main pharmacokinetic parameters ($AUC_{0-\infty}$, AUC_{0-t}, C_{max}). The parametric 90% confidence intervals for $AUC_{0-\infty}$, AUC_{0-t}, C_{max} values were 85%–112%, 88%–102%, 90%–103% respectively and were entirely within the bioequivalence acceptance limits. However, based on the results from the nonparametric Wilcoxon test, there was a significant difference ($P < 0.01$) in t_{max}. The relative bioavailability of nasal formulation to oral formulation was $96.09\% \pm 15.65\%$.

All 16 subjects successfully completed both phases of the study and were discharged in good health. Most frequently reported adverse events in the study were local nasal nasopharyngeal symptoms and unusual taste. Taste disturbance occurred soon after nasal administration and might be caused by a proportion of the intranasal solution running down the back of the throat. The majority of adverse events was of short duration and of mild intensity. None of the volunteers found the adverse events distressing or intolerable. Also there was no nasal irritation. No changes in clinical laboratory parameters or vital signs were considered to be of clinical significance, and there were no clinically significant ECG abnormalities observed in any of the subjects.

3. Discussion

In recent years, the nasal route has received a great deal of attention as a convenient and reliable way for the systemic administration of drugs. The nasal cavity as a site for the systemic absorption of drugs has some advantages which include relatively large surface area, porous endothelial basement membrane, highly vascularized epithelial layer, high total blood flow per cm^3, avoiding the first pass metabolism and easy access (Cornaz and Buri 1994). Rizatriptan is an ideal drug for intranasal administration, due to its physicochemical properties. First of all, it has low molecular weight ($Mw = 269$). It is known that *in vivo* nasal absorption of drugs with a molecular weight less than 300 is not significantly influenced by their lipophilicity and ionization state (Hussain 1998). Furthermore, rizatriptan has an aqueous solubility adequate to provide the desired dose in a 70 µl volume of formulation administered per nostril. During the study, no nasal irritation from the drug was observed.

Rizatriptan was quantifiable in the plasma of all subjects 5 min postdose after nasal administration. However after oral administration, rizatriptan could not be detected in all subjects until 15 min postdose. This rapid absorption of rizatriptan potentially might result in faster headache relief compared with the oral formulation. Similarities in $AUC_{0-\infty}$, AUC_{0-t} and C_{max} between the nasal and oral formulation indicated that the extent of absorption was similar for the two routes of administration. The range of the confidence intervals for the ratio of the $AUC_{0-\infty}$, AUC_{0-t} and C_{max} of the nasal formulation to the oral tablet also met standard criteria for bioequivalence. Following administration of rizatriptan nasal spray, the terminal half-life was approximately 2.5 h, which was similar to the value after administration of the oral tablet.

Rizatriptan nasal spray has a systemic tolerability profile similar to that of oral tablet. The most frequently reported adverse events were local nasopharyngeal symptoms and unusual taste, but this was tolerable and no subjects withdrew from the study due to adverse events. Importantly, there was no nasal irritation.

Overall, rizatriptan nasal spray offers a more rapidly absorption characteristic than the oral formulation which may be particularly beneficial to those patients who have gastrointestinal disturbances during their migraine attack or who have difficulty in swallowing a tablet.

4. Experimental

4.1. Drugs

The oral formulation was Maxalt^{TM} (rizatriptan 5 mg tablet, Merck & CO., INC); batch No.: 0124980. The nasal formulation was rizatriptan nasal spray (rizatriptan 25 mg/ml solution, Department of Pharmaceutics, Fudan University); batch No.: 031030.

4.2. Subjects

Sixteen healthy male volunteers (average age 22.6 ± 0.6 years, body height 174.1 ± 3.9 cm, body weight 65.8 ± 5.8 kg) participated in the study. Volunteers were judged normal on the basis of prestudy medical history, physical examination and clinical laboratory tests (biochemical tests of blood and urine). None of the volunteers had any acute or chronic gastrointestinal, cardiovascular, hepatic, renal, endocrine or metabolic disease. The use of any other drug was forbidden one week before and during the study period. No coffee, tea or alcoholic beverage was consumed for 24 h prior to the start of each treatment period until blood sampling was completed. All the subjects wrote informed consent before entering the study.

4.3. Study design

The study was carried out as a two treatments, two periods, randomized crossover investigation in which the two formulations were given in a single oral or nasal dose of 5 mg of rizatriptan. Subjects were randomly assigned to one of the two groups taking either the oral or the nasal formulation. For intranasal administration, 70 µL of the nasal formulation was sprayed into each nostril using a metered-dose pump spray device (Pfeiffer, Germany). Volunteers were instructed not to blow their noses for up to 2 h postdose. After a seven-day washout period the subjects were crossover. Prior to treatment each subject underwent an overnight fast for at least 10 h and during each treatment, a standard meal was served 4 h after dosing. The protocol was approved by the Ethical Committee of Shanghai Zhong Shan Hospital.

4.4. Blood sampling

Blood samples were collected in heparinized tubes prior to the drug administration(-zero time), and at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9 and 12 h after dosing. Blood samples were centrifuged at 3000 $r \cdot min^{-1}$ for 15 min and the plasma samples received were stored at $-18\ ^\circ C$ until analysis.

Table 2: Statistical evaluation (parametric analysis, logarithmically transformed data) for $AUC_{0-\infty}$, AUC_{0-t}, C_{max} of rizatriptan preparations

Parameter	C_{max}	AUC_{0-T}	$AUC_{0-\infty}$
Point estimate	100.70%	95.78%	97.06%
90% confidence interval	85.3%–111.9%	88.1%–101.9%	90.1%–103.3%

4.5. Analytical method

Plasma rizatriptan concentrations were determined by HPLC (Chen et al. 2004). The detection technique was liquid-liquid extraction followed by reverse-phase HPLC with fluorescence detection. A reversed-phase column, Dikma Diamonsil® C_{18} (200 × 4.6 mm, 5 μm) was used. The mobile phase was composed of 0.05% (v/v) triethylamine in water (adjusted to pH 2.75 with 85% phosphoric acid) and acetonitrile (92 : 8, v/v). The flow rate was set at 1.2 $ml \cdot min^{-1}$. The column was maintained at 40 °C. Fluorescence detection was performed at an excitation wavelength of 225 nm and an emission wavelength of 360 nm.

To an 1 ml aliquot of plasma in a 15 ml glass tube, 50 μl of I.S. solution (0.2 μg/ml of zolmitriptan solution) and 50 μl of 1 M sodium hydroxide solution were added. After vortex mixing, 4 ml of methyl tertiarybutyl ether was added. The mixture was then shaken for 2 min and centrifuged at 3000 $r \cdot min^{-1}$ for 10 min. The organic phase was decanted into a 10 ml conical glass tube. The organic phase was evaporated to dryness in a water bath at 50 °C under a stream of nitrogen. The residue was then reconstituted in 100 μl of mobile phase, and 20 μl of this solution was subsequently injected into the chromatographic system for HPLC analysis.

The linear response ranged from 0.5 to 50 $ng \cdot ml^{-1}$ and the detection limit was 0.25 $ng \cdot ml^{-1}$. The absolute recovery was more than 82% and the relative recovery was 98 ∼ 102%. The accuracy data, documented by the relative standard deviation (RSD) (within-day RSD of control samples of 0.5 $ng \cdot ml^{-1}$, 5 $ng \cdot ml^{-1}$, 50 $ng \cdot ml^{-1}$ were 7.7%, 5.8%, 3.3%, respectively; day-to-day RSD of control samples of 0.5 $ng \cdot ml^{-1}$, 5 $ng \cdot ml^{-1}$, 50 $ng \cdot ml^{-1}$ were 3.4%, 3.2%, 4.3% respectively) showed the high reproducibility of this method.

4.6. Pharmacokinetic and statistical analysis

The pharmacokinetic parameters used for determination of the bioavailability of the two formulations were evaluated assuming linear elimination kinetics. Maximum plasma concentration (C_{max}) and time to maximum concentration (t_{max}) were obtained directly from the experimental data. Area under the plasma concentration-time curve from administration to infinite time ($AUC_{0-\infty}$) was calculated using the trapezoidal method: trapezoidal area from zero time to the last measurable concentration (AUC_{0-t}), extrapolated to infinite time, by addition of the area obtained from the last measurable concentration divided by the terminal elimination rate constant (k). K was estimated from the linear least-squared regression of the terminal phase of the log concentration-time profile. The apparent biological half-life ($t_{1/2}$) was calculated as 0.693/k. The results of the pharmacokinetic calculations were presented as mean ± SD.

For the evaluation of relative bioavailability and bioequivalence, the calculated pharmacokinetic parameters (C_{max}, AUC_{0-T}, $AUC_{0-\infty}$) were submitted to analysis of variance (ANOVA) after log transformation, resulting in point estimates with effects were considered significant if $P < 0.05$. Two one sided t-test was applied to C_{max}, AUC_{0-T} and $AUC_{0-\infty}$, and 90% confidence intervals were calculated for the nasal formulation to oral formation ratios. T_{max} was subjected to Wilcoxon method. The formulations were concluded bioequivalent if the 90% confidence interval was fully included in the acceptance range of 0.80 ∼ 1.25 for the ratio of AUC, of 0.7 ∼ 1.43 for the C_{max}, and Wilcoxon test showed that there was no difference in the t_{max} of the two preparations.

4.7. Tolerability

Blood pressure and heart rate were recorded on each dosing day at the time of drug administration and at 30 min and 2, 5, 12 h postdose. Adverse events were monitored using a standardized nonleading question, and any spontaneously reported adverse events were also recorded. Hematologic, serum biochemistry, and urinalysis laboratory tests were performed at screening and within 24 h before each dose. 12-lead ECG was recorded before and 2, 5, 12 h after administration.

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References

Chen J, Jiang XG, Jiang WM, Nei N, Gao XL, Zhang QZ (2004) Liquid chromatographic method for the determination of rizatriptan in human plasma. J Chromatogr B 805: 169–173.

Cornaz AL, Buri P (1994) Nasal mucosa as an absorption barrier. Eur J Pharm Biopharm 40: 261–270.

De-Hoon JN, Willigers JM, Troost J, Struijker-boudier HA, Van Bortel LM (2000) Vascular effects of 5-HT1B/1D-receptor agonists in patients with migraine headaches. Clin Pharmacol Ther 68: 418–426.

Goldstein J, Ryan R, Jiang K, Getson A, Norman B, Block GA, Lines C (1998) The rizatriptan protocol 046 study group crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Headache 38: 737–747.

Hussain AA (1998) Intranasal drug delivery. Adv Drug Deliver Rev 29: 39–49.

Lee Y, Conroy JA, Stepanavage ME, Mendel CM, Somers G, McLoughlin DA, Olah TV, De-Smet M, Keymeulen B, Rogers JD (1999) Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers. Br J Clin Pharmacol 47: 373–378.

Tokola RA, Neuvonen PJ (1984a) Effect of migraine attacks on paracetamol absorption. Br J Clin Pharmacol 18: 867–871.

Tokola RA, Neuvonen PJ (1984b) Effects of migraine attacks and metoclopramide on the absorption of tolfenamic acid. Br J Clin Pharmacol 17: 67–75.

Volans GN (1978) Migraine and drug absorption. Clin Pharmacokinet 3: 313–318.

Vyas KP, Halpin RA, Geer LA, Ellis JD, Liu LD, Cheng HY, Chavez-Eng C, Matuszewski BK, Varga SL, Guiblin AR, Rogers JD (2000) Disposition and pharmacokinetics of the antimigraine drug, rizatriptan, in human. Drug Metab Dispos 28: 89–95.