Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers

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Aims The pharmacokinetics and dose proportionality of rizatriptan single oral doses from 2.5 to 15 mg administered as solutions to healthy volunteers were studied.

Methods In a randomized, crossover study with four periods, twenty-four healthy volunteers (12 males and 12 females) took single oral doses of 2.5, 5, 10, and 15 mg rizatriptan in Periods 1–4. In a fifth period, subjects received 4 mg intravenous (i.v.) rizatriptan as a reference. Plasma and urine rizatriptan concentrations were determined at several timepoints/intervals for 12 and 24 h, respectively.

Results The arithmetic mean AUC values following single oral doses of 2.5, 5, 10, and 15-mg rizatriptan were 16, 33, 72, and 127 ng ml⁻¹ h, respectively, in males; and 19, 42, 97, and 161 ng ml⁻¹ h, respectively, in females. The overall bioavailability (*F*) of rizatriptan was ~40% in males. Following the 4 mg reference i.v. dose, the apparent plasma clearance (CL) and renal clearance (CL_r) were 1042 and 225 ml min⁻¹, respectively, in males; and 821 and 174 ml min⁻¹, respectively, in females.

Conclusions The disposition kinetics of oral rizatriptan were linear for doses of 2.5–10 mg in males, and for doses of 2.5–5 mg in females. However, the degree of nonlinearity for higher doses was minor for both genders. The plasma concentrations of rizatriptan were slightly greater in women compared to men but the difference was not considered to be clinically meaningful. Also, the clearance of rizatriptan appeared to be mainly nonrenal.

Keywords: rizatriptan, pharmacokinetics, migraine

Introduction

Migraine headache is a common disorder afflicting women more frequently than men. A recent study estimated that 8.7 million women and 2.6 million men in the US suffer from moderate-to-severe migraine symptoms with the greatest prevalence in both genders between the ages of 35 to 45 years [1]. Rizatriptan (*N,N*-dimethyl-2-[5-(1,2,4-triazole-1-ylmethyl)-1H-indole-3-yl] ethylamine benzoate, Figure 1), a novel serotonin 5-HT_{1B/1D} receptor agonist, is being evaluated for the acute treatment of migraine [2, 3]. The intravenous (i.v.) pharmacokinetics and tolerability of rizatriptan have previously been characterized in healthy male [4] and female [5] subjects. The results show that the plasma concentrations of rizatriptan increased proportionately with i.v. doses up to ~5 and 2.5 mg in males and females, respectively [4, 5]. Rizatriptan was also found to

be safe and well tolerated in the i.v. dose range of ~0.4 to ~6.8 mg in males and 0.5 to 5 mg in females [4, 5]. In males, the oral bioavailability was about 40% [4].

In clinical trials, rizatriptan is efficacious and generally well tolerated in relieving migraine headache at oral doses of 5 and 10 mg [6–8]. This report describes the results of a clinical study that was conducted to assess the pharmacokinetics and tolerability of rizatriptan in healthy volunteers over a range of oral doses above and below 10 mg. Since migraine is more prevalent in women, a comparison of oral pharmacokinetics of rizatriptan between males and females was also made.

Figure 1 Chemical structure of rizatriptan benzoate.

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Methods

Subjects

Twenty-four healthy volunteers (12 men and 12 women) completed the study. Their ages ranged from 22 to 41 years. The mean weight and height of male subjects were 77.6 kg and 183.6 cm with ranges from 60.8 to 93.1 kg and from 170.2 to 193.0 cm, respectively. The mean weight and height of female subjects were 60.8 kg and 167.1 cm with ranges from 54.0 to 70.8 kg and from 157.5 to 182.9 cm, respectively. All volunteers gave written informed consent. Subjects were non-smokers for at least 6 months and were judged to be in good health on the basis of the medical history, physical examination, electrocardiogram, and laboratory screening tests (routine hematology, blood chemistry, and urinalysis). Subjects did not have a history of hypertension, syncope, or significant disease, including cardiovascular and gastrointestinal disease. Physical examination included measurements of vital signs: weight, height, oral temperature, resting blood pressure (<140 mmHg systolic, or <90 mmHg diastolic), resting pulse (between 40 and 100 beats min^{-1}), and respiration rate. If female subjects were of childbearing potential, they were not pregnant or breast-feeding and agreed to use a barrier method of contraception from 1 month prior to the start of the study until 1 month after completion of the study.

Study design

This was a four-period, randomized, crossover study to examine the pharmacokinetics and tolerability of single oral doses of rizatriptan. Subjects received single oral doses of 2.5, 5, 10, and 15 mg rizatriptan in solution on 4 separate study days. In a fifth period, subjects received 4 mg rizatriptan solution infused intravenously over 30 min. For each subject there was at least a 7 day interval between the administration of each dose. The concentration of rizatriptan used in oral and i.v. treatments was 1 mg ml^{-1} . In order to measure the actual oral dose, the drug solution was withdrawn from the vial(s) by syringe and placed into a small cup resting on a balance that had been tared. The assembled syringe and infusion tubing used for drug administration was weighed before and after the i.v. infusion. The actual i.v. dose was estimated from the assayed concentration of the infusate and the volume administered.

Subjects were not permitted alcoholic beverages for 24 h before, during or for 24 h after each treatment period. Caffeinated beverages were limited to no more than the equivalent of six cups of coffee per day, except for treatment days when caffeinated beverages were not permitted from midnight prior to treatment until com-

pletion of the 24 h postdose evaluations. Orange juice (240 ml) was provided at 2 h postdose. Meals were provided at approximately 4 and 8 h postdose. No other medications were taken within 14 days prior to the study.

Sample collections

Blood samples (5 ml, to yield at least 2 ml plasma) were collected in heparinized tubes predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 h postdose during each treatment. The 0.5 h collection coincided with the time the i.v. infusion was complete. Blood samples were placed on ice after collection, centrifuged within 30 min, and the resulting plasma stored frozen at -20°C until assayed for rizatriptan. The total urine voided was collected in volumetric containers during the time intervals of 0–6, 6–12, and 12–24 h postdose. Following accurate determination of the volume voided, samples were mixed well, then $2 \times 10 \text{ ml}$ aliquots were obtained and immediately frozen at -20°C until the time of analysis.

Analytical method

Rizatriptan was isolated from plasma and urine using automated solid-phase extraction and determined quantitatively by an LC/MS/MS method (positive ion mode) [9]. The *N,N*-diethyl analog of rizatriptan was used as the internal standard. The assay was run using a Sciex API III mass spectrometer equipped with an upgraded collision cell interfaced *via* Sciex's heated nebulizer to a Hewlett Packard 1050 liquid chromatography system. The calibration curves (0.5 – 100 ng ml^{-1} for plasma and 1 – 200 or 5 – 500 ng ml^{-1} for urine) were constructed by plotting the peak area ratios against the concentrations of rizatriptan in standard plasma and urine samples. The intra-assay accuracy was acceptable if the mean concentration of standard replicates did not exceed $\pm 115\%$ of the nominal concentration. The intra-assay precision, defined as the coefficient of variation ($n=5$) calculated in the determination of accuracy, was acceptable if the coefficient of variation was less than 10%. Since the lowest standards on the calibration curves for both plasma and urine were within the satisfactory ranges of the intra-assay accuracy and precision, the lower quantifiable limits of rizatriptan was 0.5 ng ml^{-1} for plasma, 1 ng ml^{-1} for urine at the 2.5 and 5 mg oral doses, and 5 ng ml^{-1} for urine at the 10 and 15 mg oral and the 4 mg i.v. doses.

Pharmacokinetic calculations

Following i.v. doses, the area under the plasma concentration-time curve from time zero to time infinity (AUC), plasma clearance (CL), steady-state volume of distribution (V_{ss}), and plasma terminal half-life ($t_{1/2}$) were calculated

using the LAGRAN computer program [10]. For oral data, the maximum plasma concentration ($C_{\max}$) and its corresponding time of occurrence ($t_{\max}$) were noted directly and AUC and $t_{1/2}$ were calculated using the LAGRAN computer program [10]. The values for AUC and $C_{\max}$ were linearly normalized to the nominal dose and then dose-adjusted to a 2.5 mg dose for purposes of comparison. The bioavailability (F) of rizatriptan was calculated as $(AUC_{p.o.} \times Dose_{i.v.}) / (AUC_{i.v.} \times Dose_{p.o.})$, where the subscripts p.o. and i.v. denote oral and i.v. administration, respectively. The percentage of the dose excreted in urine (U_e) was calculated as the ratio of amount excreted to actual dose administered. The renal clearance (CL_r) was calculated as the ratio of the amount of rizatriptan excreted in urine to the plasma AUC of rizatriptan.

Statistical analysis

An analysis of variance (ANOVA) for a four-period crossover design was used to assess the dose proportionality of rizatriptan AUC and $C_{\max}$ in men and women across the dose range of 2.5 to 15 mg. After confirming the absence of period and carryover effects, the ANOVA model included terms for subject (11 degrees of freedom) and treatment (3 degrees of freedom). Estimation of the relative differences between the AUC and $C_{\max}$ dose-adjusted parameters was determined by 90% confidence intervals (C.I.) for the geometric mean ratio of ≥ 5 mg treatments to the 2.5 mg treatment. The dose-adjusted AUC and $C_{\max}$ values were log transformed to satisfy ANOVA assumptions of normality and homogeneity of variance. Geometric means for each treatment were obtained by exponentiating the least square means of the log-transformed data from the ANOVA model [11, 12]. The C.I. values were calculated on the differences in the treatment means in natural log units using the mean square error from the ANOVA. The upper and lower limits were then exponentiated to obtain intervals for the ratios for all dose comparisons. Adopting from standard bounds used typically in clinical trials, a difference of 30% on the log scale which back transforms to the interval of (0.70, 1.43) on the arithmetic scale was chosen to represent the predefined comparability interval for assessing dose proportionality. That is, the limits of 90% C.I. for the geometric mean ratio of dose-adjusted AUC and $C_{\max}$ that fell within the interval of 0.70 to 1.43 were considered to be dose proportional in the perspective of clinical meaning. The t -distribution was assumed for calculation of all C.I. values.

Clinical assessments

Laboratory safety tests were done pre- and poststudy, and pre- and 24 h postdose in each study period. Blood

pressure and heart rate were recorded on each dosing day at -30 , -15 , and 0 min predose, at 15, 30, 45, 60, 90, and 120 min and at 4, 6, 8, 12, and 24 h postdose. Baseline values were defined as the mean of the three predose (-30 min, -15 min, and 0 h) values. All measurements of vital sign, unless otherwise indicated, were made in the sitting position. Respiratory rate and oral temperature were obtained at 30 min predose and 24 h postdose. Vital signs were also obtained prestudy and poststudy as part of the physical examination. A decrement of 20 mmHg in systolic blood pressure or increment of 20 beats min^{-1} upon standing for 1 min was considered significant.

Results

Pharmacokinetics

Mean plasma concentration-time profiles of rizatriptan following oral administration of this compound in healthy males and females are depicted in Figure 2. In males,

Figure 2 Mean ($\pm$ s.d.) plasma concentration-time profiles of rizatriptan in healthy a) males ($n=12$) and b) females ($n=12$) receiving single oral solution doses of 2.5 ($\bullet$), 5 ($\circ$), 10 ($\blacksquare$), and 15 ($\square$) mg rizatriptan.

arithmetic mean AUC values were 16, 33, 72, and 127 ng ml⁻¹ h following doses of 2.5, 5, 10, and 15 mg, respectively (Table 1). The dose-adjusted AUC geometric means were 14.3, 15.8, 17.1, and 19.8 ng ml⁻¹ h over the same dose range. The AUC geometric mean ratios (90% C.I.) for the 5, 10, and 15 mg treatments relative to the 2.5 mg treatment were 1.10 (0.98, 1.24), 1.19 (1.06, 1.34), and 1.38 (1.23, 1.56), respectively. The upper limit of the 90% C.I. fell outside the interval of 0.70 to 1.43 for the 15 mg dose. In men, $C_{\max}$ showed generally consistent results to those reported for AUC. The $C_{\max}$ geometric mean ratios (90% C.I.) for the 5, 10, and 15 mg treatments relative to the 2.5 mg treatment were 1.05 (0.88, 1.24), 1.14 (0.97, 1.35), and 1.22 (1.03, 1.45), respectively. The upper limit of the 90% C.I. fell outside the interval of 0.70 to 1.43 for the 15 mg dose. Thus, the plasma concentrations of oral rizatriptan in males increased proportionately with doses up to 10 mg but disproportionately from 10 to 15 mg.

The extent of deviation from linearity was greater in females than in males. For 2.5, 5, 10, and 15 mg rizatriptan, arithmetic mean AUC estimates in females were 19, 42, 97, and 161 ng ml⁻¹ h, respectively (Table 2). The dose-adjusted AUC geometric means were 18.0, 20.2, 23.2, and 26.1 ng ml⁻¹ h over the same dose range. The AUC geometric mean ratios (90% C.I.) for the 5, 10, and 15 mg treatments relative to the 2.5 mg treatment were 1.12 (1.04, 1.21), 1.29 (1.19, 1.39), and

1.45 (1.34, 1.56), respectively. The upper limit of the 90% C.I. fell outside the interval of 0.70 to 1.43 for the 15 mg dose. On the other hand, the $C_{\max}$ geometric mean ratios (90% C.I.) in women for the 5, 10, and 15 mg treatments relative to the 2.5 mg treatment were 1.09 (0.96, 1.25), 1.30 (1.14, 1.48), and 1.47 (1.29, 1.68), respectively. The upper limits of the 90% C.I. fell outside the interval of 0.70 to 1.43 for the 10 and 15 mg doses. This suggests that the plasma levels of oral rizatriptan in females increased proportionately up to 5 mg and somewhat disproportionately for higher doses.

Females tended to show higher concentrations of rizatriptan than males. Following oral administration, the arithmetic mean AUC values of rizatriptan were slightly higher (~17–34%) in females than in males across the 2.5 to 15 mg dose range. Similarly, the arithmetic mean $C_{\max}$ values of rizatriptan in females were somewhat higher (<20%) than those in males. The $t_{\max}$ of rizatriptan was less than 1 h and the harmonic mean of the apparent $t_{1/2}$ of rizatriptan was between 2 and 3 h in both men and women without significant differences among administered doses. The urinary excretion (U_e) of rizatriptan averaged between 7 and 14% of the dose in both males and females. The CL_r of rizatriptan in males averaged from 225 to 340 ml min⁻¹ and the apparent CL_r of rizatriptan in females was between 179 and 244 ml min⁻¹ (Tables 1 and 2). Using the 4 mg dose of i.v. rizatriptan as a reference, rizatriptan was found to be approximately 40% bioavailable

Parameter	Rizatriptan dose (mg)			
	2.5	5	10	15
AUC (ng ml ⁻¹ h)	16 ± 7	33 ± 9	72 ± 22	127 ± 45
$C_{\max}$ (ng ml ⁻¹)	6.2 ± 2.8	12.7 ± 4.8	28.6 ± 13.5	44.8 ± 17.8
$t_{\max}$ (h)	0.8 ± 0.5	0.7 ± 0.3	0.7 ± 0.2	0.9 ± 0.4
U_e (%)	7.6 ± 2.4	13.0 ± 4.7	11.9 ± 6.4	13.2 ± 4.7
CL_r (ml min ⁻¹)	225 ± 85	340 ± 122	295 ± 121	271 ± 43 ^c
Apparent $t_{1/2}$ ^a (h)	2.1	2.2	2.4	2.4
F ^b	35%	38%	42%	— ^d

^aHarmonic mean. ^bGeometric mean. ^cApparent value because of slight nonlinearity.

^dNot estimated because of nonlinearity.

Table 1 Arithmetic mean ($\pm$ s.d., $n=12$) values of pharmacokinetic parameters for rizatriptan in healthy males receiving single oral solution doses of 2.5, 5, 10, and 15 mg rizatriptan.

Parameter	Rizatriptan dose (mg)			
	2.5	5	10	15
AUC (ng ml ⁻¹ h)	19 ± 5	42 ± 12	97 ± 28	161 ± 42
$C_{\max}$ (ng ml ⁻¹)	6.1 ± 1.9	13.2 ± 3.7	32.1 ± 11.9	54.0 ± 18.7
$t_{\max}$ (h)	0.8 ± 0.3	0.9 ± 0.4	0.7 ± 0.2	1.0 ± 0.6
U_e (%)	7.9 ± 2.0	12.1 ± 3.5	13.5 ± 6.9	13.8 ± 3.2
CL_r (ml min ⁻¹)	179 ± 27	244 ± 54	242 ± 135 ^b	223 ± 59 ^b
Apparent $t_{1/2}$ ^a (h)	2.2	2.4	2.6	2.4

^aHarmonic mean. ^bApparent value because of slight nonlinearity.

Table 2 Arithmetic mean ($\pm$ s.d., $n=12$) values of pharmacokinetic parameters for rizatriptan in healthy females receiving single oral solution doses of 2.5, 5, 10, and 15 mg rizatriptan.

Table 3 Arithmetic mean ($\pm$ s.d.) values of pharmacokinetic parameters for rizatriptan in healthy males ($n=12$) and females ($n=12$) receiving a single i.v. dose of 4 mg rizatriptan.

Gender	AUC ($\text{ng ml}^{-1} \text{ h}$)	CL (ml min^{-1})	CL _r (ml min^{-1})	U _e (%)	V _{ss} (l)	t _{1/2} ^a (h)
Male	68 $\pm$ 16	1042 $\pm$ 281	225 $\pm$ 35	23.4 $\pm$ 7.5	141 $\pm$ 31	2.9
Female	84 $\pm$ 17	821 $\pm$ 148 ^b	174 $\pm$ 28 ^b	20.8 $\pm$ 2.9	102 $\pm$ 29 ^b	2.4 ^b

^aHarmonic mean. ^bApparent value because of slight nonlinearity.

in male volunteers over the oral dose range of 2.5–10 mg (Table 1). Bioavailability estimates were not calculated for oral doses of rizatriptan in females since the concentrations achieved with the 4 mg i.v. dose for females appeared to be in the nonlinear range [5].

Following the 4 mg i.v. dose, the arithmetic mean AUC of rizatriptan was again slightly higher ($\sim 25\%$) in females than in males (Table 3). This difference between genders was reflected by a lower apparent CL in females (821 ml min^{-1}) than in males (1042 ml min^{-1}). The arithmetic mean value of apparent CL_r in females (174 ml min^{-1}) was lower than that in males (225 ml min^{-1}). Therefore, approximately 20% of the apparent plasma clearance (CL) of rizatriptan in males and females resulted from renal excretion, indicating that the majority of the clearance of rizatriptan was nonrenal. The harmonic mean apparent t_{1/2} of rizatriptan was similar in males and females (2.4–2.9 h). The arithmetic mean U_e was similar for both men and women with values being larger following the i.v. dose (20–24%) than following the oral dose (7–14%). This suggests that the bioavailability of rizatriptan was similar in males and females.

Tolerability

A number of subjects reported headache, dizziness, or fatigue. One of the 12 female subjects had severe abdominal cramps and pain at the right colon after a 15 mg rizatriptan oral dose. This clinical adverse experience was diagnosed as spastic colon and rated as serious and probably not drug related. None of the subjects were discontinued from the study due to a clinical adverse experience. Mean changes of systolic blood pressure from baseline were generally within ± 5 mmHg up to 8 h postdose in male subjects and also within ± 5 mmHg across the 0 to 24 h interval in female subjects. Similarly, mean diastolic changes from baseline were within ± 5 mmHg in male and female subjects. No other meaningful clinical changes from pretreatment values were observed during ECGs, physical examinations, or other safety tests.

Discussion

Plasma concentrations (AUC and C_{max}) of oral rizatriptan generally increased with dose over the range of

2.5–15 mg. The increase was proportional with dose up to 10 mg in males, and up to 5 mg in females. The somewhat greater degree of nonlinearity in women probably has its basis in saturable metabolic events since the nonlinearity increased with dose and plasma concentrations of rizatriptan were higher in women. Because $\sim 50\%$ of the elimination of rizatriptan derives from metabolism by MAO-A to the indole acetic acid metabolite, saturation of this pathway is the likely contribution to these slight nonlinearities. Nevertheless, this slight nonlinearity is considered not to be clinically meaningful. The extent of deviation from linearity between two clinical doses, 5 and 10 mg, was small (approximately 15% for women), i.e., in clinical practice, increasing a patient's dose within this dose range would result in a close-to-expected increase in plasma drug concentrations.

AUC of oral rizatriptan in this study was $\sim 30\%$ higher in females than in males. Accordingly, plasma clearance of rizatriptan was $\sim 25\%$ higher in men than in women. In any event, it is important to emphasize that the observed 30% difference in AUC between men and women is not likely to be of clinical relevance. In particular, from a safety perspective, there is extensive clinical experience showing that rizatriptan at a 40 mg dose is well tolerated [13], despite the fact that the projected clinical doses are 5 and 10 mg. Dosing recommendations are based on evaluation of both doses in males and females and no difference in the dose–effect relationship between the genders was noted [3].

Other pharmacokinetic parameters of rizatriptan determined in this study were a bioavailability (in males) of $\sim 40\%$, a t_{max} of less than 1 h, and an apparent plasma half-life of between 2 and 3 h. Both t_{max} and apparent t_{1/2} were similar in males and females. Although an oral solution was used in this study, the bioavailability estimate was similar to that previously reported for a tablet similar in composition to the marketed tablet [4]. Also of note is the finding that the majority of the clearance of rizatriptan appeared to be nonrenal.

Rizatriptan, at doses up to and above the projected clinical doses, was well tolerated in this study. Although there were reported occasional mild or moderate symptoms of headache, lightheadedness, dizziness, or fatigue, none of these would have taken on clinical significance within the context of treatment of a migraine headache.

Furthermore, there was no evidence of dose-relationship of these events, and their interpretation should consider the lack of placebo control.

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