

# Absolute Bioavailability, Pharmacokinetics, and Urinary Excretion of the Novel Antimigraine Agent Almotriptan in Healthy Male Volunteers

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*Absolute bioavailability, pharmacokinetics, and urinary excretion of almotriptan, a novel 5-HT<sub>1B/1D</sub> receptor agonist, were studied in 18 healthy males following single intravenous (i.v.) (3 mg), subcutaneous (s.c.) (6 mg), and oral (25 mg) doses. Volunteers received each dose in a randomized sequence separated by a 7-day washout. Blood and urine samples for pharmacokinetic evaluations were taken for up to 24 hours after dosing. The disposition kinetics of almotriptan after i.v. and s.c. administration showed biphasic decline described by a two-compartment model. The fastest disposition phase was well observed, although estimates of the rate constant showed high variability. After s.c. administration of almotriptan, the bioavailability was 100% with a time to maximum plasma concentration (t<sub>max</sub>) of 5 to 15 minutes, whereas after oral administration, the bioavailability was*

*about 70% with a t<sub>max</sub> of 1.5 to 3.0 hours. No significant differences were observed between administration routes in the elimination half-life (t<sub>1/2</sub>), obtaining mean values ranging from 3.4 to 3.6 hours. The volume of distribution, total clearance, and t<sub>1/2</sub> indicated that almotriptan was extensively distributed and rapidly cleared from the body irrespective of dose or route of administration. The primary route of elimination was renal clearance (approximately 50%-60% of total body clearance). About 65% of the i.v. and s.c. dose and 45% of the oral dose were excreted unchanged in urine in 24 hours, with nearly 90% of this in the first 12 hours. Renal clearance was approximately 2- to 3-fold that of the glomerular filtration rate in man, suggesting that almotriptan is eliminated in part by renal tubular secretion.*

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**S**erotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter located in the brain, spinal cord, and myenteric plexus and is also a local hormone released by platelets, enterochromaffin cells, and paracrine cells in the thyroid. There are several receptor subtypes that are acted upon by 5-HT (classified as 5-HT<sub>1</sub> to 5-HT<sub>7</sub>), with several of these subtypes also existing in dif-

ferent forms. The 5-HT<sub>1B/1D</sub> receptors, found in intracranial blood vessels, the main carotid arterial tree, and pial and dural vessels, may play a role in the relief of migraine pain by mediating vasoconstriction of some cerebral blood vessels.<sup>1</sup>

Almotriptan, 3-(2-dimethylaminoethyl)-5-(1-pyrrolidinylsulfonylmethyl)-1H-indole (Figure 1), is a novel 5-HT<sub>1B/1D</sub> receptor agonist developed for the symptomatic relief of migraine. Studies investigating the pharmacokinetics, tolerability, and safety of oral doses up to 200 mg have shown that almotriptan was well tolerated up to doses of 150 mg. The compound was well absorbed at each dose level, and it was mainly excreted, in an unmetabolized state, in urine.<sup>2</sup> Moreover, plasma concentrations increased proportionally with dose, indicating the accomplishment of the principle of superposition and therefore confirming the as-

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sumption that the pharmacokinetics was linear over the dose range studied. In vitro, at least four different enzymes are involved in the oxidative metabolism of almotriptan.<sup>3</sup> These enzymes are monoamine oxidase A (MAO-A), which catalyzes the oxidative deamination of almotriptan to the indoleacetic acid metabolite; the isoforms CYP3A4 and, to a minor extent, CYP2D6, which are responsible for the  $\alpha$ -carbon hydroxylation of the pyrrolidine group and N-demethylation of the dimethylaminoethyl side chain; flavin monooxygenase (FMO), which catalyzes N-oxidation of the dimethylaminoethyl side chain; and aldehyde dehydrogenase, which catalyzes the conversion of the hydroxypyrrolidine metabolite intermediate to the  $\gamma$ -aminobutyric acid metabolite. Only two metabolites have been observed in human plasma: the indoleacetic acid derivative (main metabolite) and the  $\gamma$ -aminobutyric acid metabolite. Their plasma concentrations are low compared with those of the unchanged compound, and both are devoid of activity.

Although almotriptan is converted to several metabolites, the predominance of the urinary excretion of the unchanged compound suggests that biotransformation is not a prerequisite for urinary excretion. Therefore, drugs or disease states that might impair the biotransformation of almotriptan would not be expected to alter drastically the disposition and urinary excretion of almotriptan. In addition, the pharmacokinetics of almotriptan is unaffected during a migraine attack, indicating that changes in gut motility and states of gastric stasis and delayed gastric emptying disturbances that normally accompany the attack would not significantly alter the absorption and disposition of almotriptan.<sup>4</sup>

Verapamil, an agent for migraine prophylaxis and a substrate of the CYP3A4, modestly inhibits almotriptan clearance to a degree consistent with the modest contribution of CYP3A4 to almotriptan metabolism.<sup>5</sup> Furthermore, when almotriptan is administered in the presence of fluoxetine, a potent CYP2D6 inhibitor, only a small effect has been observed on almotriptan  $C_{max}$ , whereas the mean AUC value is not significantly affected.<sup>6</sup> The administration of almotriptan in the presence of a reversible MAO-A inhibitor, the antidepressant moclobemide, showed that plasma concentrations of almotriptan are increased on average by 37%, renal clearance is unaffected, the coadministration is well tolerated, and there is no evidence of cardiovascular side effects.<sup>7</sup> Finally, a lack of pharmacokinetic interaction was observed between almotriptan and propranolol, which is often used in migraine prophylaxis. Since both compounds share a common metabolic pathway mediated by CYP2D6, the lack of inter-

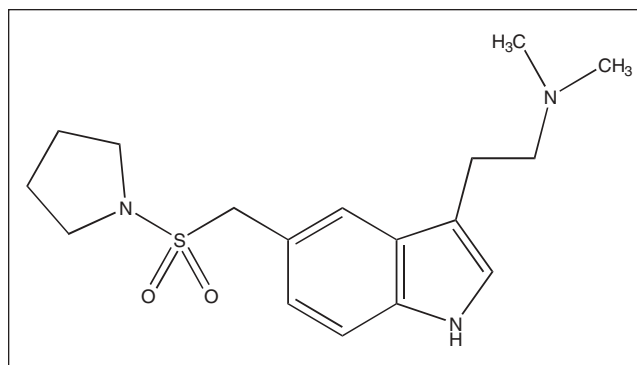


Figure 1. Chemical structure of almotriptan.

action observed indicates that the degree of metabolism of almotriptan via this route appears to be small.<sup>8</sup>

The present study was designed to investigate the absolute oral and subcutaneous (s.c.) bioavailability of almotriptan by obtaining the main pharmacokinetic parameters after single intravenous (i.v.), s.c., and oral doses of 3, 6, and 25 mg almotriptan, respectively. After an initial dose escalation study covering a range of oral doses from 5 to 200 mg,<sup>2</sup> the 25-mg dose was considered as a probable therapeutic dose and, therefore, was selected to study the oral bioavailability of almotriptan. In further oral dose-finding phase II clinical trials, the therapeutic dose chosen, based on efficacy parameters as well as the incidence of adverse effects, was 12.5 mg<sup>9</sup> (almotriptan is available in two dosage strengths: 12.5 mg and 6.25 mg tablets). The subcutaneous administration was included in the study to assess the bioavailability, tolerability, and safety of an administration route commonly used for treating migraine pain. The subcutaneous dose administered was selected based on the results of a previous escalation study covering a range of subcutaneous doses from 0.5 to 14 mg<sup>2</sup> (almotriptan is not available at the present time by this administration route). Finally, i.v. administration was included to establish the appropriate pharmacokinetic model and the absolute values of the volume of distribution and total body clearance from plasma (CL). In addition, the contribution of renal clearance from plasma ( $CL_R$ ) to CL was also investigated.

## METHODS

### Subjects

Twenty-four healthy male volunteers, between ages 19 and 33 years, participated in the clinical trial. The study was approved by the Ethics Committee of the Hospital Universitario "Germans Trias i Pujol" (Barce-

**Table I** Mean (range) Demographic Characteristics for Volunteers Included in the Preliminary and Principal Phases

Parameter	Preliminary Phase	Principal Phase
Age (years)	26.0 (22.8-31.5)	24.5 (19.9-33.2)
Weight (kg)	77.2 (71.5-83.5)	73.8 (63.7-88.0)
Height (cm)	175.8 (169-186)	174.2 (160-190)
Body mass index (kg/m <sup>2</sup> )	25.1 (22.6-28.6)	24.3 (20.9-29.4)

lona, Spain) and the National Board of Health and was conducted in accordance with the Declaration of Helsinki and good clinical practice. Fully informed written consent was obtained from volunteers before they were admitted into the study.

A complete medical history was obtained from each volunteer, with physical examinations, laboratory tests (hematology, serum chemistry, and urinalysis), and electrocardiograms (ECGs) being performed at the screening visit. The demographic characteristics of subjects included in the two phases of the trial (see below) are summarized in Table I.

### Study Design

The study was an open, randomized, crossover clinical trial. A preliminary phase was carried out in 6 healthy male volunteers, ages 22 to 31 years, with the aim of determining the safety profile of a single low i.v. dose (1.5 mg) before starting the principal phase of the study. Since there were no safety issues with dosing at this level, another 18 male volunteers, ages 19 to 33 years, were recruited to receive higher doses of almotriptan during the principal phase of the study. These volunteers were randomized to receive single doses of i.v. (3 mg), s.c. (6 mg), and oral (25 mg) almotriptan, with a washout period of 7 days between each treatment.

Intravenous doses were administered by a 15-minute infusion, at a constant flow rate of (1 ml•min<sup>-1</sup>), of a sterile isotonic solution containing 1.5 mg or 3 mg of almotriptan, whereas s.c. doses were administered by an injection of 0.5 ml of an sterile isotonic solution containing 6 mg of almotriptan into the arm deltoid region. Oral doses were given after an overnight fast as 25 mg tablets along with 100 ml of water. Two hours after dosing, a light breakfast was given to each volunteer.

Blood samples for pharmacokinetic analysis were collected into heparinized tubes at predose and at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24

hours postdose. Additional samples were collected at 5 and 10 minutes after dosing following s.c. administration. Blood samples were centrifuged immediately after collection, and the plasma was separated and stored in deep freeze until analysis.

Urine samples for pharmacokinetic analysis were collected at predose and over 0- to 4-, 4- to 8-, 8- to 12-, and 12- to 24-hour intervals postdose. Immediately after collection, urine samples were frozen until analysis.

Safety was assessed by measuring heart rate, systolic and diastolic blood pressure, body temperature, ECGs, and laboratory variables (hematology, biochemistry, and urinalysis) and by monitoring adverse events. Supine heart rate (determined at radial level during 1 min), blood pressure (determined by sphygmomanometry after 5 min of supine decubite), and body temperature were measured at different times throughout the study. A 12-lead ECG was taken predose and at 45 minutes and 1.5, 3, 6, 12, and 24 hours postdose by the i.v., s.c., and oral routes. Additional measurements were made 15 minutes after dosing by the s.c. route and 5, 10, 20, 25, and 30 minutes after dosing by the i.v. route. Blood and urine samples were taken 24 hours postdose on each day of the study for the analysis of standard laboratory variables.

### Bioanalytical Method

The determination of almotriptan in human plasma (0.5 ml) and urine (0.1 ml) was carried out by high-performance liquid chromatography (HPLC) with UV detection at 227 nm, using an automated online solid-phase extraction and injection procedure with internal standardization.

The chromatographic system used consisted of a high-pressure pump (model 590, Waters Ass.), a Prospekt system (Spark Holland) assisted by a 233XL sampling injector (Gilson Medical Electronics), a tunable absorbance detector (model 486, Waters Ass.), and a Digital Alpha Server 1000 4/266 computer with Access\*Chrom software (Perkin Elmer Nelson Systems, Inc.). The chromatographic conditions were a Spherisorb ODS-2, 5 µm, 150 × 4 mm column (Waters Ass.) with a Guardpak µ-Bondapak CN Precolumn (Waters Ass.) and a mobile phase (20:80, v/v) of acetonitrile:50 mM, pH 4.0 sodium phosphate buffer solution, containing 0.2% triethylamine at a flow rate of 1 ml•min<sup>-1</sup>. The approximate retention times of almotriptan and the internal standard were 6.5 and 10 minutes, respectively.

The extraction of almotriptan and the internal standard from plasma (0.5 ml) and urine (0.1 ml) was per-

formed on C2 cartridges (Baker) activated with 2 ml of acetonitrile and conditioned with 2 ml of water. Plasma or urine samples were then automatically diluted with 1 ml of an aqueous internal standard solution (4-[3-(2-amino-ethyl)-1H-indol-5-ylmethylsulphonyl]-piperazine-1-carboxylic acid ethyl ester), mixed, and loaded into the C2 cartridges. After washing out the cartridges with 750  $\mu$ l of acetonitrile:water (30:70, v/v) and 250  $\mu$ l of water, the remaining components were eluted with the mobile phase over 1 minute. There were no significant endogenous peaks at retention times of almotriptan and the internal standard that would interfere with its quantification.

The results obtained in the validation of the bioanalytical method in terms of linearity, precision and accuracy (intra- and interbatch), sensitivity, specificity, recovery, stability, and quality control during routine analysis demonstrated the suitability of this method for the quantitative measurements of almotriptan in human plasma and urine.

The calibration curves showed good linearity ( $r > 0.999$ ) over the concentration range of 1 to 200  $\text{ng}\cdot\text{ml}^{-1}$  in plasma and 0.05 to 10  $\mu\text{g}\cdot\text{ml}^{-1}$  in urine. The intrabatch precision of the analytical method was determined by calculating the coefficient of variation of the calibration standard samples ( $n = 6$ ) at low, medium, and high concentrations. The results in plasma were 9.0%, 1.6%, and 2.0% at concentrations of 1, 20, and 200  $\text{ng}\cdot\text{ml}^{-1}$ , respectively, whereas the results in urine were 2.0%, 3.4%, and 1.4% at concentrations of 0.05, 1, and 10  $\mu\text{g}\cdot\text{ml}^{-1}$ , respectively. The coefficients of variation of the quality control standards used in the interbatch precision study were less than 6.5% in plasma ( $n = 30$ , over 12 different analysis days) and less than 5.1% in urine ( $n = 12$ , over 5 different analysis days) at the same concentrations used in the intrabatch study. The accuracy of measurements, expressed as relative error of the experimental values compared with the theoretical concentrations, was less than 10% over the concentration range both in the intra- and interbatch studies. The precision was also determined by calculating the coefficients of variation of the calibration curve slopes throughout the study, obtaining values of 4.2% in plasma ( $n = 12$ ) and 3.2% in urine ( $n = 5$ ). The precision and accuracy obtained for the first concentration of the calibration curves allowed us to validate a low limit of quantitation of 1  $\text{ng}\cdot\text{ml}^{-1}$  in plasma and 0.05  $\mu\text{g}\cdot\text{ml}^{-1}$  in urine. The recovery of almotriptan from plasma was determined at concentrations of 1, 20, and 200  $\text{ng}\cdot\text{ml}^{-1}$  and in urine at concentrations of 0.05, 1, and 10  $\mu\text{g}\cdot\text{ml}^{-1}$ . The mean values obtained were  $> 90\%$  in all cases. Almotriptan was shown to be stable in human plasma and urine when frozen

(around  $-20^\circ\text{C}$ ), during the study period, during the analysis time at room temperature, and following three freeze/thaw cycles.

### Pharmacokinetic Analysis

Plasma concentrations of almotriptan following i.v. and s.c. administration were analyzed using a two-compartment model. The parametric estimation was performed by nonlinear regression analysis using the initial values obtained by the "peeling algorithm"<sup>10</sup> and subsequently applying a numerical algorithm based on the Powell method to minimize the objective function.<sup>11</sup> The weighting factor used was  $1/C^2$ , where C was the concentration observed. The criteria used to assess the goodness of fit of models to experimental data and the choice between different models were based on the correlation coefficient between the observed and theoretical values, the coefficient of variation of the estimation of each parameter, and the Akaike, Schwartz, and Leonard information criteria.<sup>12</sup>

Plasma concentrations of almotriptan after oral administration were evaluated using a noncompartmental approach, using a least squares linear regression analysis of the terminal phase of the semilogarithmic concentration-time curve.

All pharmacokinetic calculations were performed using SIPHAR/PC software, version 4.0 (Simed, France) on a personal computer and using equations recommended by the American College of Clinical Pharmacology.<sup>13,14</sup>

The maximum plasma concentration ( $C_{\text{max}}$ ) and the time to reach it ( $t_{\text{max}}$ ) were taken from the experimental data. The linear trapezoidal rule was used to calculate the area under the concentration-time curve (AUC) from 0 to the last time point measured ( $t_n$ ). The AUC from  $t_n$  to infinity was determined from the last concentration measured ( $C_n$ ), and the terminal rate constant ( $\lambda_z$ ) was determined using the equation  $\text{AUC} = \text{AUC}(0 - t_n) + (C_n/\lambda_z)$ . Bioavailability ( $f$ ) was calculated as  $f_x(\%) = (\text{AUC}_x/\text{AUC}_{\text{IV}}) \cdot (D_{\text{IV}}/D_x) \cdot 100$ , where D is the dose and x is either i.v., s.c., or oral dosing ( $f$  for i.v. dosing = 100%, the comparator against which s.c. and oral dosing will be assessed). The distribution half-life ( $t_{1/2\lambda_1}$ ) was calculated as  $t_{1/2\lambda_1} = \ln(2)/\lambda_1$ , whereas the elimination half-life ( $t_{1/2}$ ) was calculated as  $t_{1/2} = \ln(2)/\lambda_z$ . The volume of distribution during the terminal phase ( $V_z$ ) was calculated from  $V_z = f_x \cdot D_x/(\lambda_z \cdot \text{AUC}_x)$ . CL was calculated from  $\text{CL} = f_x \cdot D_x/\text{AUC}_x$ , whereas  $\text{CL}_R$  was calculated from  $\text{CL}_R = A_{24}/\text{AUC}_x$ , where  $A_{24}$  is the amount of unchanged drug excreted into urine from 0 to 24 hours. The mean residence time (MRT) was calculated according to the trapezoidal rule from  $\text{AUMC}_x/$

**Table II** Mean (SD) Pharmacokinetic Parameters of Almotriptan Obtained in Healthy Male Volunteers (n = 18) after Administration of Single i.v., Subcutaneous and Oral Doses of 3, 6, and 25 mg, Respectively

Parameter	Route of Administration		
	Intravenous (3 mg)	Subcutaneous (6 mg)	Oral (25 mg)
C <sub>max</sub> (ng•ml <sup>-1</sup> )	46.82 (13.87)	57.27 (16.41)	64.14 (11.16)
t <sub>max</sub> (h)	0.25 <sup>a</sup>	0.23 (0.16)	2.7 (1.2)
λ <sub>1</sub> (h <sup>-1</sup> )	5.261 (1.564)	2.357 (1.126)	—
t <sub>1/2λ1</sub> (h)	0.014 (0.05)	0.33 (0.1)	—
λ <sub>z</sub> (h <sup>-1</sup> )	0.206 (0.029)	0.209 (0.018)	0.199 (0.024)
λ <sub>z</sub> (h <sup>-1</sup> ) <sup>b</sup>	0.193	0.182	0.224
t <sub>1/2</sub> (h)	3.4 (0.4)	3.4 (0.3)	3.6 (0.4)
t <sub>1/2</sub> (h) <sup>b</sup>	3.6	3.8	3.1
MRT (h)	4.2 (0.7)	4.3 (0.4)	6.4 (0.9)
AUC (ng•h•ml <sup>-1</sup> )	78.14 (14.42)	154.9 (26.5)	442.7 (78.3)
CL (l•h <sup>-1</sup> )	40 (8)	40 (8)	40 (8)
A <sub>24</sub> (mg)	1.93 (0.57)	3.86 (0.45)	11.22 (2.06)
CL <sub>R</sub> (l•h <sup>-1</sup> )	25 (8)	26 (4)	26 (5)
V <sub>z</sub> (l)	195 (40)	191 (35)	201 (37)
f (%)	—	100.1 (13.4)	69.1 (12.6)

C<sub>max</sub>, maximum plasma concentration; t<sub>max</sub>, time to maximum plasma concentration; λ<sub>1</sub>, largest (distribution) disposition rate constant; t<sub>1/2λ1</sub>, distribution half-life; λ<sub>z</sub>, terminal rate constant; t<sub>1/2</sub>, elimination half-life; MRT, mean residence time; AUC, area under the plasma concentration-time curve; CL, total body clearance from plasma; A<sub>24</sub>, amount of unchanged drug excreted in the urine in the 24 hours after dosing; CL<sub>R</sub>, renal clearance; V<sub>z</sub>, volume of distribution during terminal phase; f, bioavailability.

a. Infusion time.

b. Obtained from the mean values of the cumulative urinary excretion.

AUC<sub>x</sub>, where AUMC<sub>x</sub> is the area under the first moment curve. The percentage of the dose excreted in urine as unchanged compound at each collection interval was calculated from the following: D (%) = [(Urine Concentration • Urine Volume • 10<sup>-3</sup>)/Dose] • 100.

**RESULTS**

The mean plasma concentration-time profiles of almotriptan found in healthy male volunteers after i.v., s.c., and oral administration of almotriptan at doses of 3, 6, and 25 mg, respectively, are shown in Figure 2. The mean values for the assessed pharmacokinetic parameters are shown in Table II, and the urinary excretion of almotriptan results are summarized in Table III.

The disposition kinetics of almotriptan after i.v. and s.c. administration showed a biphasic decline described by a two-compartment model (Figure 3). The

**Table III** Mean (SD) Urinary Excretion of Almotriptan, Expressed as a Percentage of the Administered Dose, in Healthy Male Volunteers (n = 18) after Administration of Single i.v., Subcutaneous, and Oral Doses of 3, 6, and 25 mg, Respectively

Route	Interval (h)	Dose (%)	Cumulative Dose (%)
Intravenous (3 mg)	0-4	45.4 (13.4)	45.4 (13.4)
	4-8	11.2 (5.7)	56.5 (17.6)
	8-12	4.8 (2.9)	61.3 (18.4)
	12-24	3.1 (1.0)	64.5 (18.9)
Subcutaneous (6 mg)	0-4	42.0 (5.2)	42.0 (5.2)
	4-8	12.9 (2.2)	54.9 (6.4)
	8-12	5.4 (1.7)	60.3 (6.8)
	12-24	4.1 (1.2)	64.4 (7.4)
Oral (25 mg)	0-4	20.0 (5.1)	20.0 (5.1)
	4-8	14.4 (4.3)	34.4 (6.3)
	8-12	6.2 (2.1)	40.7 (6.8)
	12-24	4.2 (1.7)	44.9 (8.2)

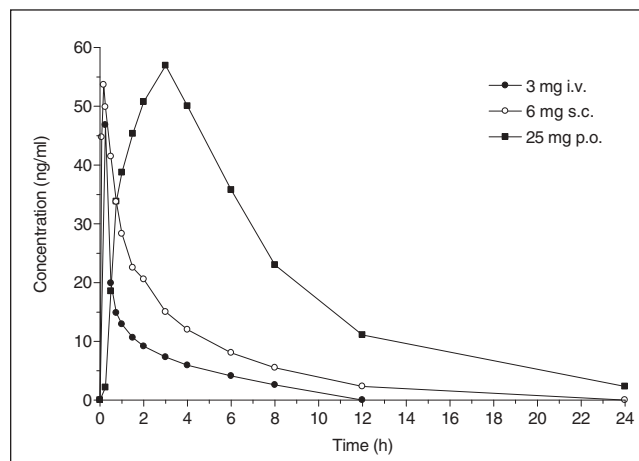


Figure 2. Mean plasma levels of almotriptan obtained in healthy male volunteers (n = 18) after administration of single i.v., subcutaneous, and oral doses of 3, 6, and 25 mg, respectively.

fastest disposition phase was well observed, although estimates of the rate constant showed high variability. The bioavailability was complete after s.c. administration (mean (SD) f<sub>s.c.</sub> = 100.2 (13.4)%), and the maximum plasma concentration was rapidly reached (between 5 and 15 min in the majority of subjects).

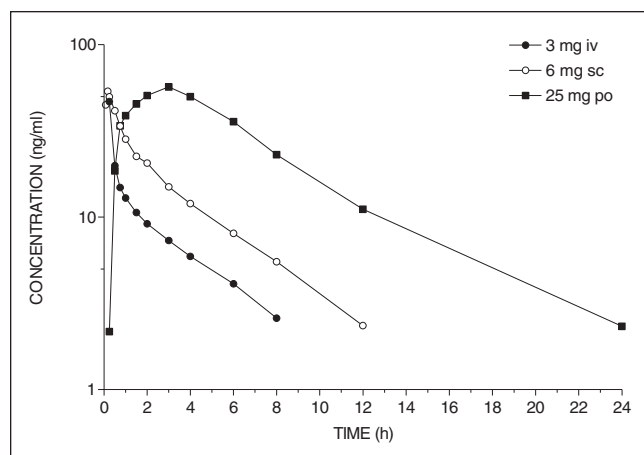


Figure 3. Mean semilogarithmic concentration-time profiles of almotriptan obtained in healthy male volunteers ( $n = 18$ ) after administration of single i.v., subcutaneous, and oral doses of 3, 6, and 25 mg, respectively.

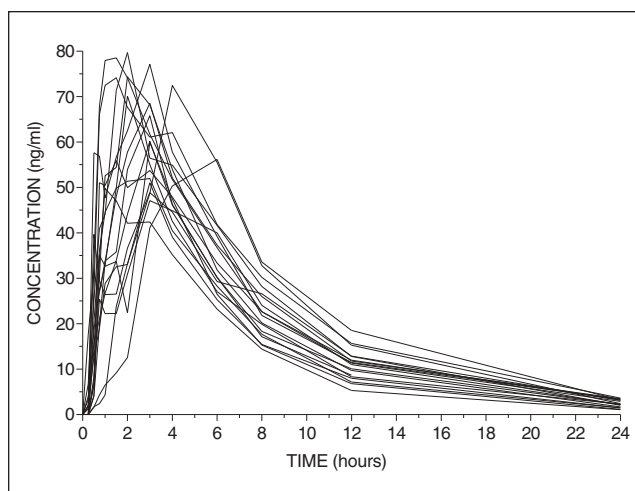


Figure 4. Individual plasma levels of almotriptan found in healthy male volunteers after administration of a single oral dose of 25 mg.

The absolute bioavailability of almotriptan obtained from the plasma AUC values was 69.1% after oral administration, whereas the bioavailability calculated using the percentages of the dose excreted in urine as unchanged compound over 0 to 24 hours, after i.v. and oral administration, was 69.6%.

Maximum plasma concentration was reached between 1.5 and 3 hours after drug intake. Interindividual variability was high during the absorption phase, and some volunteers showed irregular plasma concentration-time profiles or second peaks (Figure 4), giving a high coefficient of variation for  $t_{max}$  of 44%.

The plasma concentration found at 24 hours after oral administration belonged to a kinetic phase different from that observed up to 12 hours. As there were not enough kinetic data to correctly estimate the rate constant associated with this slow terminal phase, the 24-hour concentration values were not used for the calculation of  $\lambda_z$  and AUC. Only values visually assessed to be on the terminal phase up to 12 hours were used. The half-life calculated up to 12 hours represents the plasma elimination half-life of almotriptan ( $t_{1/2}$ ) in healthy volunteers since about 90% of the amount of unchanged drug excreted in urine is recovered in the interval of 0 to 12 hours. The influence of a possible underestimation of the AUC values obtained without considering the kinetic time point of 24 hours was irrelevant in characterizing the oral bioavailability since the differences in  $AUC_{0-24}$ , calculated with or without considering this kinetic time point, were less than 2%. In addition, the percentages of the extrapolated areas from 24 hours to infinity were less than 5%. Furthermore, although this study was not designed to estimate the

elimination rate constant ( $\lambda_z$ ) from the urinary data, the cumulative urinary excretion was used to clarify and ratify the correct estimation of the elimination half-life from plasma by using the concentration time points up to 12 hours. The elimination rate constant was evaluated by the "rate method."<sup>15</sup> According to this method, the rate of drug excretion is plotted versus time, and the elimination rate constant is estimated from the slope of the terminal section of the plot. Since the exact rate of excretion is not known, it is necessary to use the average rates of excretion over short periods of time, which are plotted versus the midpoints of the corresponding time intervals. This approach is only possible when the majority of the drug is excreted through the kidney, as is the case for almotriptan.

The elimination half-life ( $t_{1/2}$ ) from plasma showed low intra- and interindividual variability (coefficients of variation about 5%-10%), with no differences being observed between the three routes of administration. The mean (*SD*) elimination half-life obtained after i.v., s.c., and oral administration was 3.4 (0.4), 3.4 (0.3), and 3.6 (0.4) hours, respectively, whereas they were 3.6, 3.8, and 3.1 hours, respectively, using the mean values of the cumulative urinary excretion.

Mean (*SD*) renal clearance ( $CL_R$ ) was 25 (8), 26 (4), and 26 (5)  $l \cdot h^{-1}$  for the i.v., s.c., and oral routes, respectively, representing up to 65% of total body clearance. No differences were observed in  $V_z$  or  $CL$  between the i.v., s.c., and oral routes of administration; intra- and interindividual variability were low with each of the administration routes (coefficients of variation less than 8% and 15%, respectively). Mean (*SD*) volume of distribution from the i.v., s.c., and oral routes was 195

(40), 191 (35), and 201 (37) l, respectively, while mean total clearance was 40 (8)  $l \cdot h^{-1}$  for all three routes.

No adverse events were reported in the preliminary phase of the study; during the principal phase, 53 adverse events were recorded in 15 volunteers, but most of the reported events were mild and considered unrelated to the study drug. Thirty-one events had a probable or possible causal relationship: headache (12), injection site reaction (8), hot flushes (4), dizziness (3), and pain at injection site, depersonalization, abnormal thinking, and nausea (1 each). Intravenous administration was associated with 15 adverse events in 10 subjects, subcutaneous administration was associated with 25 adverse events in 13 subjects, and oral administration was associated with 10 adverse events in 6 subjects. There were no changes in blood pressure, heart rate, body temperature, or ECGs that were considered to be of clinical concern.

## DISCUSSION

Almotriptan is well absorbed after oral administration and shows one of the highest absolute bioavailabilities of the 5-HT<sub>1B/1D</sub> receptor agonist family developed for the symptomatic relief of migraine. The mean absolute oral bioavailability obtained in this study was 69.1%, whereas the values reported for other triptans were as follows: 14% (sumatriptan), 36% to 49% (zolmitriptan), 63% to 74% (naratriptan), 40% (rizatriptan), 50% (eletriptan), and 17.5% to 29.6% frovatriptan.<sup>16-23</sup> The rate of absorption of almotriptan is adequate for the treatment of migraine attacks, with an average of 33% and 70% of the maximum plasma concentration ( $C_{max}$ ) being achieved within 0.5 and 1 hour after dosing, respectively. The large apparent volume of distribution obtained suggests that almotriptan is extensively distributed throughout the body, being consistent with its low plasma protein binding in man (23%-30%, data on file).

Moreover, the CL and  $t_{1/2}$  values obtained indicate that it is rapidly cleared from the body, irrespective of the dose and the route of administration. The primary route of almotriptan elimination is renal clearance (approximately 50%-60% of the total body clearance). Approximately 65% of the i.v. and s.c. dose is excreted unchanged in urine in 24 hours, compared with 45% of the dose after oral administration. Furthermore, nearly 90% of the amount of unchanged drug excreted in urine is recovered between 0 and 12 hours after dosing. The value of renal clearance is approximately 3-fold the value of the glomerular filtration rate ( $7.5 l \cdot h^{-1}$ ), suggesting that almotriptan is eliminated in part by re-

nal tubular secretion. Review of the safety data collected during the study indicate that almotriptan is safe and well tolerated following i.v., s.c., or oral administration.

## REFERENCES

- Ferrari MD, Saxena PR: 5-HT<sub>1</sub> receptors in migraine pathology and treatment. *Eur J Neurol* 1995;2:5-21.
- Cabarrocas X, Salvà M: Pharmacokinetic and metabolic data on almotriptan, a new antimigraine drug. *Cephalalgia* 1997;17(3):421.
- Salvà M, Palacios JM, Martínez-Tobed A: Metabolism of the novel anti-migraine compound almotriptan (LAS 31416) in humans. Paper presented at the 6th European ISSX Meeting, Gothenburg, Sweden, 1997.
- Cabarrocas X, Jansat JM, Ferrer P, Luria X: Pharmacokinetics of almotriptan during and outside a migraine attack: Headache World 2000, London, 3-7 September 2000. *Cephalalgia* 2000;20(4):417.
- Fleishaker JC, Sisson TA, Carel BJ, Azie NE: Pharmacokinetic interaction between verapamil and almotriptan in healthy volunteers. *Clin Pharmacol Ther* 2000;67(5):498-503.
- Fleishaker JC, Ryan KK, Carel BJ, Azie NE: Evaluation of the potential pharmacokinetic interaction between almotriptan and fluoxetine in healthy volunteers. *J Clin Pharmacol* 2001;41(2):217-223.
- Fleishaker JC, Ryan KK, Jansat JM, Carel BJ, Bell DJ, Burke MT, et al: Effect of MAO-A inhibition on the pharmacokinetics of almotriptan, an antimigraine agent in humans. *J Clin Pharmacol* 2001;51(5):437-441.
- Fleishaker JC, Sisson TA, Carel BJ, Azie NE: Lack of pharmacokinetic interaction between the antimigraine compound almotriptan and propranolol in healthy volunteers. *Cephalalgia* 2001;21(1):61-65.
- Keam SJ, Goa KL, Figgitt DP: Almotriptan: a review of its use in migraine. *Drugs* 2002;62(2):387-414.
- Gomeni R, Gomeni C: IGPHEM: interactive graphic package for pharmacokinetic analysis. *Comput Biomed Res* 1978;11(4):345-361.
- Powell MJD: A method for minimizing a sum of squares of nonlinear functions without calculating derivatives. *Comput J* 1964;7:303-330.
- Yamaoka K, Nakagawa T, Uno T: Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J Pharm Biopharm* 1978;6:165-172.
- Allen L, Kimura K, Mackichan J, Ritschel WA: Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology: manual of symbols, equations and definitions in pharmacokinetics. *J Clin Pharmacol* 1982;22:1S-23S.
- Aronson JK, Dengler HJ, Dettli L, Follath F: Standardization of symbols in clinical pharmacology. *Eur J Clin Pharmacol* 1988;35:1-7.
- Swintosky JV: Excretion equations for interpretation of digitoxin. *Nature* 1957;179:98-99.
- Tfelt-Hansen P, De Vries P, Saxena PR: Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs* 2000;60(6):1259-1287.
- Dixon R, Warrander A: The clinical pharmacokinetics of zolmitriptan. *Cephalalgia* 1997;17(suppl. 18):15-20.
- Fuseau E, Baille P, Kempford RD: A study to determine the absolute bioavailability of naratriptan. *Cephalalgia* 1997;17(3):417.

19. Marathe PH, Greene DS, Barbhैया RH: Disposition of [<sup>14</sup>C]avitrriptan in rats and humans. *Drug Metab Dispos* 1997;25(7):881-888.
20. Morgan P, Rance D, James J, Mitchell R, Milton A: Comparative absorption and elimination of eletriptan in rat, dog and human. *Cephalalgia* 1997;17(3):414.
21. Scott AK: Sumatriptan clinical pharmacokinetics. *Clin Pharmacokinet* 1994; 27(5):337-344.
22. Seaber EJ, On N, Dixon RM, Gibbens M, Leavens WJ, Liptrot J, et al: The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). *Br J Clin Pharmacol* 1997;43(6):579-587.
23. Seaber EJ, Peck RW, Smith DA, Allanson J, Heffing NR, van Lier JJ, et al: The absolute bioavailability and effect of food on the pharmacokinetics of zolmitriptan in healthy volunteers. *Br J Clin Pharmacol* 1998;46(5):433-439.