DISPOSITION AND PHARMACOKINETICS OF THE ANTIMIGRAINE DRUG, RIZATRIPTAN, IN HUMANS

KAMLESH P. VYAS, RITA A. HALPIN, LESLIE A. GEER, JOAN D. ELLIS, LIDA LIU, HAIYUNG CHENG, CYNTHIA CHAVEZ-ENG, BOGDAN K. MATUSZEWSKI, SANDOR L. VARGA, ALEXANDER R. GUIBLIN, AND J. D. ROGERS

Department of Drug Metabolism, Merck Research Laboratories, West Point, Pennsylvania

(Received June 28, 1999; accepted October 8, 1999)

ABSTRACT:

The absorption and disposition of rizatriptan (MK-0462, Maxalt™), a selective 5-HT<sub>1B/1D</sub> receptor agonist used in the treatment of migraine headaches, was investigated in humans. In a two-period, single i.v. (3 mg, 30-min infusion), and single oral (10 mg) dose study with [<sup>14</sup>C]rizatriptan in six healthy human males, total recovery of radioactivity was approximately 94%, with unchanged rizatriptan and its metabolites being excreted mainly in the urine (89% i.v. dose, 82% p.o. dose). Approximately 26 and 14% of i.v. and oral rizatriptan doses, respectively, were excreted in urine as intact parent drug. In a second, high-dose study (60 mg p.o.), five metabolites excreted into urine were identified using liquid chromatography-tandem mass spectrometry and NMR methods. They were triazolomethyl-indole-3-acetic acid, rizatriptan-N<sup>10</sup>-oxide, 6-hydroxy-rizatriptan, 6-hydroxy-rizatriptan sulfate, and N,N-dimethyl-rizatriptan. Urinary excretion of triazolomethyl-indole-3-acetic acid after i.v. and oral administrations of rizatriptan accounted for 35 and 51% of the dose, respectively, whereas the corresponding values for rizatriptan-N<sup>10</sup>-oxide were 4 and 2% of the dose. Plasma clearance (CL) and renal clearance (CL<sub>r</sub>) were 1325 and 349 ml/min, respectively, after i.v. administration. A similar CL<sub>r</sub> value was obtained after oral administration (396 ml/min). The primary route of rizatriptan elimination occurred via nonrenal route(s) (i.e., metabolism) because the CL<sub>r</sub> of rizatriptan accounted for 25% of total CL. Furthermore, the CL<sub>r</sub> was higher than normal glomerular filtration rate (~130 ml/min), indicating that this compound was actively secreted by renal tubules. The absorption of rizatriptan was approximately 90%, but it experienced a moderate first-pass effect, resulting in a bioavailability estimate of 47%.

An estimated 23 million Americans suffer from migraine headaches, which frequently impair their ability to carry out normal daily activities. Symptoms of migraine usually last between 4 and 72 h, and include intense one-sided or bilateral throbbing headache, and can also include nausea, photophobia, and/or phonophobia. Migraine is thought to be caused by neurogenic vascular and inflammatory mechanisms(s). Recently, successful treatment of migraine has been achieved by administration of 5-HT<sub>1B/1D</sub> agonists (reviewed in Saxena and Ferrari, 1989). Structure-activity relationship studies on the 5-HT<sub>1B/1D</sub> receptor (Glennon et al., 1991; Dechant and Clissold, 1989; ena and Ferrari, 1989). Structure-activity relationship studies on the 5-HT<sub>1B/1D</sub> receptor agonist used in the treatment of migraine headaches, was investigated in humans. In a two-period, single i.v. (3 mg, 30-min infusion), and single oral (10 mg) dose study with [<sup>14</sup>C]rizatriptan in six healthy human males, total recovery of radioactivity was approximately 94%, with unchanged rizatriptan and its metabolites being excreted mainly in the urine (89% i.v. dose, 82% p.o. dose). Approximately 26 and 14% of i.v. and oral rizatriptan doses, respectively, were excreted in urine as intact parent drug. In a second, high-dose study (60 mg p.o.), five metabolites excreted into urine were identified using liquid chromatography-tandem mass spectrometry and NMR methods. They were triazolomethyl-indole-3-acetic acid, rizatriptan-N<sup>10</sup>-oxide, 6-hydroxy-rizatriptan, 6-hydroxy-rizatriptan sulfate, and N,N-dimethyl-rizatriptan. Urinary excretion of triazolomethyl-indole-3-acetic acid after i.v. and oral administrations of rizatriptan accounted for 35 and 51% of the dose, respectively, whereas the corresponding values for rizatriptan-N<sup>10</sup>-oxide were 4 and 2% of the dose. Plasma clearance (CL) and renal clearance (CL<sub>r</sub>) were 1325 and 349 ml/min, respectively, after i.v. administration. A similar CL<sub>r</sub> value was obtained after oral administration (396 ml/min). The primary route of rizatriptan elimination occurred via nonrenal route(s) (i.e., metabolism) because the CL<sub>r</sub> of rizatriptan accounted for 25% of total CL. Furthermore, the CL<sub>r</sub> was higher than normal glomerular filtration rate (~130 ml/min), indicating that this compound was actively secreted by renal tubules. The absorption of rizatriptan was approximately 90%, but it experienced a moderate first-pass effect, resulting in a bioavailability estimate of 47%.

The objectives of the present studies, which were carried out in healthy male subjects, were as follows: 1) to determine the primary route of excretion of [<sup>14</sup>C]rizatriptan after i.v. and oral administration; 2) to establish the metabolic pathways of rizatriptan after i.v. and oral dosing; and 3) to determine the preliminary pharmacokinetic parameters of rizatriptan in humans.

Experimental Procedures

Materials. [<sup>14</sup>C]Rizatriptan was synthesized as the benzoate salt (radiochemical purity >99%) by the Labeled Compound Synthesis Group (Merck Research Laboratories, Rahway, NJ) and was formulated by the Pharmaceutical Research and Development Department (West Point, PA). Reference standards of rizatriptan, rizatriptan metabolites, and the N,N-diethyl-analog of rizatriptan (internal standard) were synthesized by the Medicinal Chemistry Department (Terlings Park, England). The solid-phase extraction cartridges used to isolate urinary metabolites were purchased from J. T. Baker (Phillips-
burg, NJ). All other reagents were analytical grade and were purchased from Fisher Scientific (Pittsburgh, PA).

\textbf{[14C]Rizatriptan Study}. An open, two-period, crossover single i.v. and single oral dose study was carried out in six healthy males to investigate the metabolism, excretion, and pharmacokinetics of [14C]rizatriptan. In the first period, each subject (fasted overnight) received an i.v. infusion of [14C]rizatriptan (3 mg, 75 μCi) over 30 min, and in the second period (at least 2 weeks later), each subject received an oral dose of [14C]rizatriptan (10 mg, 75 μCi). In both study periods, blood, urine, and feces were collected from each subject for 5 days postdose, and samples were stored at −20°C until analyzed. No other medications were taken by the subjects within the period from 14 days before the start of the study to completion of the study.

\textbf{Rizatriptan Study}. Six healthy male subjects were given a single oral dose of unlabeled rizatriptan (60 mg) as part of a single rising dose safety and tolerability study. Urine samples were collected, pooled (0–24 h), stored at −20°C, and used for metabolite isolation and identification.

\textbf{Rizatriptan Assay}. The rizatriptan assay was based on the method developed by McLoughlin and coworkers (1996). Liquid chromatography-tandem mass spectrometry (LC-MS/MS)\(^1\) was performed on a Sciex API III triple quadrupole mass spectrometer (Thornhill, Ontario, Canada) and a Hewlett Packard 1050 HPLC pump equipped with a Spherisorb CN column (4.6 × 250 mm, 5 μm; Thomson Instrument Co., Springfield, VA). Isocratic elution of the mobile phase was carried out with a 54:4:42 mixture of acetonitrile/methanol/trifluoroacetic acid (TFA), at a flow rate of 1 ml/min.

The nebulizer probe was set at 500°C, with the nebulizing gas pressure and auxiliary flow set at 80 p.s.i. and 2.0 liters/min, respectively. The orifice potential was set at 45V. Detection of rizatriptan was carried out by multiple reaction monitoring, whereby the first quadrupole (Q1) transmitted the [M+H]\(^+\) ions of rizatriptan at m/z 270, and the internal standard (an N,N-diethyl analog of rizatriptan) at m/z 324. After collision-induced dissociation (CID) of the [M+H]\(^+\) ions in the second quadrupole (Q2), product ions of m/z 201 and 251 were selected in the third quadrupole (Q3) for rizatriptan and internal standard, respectively.

\textbf{Radioactivity Assay}. Sample work-up before measurements of radioactivity from the [14C]rizatriptan study included centrifugation of plasma and urine samples, followed by combination of an aliquot (0.5–1.0 ml) of the supernatant with scintillation cocktail (15 ml) in polyethylene vials for scintillation counting. Feces were thawed overnight at room temperature, water was added, samples were homogenized (Omni Mixer homogenizer; Omni International, Inc., Gainesville, VA), aliquots (2 × 1 g) were transferred to combustion cups, allowed to dry overnight, and, finally, combusted in a tissue oxidizer (Packard Model B360) and counted for radioactivity. Radioactivity measurements were carried out with a Beckman LS5000CE liquid scintillation spectrometer.

\textbf{Metabolite Profiles and Identification from [14C]Rizatriptan Study. Sample treatment}. For LC-MS/MS analysis and quantitative radiocromatography of metabolites, an aliquot of urine (2 ml), was adjusted to pH 4 by the addition of glacial acetic acid and was applied to a solid-phase cartridge (strong cation exchange, SCX/SPE). The SCX/SPE cartridge was preconditioned sequentially with two column volumes each of methanol, water, and sodium acetate (0.01 N, pH 5.0). The sample was loaded onto the cartridge and washed with water (2 × 1 ml) and finally with methanol (2 × 1 ml). Drug-related materials were eluted with ammonium hydroxide in methanol (3.5%, 4 × 1 ml). The eluate was evaporated to dryness under nitrogen (44°C), and the residue was stored at −20°C until analyzed.

\textbf{Radiochromatography}. Radiocromatography was carried out on a Zorbax RX-C4 column (4.6 × 250 mm), which was eluted at a flow rate of 1 ml/min with a mobile phase of 0.1% aqueous TFA (solvent A) and methanol (solvent B). The following gradient was used: 85% A/15% B for 10 min, increasing the organic content at 1%/min to 30% B, and remaining at this composition for an additional 15 min for a total run time of 40 min. The effluent was monitored by UV (224 nm) and by an inline radiocromatographic detector (Ramona 5-LS, Raytest Istopenmessgerate GmbH, Straubing, Germany) using a 3 ml/min flow rate for the scintillation cocktail, resulting in an overall flow rate of 4 ml/min through the radiochemical detector. Radioactive peaks were characterized based on LC-MS/MS and NMR analyses of metabolites isolated from human urine after the unlabeled rizatriptan study and comparison with authentic standards.

\textbf{LC-MS/MS}. The dried SCX solid phase-extracted sample was dissolved in water (500 μl, assisted by sonication) and was centrifuged (5 min at 13,000 rpm) before analysis of the supernatant. Chromatography for LC-MS/MS analyses was conducted using a Zorbax RX-C18 column (2.1 × 150 mm) with a mobile phase of 0.1% aqueous TFA (solvent A) and acetonitrile (solvent B) at a flow rate of 200 μl/min. Gradient elution commenced at 95% A/5% B, with solvent B increasing 1%/min to 20%, which was held for 5 min. The column effluent entered a Sciex API III triple-stage quadrupole mass spectrometer via a Sciex heated nebulizer probe. The effluent stream was split such that 40 μl/min was directed to the mass spectrometer. Metabolites were detected on the basis of their [M+H]\(^+\) ions, which were subjected to CID to generate product ion mass spectra. Finally, the identities of urinary metabolites of rizatriptan were confirmed, in part, by comparison of their LC-MS/MS characteristics with those of authentic standards prepared by synthesis.

\textbf{Isolation and Metabolite Identification from Rizatriptan Study. Sample treatment and metabolite purification}. Before HPLC and LC-MS/MS analyses, we...
urine samples (0–24 h) from six subjects who had been dosed with rizatriptan (60 mg p.o.) were pooled. The resulting sample was loaded on a low pressure, anion exchange column (28 × 270 mm, flow rate of 2 ml/min), from which phosphate buffers (5–250 mM) were used to elute the acidic metabolites. The basic and neutral metabolites passing through the column subsequently were concentrated on cation-exchange cartridges (3 ml, Baker Bond aromatic sulfonic acid; J. T. Baker Chemical Co., Phillipsburg, NJ), and eluted with NH₄OH (3.5% in MeOH). All of the metabolites were purified further by reversed phase HPLC, which consisted of a Rainin pump and a semi preparative C₈ column (Zorbax, 5 μm, 9.4 × 250 mm). The mobile phase consisted of 0.1% aqueous TFA (solvent A) and methanol (solvent B), and was eluted at 3.5 ml/min with the following gradient system: 0 to 15 min, 90% A; 15 to 40 min, 90% A; 40 to 55 min, 70% A; 55.1 to 60 min, 90% A. The analytes were monitored by UV absorption (λ = 224 and 282 nm, Varian 9060 Polychrom detector).

1 H-NMR analysis. In addition to analysis by HPLC and mass spectrometry, metabolites of rizatriptan were characterized by NMR spectroscopy and comparison with authentic standards. Proton NMR spectra were recorded at either 400 or 500 MHz using either a Varian VXR-400S or Varian VXR-500S spectrometer. Methanol-d₄ and deuterium oxide (D₂O) were used as solvents. Chemical shifts are reported in ppm (δ) and referenced to internal tetramethylsilane in CD₃OD and to trimethylsilyl propionic acid in D₂O.

Pharmacokinetic Calculations. The area under the plasma concentration-time profile from time zero to time infinity (AUC), CL, steady-state volume of distribution (Vss), and plasma terminal half-life (T 1/2 ) were calculated by using the LAGRAN computer program (Rocci and Jusko, 1983). CLr was calculated as the ratio of the amount of rizatriptan excreted into urine to the AUC of rizatriptan. The bioavailability (F) of rizatriptan was calculated as the ratio of the dose-normalized AUC after oral administration (10 mg) to that after i.v. administration (3 mg) of rizatriptan.

Results

Absorption and Excretion. After both i.v. (3 mg, 75 μCi) and oral (10 mg, 75 μCi) dosing of [14C]rizatriptan to six healthy male subjects, the major pathway of excretion of total radioactivity (Table 1) was via the urine (89.5 and 82.4% of the dose, respectively), whereas minor amounts were excreted through the feces (4.4 and 15.2% of the dose, respectively). The majority of radioactivity after either route of administration was excreted in the first 24 h. The relative urinary excretion of total radioactivity indicated that the drug was well absorbed (~90%). The mean concentrations of total radioactivity and rizatriptan in plasma as a function of time (0–12 h) are shown in Fig. 2. The profiles indicate that: 1) [14C]rizatriptan was absorbed rapidly from the gastrointestinal tract after oral administration (Tmax = 1.8 h); 2) after reaching the Cmax, total radioactivity and rizatriptan concentrations decreased with time in a parallel fashion; and 3) the majority of the [14C]rizatriptan was eliminated from the plasma by 12 h postdose after both routes of administration.

A representative urinary radiochromatographic profile after admin-

![Fig. 2. Mean concentrations of total radioactivity and rizatriptan in plasma after i.v. (3 mg) and oral (10 mg) administration of [14C]rizatriptan. Plasma samples were obtained at time points of 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, and 12 h.](image)

![Fig. 3. A representative radiochromatographic profile of urinary radioactivity from subject no. 005 (concentrated 0- to 24-h urine sample) after a 3-mg i.v. dose of [14C]rizatriptan. Major radioactive peaks were observed at 23 min (peak 1), 28 min (peak 2), and 33 min (peak 3).](image)
### TABLE 2
Pharmacokinetic parameters following intravenous (3 mg, A) and oral (10 mg, B) administration of \(^{14}C\)rizatriptan to humans

<table>
<thead>
<tr>
<th></th>
<th>Rizatriptan</th>
<th>Radioactivity</th>
<th>AUC Ratio(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>CL (\text{Vss})</td>
<td>(t_{1/2})</td>
</tr>
<tr>
<td></td>
<td>(\text{ng/hr/ml})</td>
<td>(\text{mL/min})</td>
<td>(\text{L})</td>
</tr>
<tr>
<td>A i.v.</td>
<td>Mean</td>
<td>38.1</td>
<td>1325</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>5.4</td>
<td>195</td>
</tr>
<tr>
<td>B Oral</td>
<td>Mean</td>
<td>59.8</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>23.6</td>
<td>9.8</td>
</tr>
</tbody>
</table>

\(^a\) Calculated as AUC of rizatriptan/AUC of \(^{14}C\) radioactivity.

### TABLE 3
Product ion mass spectrometric data for metabolites of rizatriptan isolated from human urine (0–24 h) after an oral dose (60 mg) of the drug

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Ions Observed (m/z values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolomethyl-Indole-3-Acetic Acid</td>
<td>257, 188*, 160, 143</td>
</tr>
<tr>
<td>Rizatriptan-(N^{\text{10}})-Oxide</td>
<td>286, 268, 241, 225, 217*, 172*, 156, 144, 58</td>
</tr>
<tr>
<td>(N^{\text{10}})-Monodesmethyl-Rizatriptan</td>
<td>256, 187*, 170, 158, 144</td>
</tr>
<tr>
<td>6-Hydroxy-Rizatriptan</td>
<td>286, 217, 172, 58*</td>
</tr>
<tr>
<td>6-Hydroxy-Rizatriptan Sulfate</td>
<td>366, 286, 217*, 174, 58</td>
</tr>
</tbody>
</table>

* Denotes base peak in the spectrum.
of CL and CLr were 1325 and 349 ml/min, respectively, after the i.v.
rizatriptan indicated that the drug was 47% bioavailable. Mean values
administration, respectively. Comparison of dose-normalized AUC of
ml. Therefore, based on AUC ratios, unchanged rizatriptan in plasma
59.8 ng
z
ng Eq
z
ng h/ml and 333.8 ng Eq
h/ml. Therefore, based on AUC ratios, unchanged rizatriptan in plasma
accounted for 30 and 17% of drug-related material after i.v. and oral
administration, respectively. Comparison of dose-normalized AUC of
rizatriptan indicated that the drug was 47% bioavailable. Mean values of
CL and CLr were 1325 and 349 ml/min, respectively, after the i.v.
dose. A similar mean CLr value was obtained after the oral dose (396
ml/min). Therefore, the CLr of rizatriptan was higher than normal
glomerular filtration rate (130 ml/min) and accounted for approximately
25% of CL, indicating that the primary route of rizatriptan
elimination is via nonrenal route(s) and that this compound is actively
metabolized at ASPET Journals on September 30, 2017 dmd.aspetjournals.org Downloaded from

Metabolism. After oral administration of unlabeled rizatriptan (60
mg) to healthy subjects, five metabolites of the drug that were excreted
in urine were identified by comparing their LC-MS/MS and NMR
classifications to those of authentic standards. The product ion
spectra of the five urinary metabolites of rizatriptan are presented in
Table 3. CID of the [M+H]+ parent ion of the triazolomethyl-indole-3-acetic acid metabolite (m/z 286) also was accompanied by the loss of the triazolomethyl moiety to afford the product ion at m/z 217, whereas tandem mass spectrometry of 6-hydroxy-rizatriptan ([M+H]+, m/z 286) yielded a product ion at m/z 58, which corresponds formally to protonated trimethylamine and indicates that oxidation did not occur on the alkyl nitrogen atom. The other prominent fragment ion (m/z 217) in the spectrum of the 6-hydroxy metabolite corresponds to loss of the triazolomethyl moiety; taken together with the NMR data (see below), the site of oxidation in this metabolite was determined to be at the 6-position of the indole moiety. The 6-hydroxy-rizatriptan sulfate conjugate yielded an [M+H]+ ion at m/z 366 which, on CID, afforded a product ion at m/z 286 through the loss of the neutral species SO3 (80 Da). The parent ion of N10-monodesmethyl-rizatriptan ([M+H]+, m/z 256) gave rise to a fragment ion at m/z 225, which corresponds to the loss of the N-methyl moiety.

Urinary metabolites also were characterized by 1H-NMR analysis (Table 4). The triazolomethyl-indole-3-acetic acid metabolite spectrum showed no signals corresponding to the H-9 methylene protons or the N,N-dimethyl protons (H-11 and H-12). In addition, the H-8 methylene protons were shifted downfield compared with the other metabolites, which was due to the influence of the neighboring carboxylic moiety. The spectrum of the rizatriptan-N10-oxide metabolite showed that H-9, H-11, and H-12 protons were shifted downfield compared with the other metabolites, as a result of being located alpha to the N-oxide moiety. The H-6 proton signal was absent in the spectra of both the 6-hydroxy-rizatriptan and 6-hydroxy-rizatriptan sulfate metabolites. NMR analysis of the N10-monodesmethyl-rizatriptan metabolite in urine was not possible due to very low levels excreted by that route.

To relate back to the radioactivity profile data (Fig. 3), peaks 1 to
3 were identified as parent drug, rizatriptan-N10-oxide, and triazolomethyl-indole-3-acetic acid, respectively. A scheme illustrating the proposed metabolic fate of rizatriptan in humans is shown in Fig. 4.

### Table 4

<table>
<thead>
<tr>
<th>Proton(s)</th>
<th>Triazolomethyl-indole-3-acetic acid</th>
<th>Rizatriptan-N10-oxide</th>
<th>6-Hydroxy-rizatriptan</th>
<th>6-Hydroxy-rizatriptan sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-2</td>
<td>7.19 (s, 1H)</td>
<td>7.25 (s, 1H)</td>
<td>7.22 (s, 1H)</td>
<td>7.39 (s, 1H)</td>
</tr>
<tr>
<td>H-4</td>
<td>7.63 (d, J = 1 Hz, 1H)</td>
<td>7.66 (broad, 1H)</td>
<td>7.62 (s, 1H)</td>
<td>7.7 (s, 1H)</td>
</tr>
<tr>
<td>H-6</td>
<td>7.09 (dd, J = 1 &amp; 8 Hz, 1H)</td>
<td>7.14 (d, J = 8 Hz, 1H)</td>
<td>N/S’</td>
<td>N/S’</td>
</tr>
<tr>
<td>H-7</td>
<td>7.33 (d, J = 8 Hz, 1H)</td>
<td>7.38 (d, J = 8 Hz, 1H)</td>
<td>7.02 (s, 1H)</td>
<td>7.57 (s, 1H)</td>
</tr>
<tr>
<td>H-8</td>
<td>3.67 (s, 2H)</td>
<td>3.38 (m, 2H)</td>
<td>3.22 (t, J = 7 Hz, 2H)</td>
<td>3.26 (t, J = 7 Hz, 2H)</td>
</tr>
<tr>
<td>H-9</td>
<td>N/S’</td>
<td>3.92 (m, 2H)</td>
<td>3.47 (t, J = 7 Hz, 2H)</td>
<td>3.51 (t, J = 7 Hz, 2H)</td>
</tr>
<tr>
<td>H-11,-12</td>
<td>N/S’</td>
<td>3.58 (s, 6H)</td>
<td>2.91 (s, 6H)</td>
<td>2.92 (s, 6H)</td>
</tr>
<tr>
<td>H-13</td>
<td>5.47 (s, 2H)</td>
<td>5.48 (s, 2H)</td>
<td>5.51 (s, 2H)</td>
<td>5.61 (s, 2H)</td>
</tr>
<tr>
<td>H-16</td>
<td>7.97 (s, 1H)</td>
<td>7.98 (s, 1H)</td>
<td>8.02 (s, 1H)</td>
<td>8.04 (s, 1H)</td>
</tr>
<tr>
<td>H-18</td>
<td>8.45 (s, 1H)</td>
<td>8.49 (s, 1H)</td>
<td>8.49 (s, 1H)</td>
<td>8.57 (s, 1H)</td>
</tr>
</tbody>
</table>

* No NMR data available for the N10-monodesmethyl-rizatriptan metabolite due to very low levels excreted into urine.
* NMR solvent was CD3OD.
* NMR solvent was D2O.
* Signal splitting patterns: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet.
* No signal detected.
Discussion

The absorption, metabolism, and elimination of rizatriptan after oral and i.v. administration were examined in healthy humans. Rizatriptan was well absorbed (~90%) from the gastrointestinal tract, but was 47% bioavailable, indicating that the drug was subjected to a significant first pass metabolism. The metabolic pathways of rizatriptan included oxidative deamination, aromatic hydroxylation followed by sulfation, N-oxidation, and N-demethylation. Among these, the oxidative deamination reaction to generate the triazolomethyl-indole-3-acetic acid metabolite was the most prominent, as 35 and 51% of i.v. and oral doses, respectively, was excreted into the urine as this metabolite. Rizatriptan and its metabolites were excreted mainly in urine; in humans, only minor amounts were found in the stool. That metabolism was the primary pathway of rizatriptan elimination was evident from the observation that the CLr (349 ml/min) of rizatriptan accounted for only 25% of the total clearance. Both glomerular filtration and tubular secretion contributed to the renal elimination of intact rizatriptan.

Analysis of urine (0–24 h) from a quantitative, radiolabeled [14C]rizatriptan study showed the presence of parent drug, triazolomethyl-indole-3-acetic acid, and rizatriptan-N10-oxide. The percentage of the dose excreted in urine after i.v. (3-mg) and oral (10-mg) administration of [14C]rizatriptan are indicated. Analysis of urine (0–24 h) from a high oral dose (60 mg) study with unlabeled rizatriptan showed the presence of parent drug, triazolomethyl-indole-3-acetic acid, rizatriptan-N10-oxide, 6-hydroxy-rizatriptan, 6-hydroxy-rizatriptan sulfate, and N10-monodesmethyl-rizatriptan.

Fig. 4. Proposed pathways for the metabolism of rizatriptan in humans.

Triazolomethyl-Indole-3-Acetic Acid

Rizatriptan

N10-Monodesmethyl-Rizatriptan

6-Hydroxy-Rizatriptan

6-Hydroxy-Rizatriptan Sulfate
Because women are the primary patient population for migraine headaches, subsequent studies evaluated the pharmacokinetics of rizatriptan in healthy women (Lee et al., 1998, 1999). The pharmacokinetics of rizatriptan are very similar for men and women with regard to bioavailability, urinary excretion, and half-life. The CL of rizatriptan is approximately 30% greater in men, but this is not of clinical significance.

Clinically, the results of this study define a number of important characteristics of the profile of rizatriptan. Thus, in comparison to sumatriptan (Fig. 1), the drug is rapidly absorbed ($T_{\text{max}} = 1.4$ versus 2.5 h; Dechant and Clissold, 1992; Sciberras et al., 1997) and shows a 3.5-fold greater oral bioavailability (47 versus 14%). Like sumatriptan, the principal metabolite of rizatriptan is the indole-3-acetic acid derivative generated via oxidative deamination, which is catalyzed by monoamine oxidase A (Dixon et al., 1994; Slaughter et al., 1996). Thus, inhibitors of cytochrome P-450 isoforms would be anticipated to have minimal effects on the plasma profile of rizatriptan. Lastly, both renal and nonrenal routes of elimination of rizatriptan are important, suggesting that neither renal dysfunction nor hepatic impairment would alter the plasma concentration profile of rizatriptan to a clinically notable degree.

Acknowledgments. We thank Dr. D. Slaughter and D. Walsh for carrying out confirmatory mass spectrometric analyses during the radiolabeled rizatriptan study, and Dr. K. M. Schultz for her assistance in preparing this manuscript. The Clinical Pharmacology Group, including A. Freeman, and the Robert Wood Johnson Medical School Clinical Research Center, including Dr. J. Seibold, are acknowledged for conducting the clinical aspects of this study.

References


