DISPOSITION OF [14C]AVITRIPTAN IN RATS AND HUMANS

P. H. MARATHE, D. S. GREENE, AND R. H. BARBHAIYA

Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute

(Received December 3, 1996; accepted March 17, 1997)

ABSTRACT:

Avitriptan is a new 5-HT1-like agonist with abortive antimigraine properties. The study was conducted to characterize the pharmacokinetics, absolute bioavailability, and disposition of avitriptan after intravenous (iv) and oral administrations of [14C]avitriptan in rats and oral administration of [14C]avitriptan in humans. The doses used were 20 mg/kg iv and oral in the rat, 10 mg iv in humans, and 50 mg oral in humans. The drug was rapidly absorbed after oral administration, with peak plasma concentrations occurring at 0.5 hr postdose. Absolute bioavailability was 19.3% in rats and 17.2% in humans. Renal excretion was a minor route of elimination in both species, with the majority of the dose being excreted in the feces. After a single oral dose, urinary excretion accounted for 10% of the administered dose in rats and 18% of the administered dose in humans, with the remainder excreted in the feces. Extensive biliary excretion was observed in rats. Avitriptan was extensively metabolized after oral administration, with the unchanged drug accounting for 32% and 22% of the total radioactivity in plasma in rats and humans, respectively. Plasma terminal elimination half-life was −1 hr in rats and −5 hr in humans. The drug was extensively distributed in rat tissues, with a tendency to accumulate in the pigmented tissues of the eye.

Avitriptan (3-[3-[4-(5-methoxy-4-pyrimidinyl)-1-piperazinyl]propyl]-N-methyl-1H-indole-5-methanesulfonamide) is a new indolypiperazine compound with abortive antimigraine properties. It is structurally and metabolically distinct from the antimigraine drug sumatriptan. Avitriptan interacts with vascular 5-HT1-like receptors to constrict cerebral blood vessels and reduce carotid artery blood flow by closing AV anastomoses (AV shunts) that have been implicated in causing migraine pain (1, 2). In a variety of in vitro preparations that assess 5-HT1-like interactions, avitriptan demonstrates greater potency and comparable efficacy to sumatriptan, and is devoid of activity in vascular preparations that reflect interactions at the peripheral vascular 5-HT1 receptor (3, 4). Avitriptan is structurally and metabolically different from sumatriptan. Sumatriptan undergoes oxidation to an indole acetic acid metabolite mediated by monoamine oxidase. Avitriptan is a cytochrome P450 substrate and undergoes hydroxylation, followed by conjugation at several sites in the molecule. The anticipated oral therapeutic dose of avitriptan in humans is in the range of 50–150 mg.

The SD rat has been used as one of the primary species for toxicological evaluation of avitriptan. Single dose and multiple dose pharmacokinetics after oral administration have been evaluated in the rat. The exposure to avitriptan as measured by Cmax and AUC increased more than proportionately to dose in the dose range of 12–400 mg/kg/day in rats (5).

The objective of this study was to assess the pharmacokinetics, absolute bioavailability, and disposition of avitriptan; its routes and extent of excretion; and comparison of disposition in rats and humans after oral and iv administrations of radiolabeled avitriptan.

Materials and Methods

Chemicals. Radiolabeled [14C]avitriptan as a fumarate salt, labeled in the piperazine ring (fig. 1), had a radiochemical purity of 98% and specific activity of 25.6 μCi/mg. Radiolabeled avitriptan was synthesized at Bristol-Myers Squibb Pharmaceutical Research Institute (Syracuse, NY). Unlabeled avitriptan as a fumarate salt (purity of 96.5%) was obtained from Bristol-Myers Squibb Pharmaceutical Research Institute (New Brunswick, NJ).

Animal Studies. Male SD and LE rats (200–350 g) obtained from Charles River, Inc. (Wilmington, MA) were used in this study. The animals were acclimated for 3 days before used in the study. The animals were fed with Purina brand rodent Chow. The animals were housed in stainless-steel cages before dosing. After dosing, they were housed in individual stainless-steel metabolism cages. Food was withdrawn about 18 hr before dosing, but the animals had free access to water at all times. Food was provided again at 4 hr postdosing. Rats used for serial blood collection had catheters implanted in the jugular vein (for oral dosing) or both in the jugular vein and carotid artery (iv dosing). Rats used for bile collection had catheters placed in the bile duct. After completion of study procedures, the rats were killed by an overdose of metofane or by cardiac puncture exsanguination under light metofane anesthesia.

The dosing solutions were prepared in 0.9% sodium chloride. The oral dosing solution was administered by gavage using a stainless-steel feeding needle. Each rat received ~1 ml of the oral dosing solution (5 mg/ml, 10 μCi/ml). The iv dose was administered as a bolus at a rate of 1–2 ml/min in the dorsal penis vein under light metofane anesthesia. Each rat received ~0.5 ml of the iv dosing solution (10 mg/ml, 20 μCi/ml). The ia dose was administered through a catheter in the carotid artery as a 5-min infusion. Each rat received about 0.5 ml volume of the ia injection (10 mg/ml, 20 μCi/ml).

In the iv/oral disposition study, six SD rats were administered 20 mg/kg (40 μCi/kg) of [14C]avitriptan (as free base) as an oral solution, and six other rats received the same dose by iv injection in the dorsal penis vein. Urine and feces were collected from each rat over 168 hr postdose. Aliquots of urine, feces, and carcass were analyzed for total radioactivity. Eight additional SD rats were used for serial blood collection. Four of these rats were administered 20 mg/kg (40 μCi/kg) of [14C]avitriptan as an oral solution, and four rats received the
same dose by ia injection into the carotid artery. The ia administration of the
drug in the rat was chosen to allow iv sampling of blood from the jugular vein
for pharmacokinetic measurements. The ia dose was infused for 5 min. Blood
samples were collected from the jugular vein for 24 hr postdose. Plasma was
separated and analyzed for total radioactivity and unchanged avitriptan. For
biliary excretion study, two SD rats were administered 10 mg/kg (36 μCi/kg)
of [14C]avitriptan as an oral solution, and two rats received the same dose as
a bolus in the dorsal penis vein. Bile was collected through a catheter in the bile
duct at hourly intervals up to 12 hr postdose. Urine was collected from 0 to 6
and from 6 to 12 hr postdose. Bile and urine samples were analyzed for total
radioactivity.

Urine and feces were collected at 0–6, 6–24, 24–48, 48–72, 72–96, 96–120, 120–144, and 144–168 hr postdose. After each collection interval, the metabolism cages were washed with water and the cagewashes were also
analyzed for radioactivity. Serial blood samples (500 μl each) were collected
at 5, 10, and 30 min and at 1, 2, 4, 6, 8, and 24 hr after ia dose, and at 10 and
30 min at and 1, 2, 3, 4, 6, 8, and 24 hr after oral dose. Blood samples were
collected through a catheter in the jugular vein that was flushed with hepa-
rinized saline after each collection. The samples were transferred to labeled
microtainer tubes containing EDTA as anticoagulant. After gentle mixing, the
blood was placed in chipped ice and centrifuged to obtain plasma. A 50-μl
aliquot of each plasma sample was preserved for total radioactivity determi-
nation, and the remaining was used for determination of unchanged avitriptan
by HPLC. Bile was collected from the bile duct-cannulated rats at hourly
intervals up to 12 hr postdose. Urine was also collected from these rats in two
intervals: 0–6 and 6–12 hr postdose. Two additional rats not receiving
[14C]avitriptan were killed to obtain control samples of plasma, urine, feces,
and carcass for determination of background radioactivity and the LLQ.

In the tissue distribution study, 50 SD and 20 LE rats were divided in two
groups. Rats in the first group received 20 mg/kg (40 μCi/kg) of [14C]avitriptan
as an oral solution by gavage, and rats in the second group received the
same dose by iv injection in the dorsal penis vein. Five SD rats dosed orally
were killed at each of the following times postdose: 0.5, 2, 8, 24, and 168 hr.
Similarly, five SD rats dosed intravenously were killed at 0.08, 2, 8, 24, and
168 hr postdose. Five LE rats from each group were killed at 2 hr and the
remaining five at 168 hr postdose. Two of the five rats from each group were
frozen in a mixture of acetone and dry ice. One of these two rats per group was
prepared for whole-body autoradiography, and the other rat was stored frozen
for any repeat analysis. From the remaining three rats, various tissues were
removed for quantitation of radioactivity.

Tissues and fluids from three rats at each collection time were removed for
the determination of radioactivity. Blood was collected by cardiac puncture
while the rat was under anesthesia and was placed in a tube containing
K₃EDTA and mixed. Aliquots of each blood specimen were taken for the
determination of radioactivity, and the remaining blood was used to prepare
plasma. In addition to blood and plasma, the following tissues and fluids were
removed from each rat: adrenal glands, aorta, aqueous humor, blood, bone,
bone marrow, brain, CSF, eye, fat, heart, kidneys, liver, large intestine and
contents, lungs, lymph nodes, muscle, skin, small intestine and contents, spleen,
stomach and contents, pancreas, pituitary gland, prostate, salivary gland,
testes, thymus, thyroid, tongue, trachea, urinary bladder, and vena cava.
Two additional rats not receiving [14C]avitriptan were killed to obtain control
samples of tissues and fluids for determination of background radioactivity and
the LLQ. All study samples and blank specimens were stored at −20°C before
analysis of radioactivity by scintillation counting.

Human Study. The study was conducted as a randomized, single dose,
cross-over design in 12 healthy male subjects. Each subject received 10 mg
avitriptan as an iv solution infused for 30 min and 50 mg of [14C]avitriptan (75
μCi) as an oral solution in water. The two treatments were separated by at least
a 2-week washout. Both treatments were administered after a 10-hr fast. The
subjects continued to fast until 4 hr after dosing, at which time they were
served lunch.

The study protocol was approved by the Institutional Review Board and
Radiation Safety Committee at the investigational site. All subjects gave
consent to participate in the study by signing and dating an informed consent
form after the study was completely explained to each person.

All subjects were in good health based on medical history, prestudy physical
examinations, and clinical laboratory testing. The mean ± standard deviation
age of all subjects who entered the study was 29 ± 5.2 years, with a range of
21–38 years.

Serial blood samples were collected at predose, 0.25, 0.5, 0.75, 1, 1.5, 2.5,
3, 4, 6, 8, 10, 12, 24, 36, and 48 hr postoral dose and at predose, 10, 20, 30,
35, and 45 min and at 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hr from
the start of the iv infusion. Immediately after collection, each blood sample was
gently inverted a few times for complete mixing with the anticoagulant
(K₃EDTA) and placed in chipped ice. Within 1 hr of collection, a 0.5-ml
aliquot of blood taken after the oral treatment was separated and stored frozen
for total radioactivity measurement. The remainder of the blood sample was
centrifuged appropriately to obtain plasma. A 0.5-ml aliquot of the plasma
sample was also stored for total radioactivity measurement, and the remain-
der was stored frozen for analysis of unchanged avitriptan. All blood samples
collected from the iv treatment were centrifuged in their entirety, and plasma
was stored frozen for analysis of unchanged avitriptan. All blood samples
consisted of a Waters model 600E pump, a Waters model 715 sample proces-
sor, and a Waters model 486 UV absorbance detector at 287 nm. Data were
acquired using a model 3357 laboratory automation system from Hewlett-Packard. Peak heights were used in the calibration curve and in the calculation of unknown concentrations. The retention times of avitriptan and BMY-46317 were 6.5 and 9 min, respectively. Human plasma samples were assayed by a validated HPLC method with electrochemical detection (5). Spiked QC samples were prepared, before the initiation of the study in control plasma using a reference standard for avitriptan, and stored with the study samples. QC samples were analyzed with study samples to establish stability, assay accuracy, and precision.

The standard curves were linear with correlation coefficients of 0.999. The standard curve range was 10–2000 ng/ml for rat plasma and 1–100 ng/ml for human plasma. The LLOQ for avitriptan was 10 ng/ml in rat plasma and 1 ng/ml in human plasma. During analyses of study samples, the mean observed concentrations of the QC samples were within 15% from nominal values. The between- and within-day variations were within 11%. These results indicated that the assay methods were precise, accurate, and reproducible, and that avitriptan was stable in plasma under sample storage and assay conditions.

Aliquots of plasma (50 μl for rat and 100 μl for human), urine (100 μl for rat and 200 μl for human), and bile (100 μl) samples were accurately pipetted and digested with an appropriate amount of Soluteene-350 (Packard Instrument Company, Meriden, CT). Samples were neutralized with 0.1 ml of a mixture of saturated solution of sodium pyruvate in methanol, glacial acetic acid, and methanol in a 4:3:1 ratio, and mixed with 15 ml of Hionic Fluor (Packard Instrument Company). Feces and carcass were prepared for scintillation counting by homogenization with water. The total sample was weighed before and after adding water, and was homogenized with a Polytron (Brinkmann Instruments, Inc., Westbury, NY). An accurately weighed sample of the homogenate (~200 mg) was digested with 1 ml of Soluteene-350 and bleached with 20% solution of benzoyl peroxide in toluene. Blood samples were also bleached when necessary. Samples were then neutralized and prepared for liquid scintillation counting by the same method used for direct solubilization.

In the rat tissue distribution study, samples of the following tissues were solubilized directly for scintillation counting: adrenal glands, blood, bone marrow, brain, CSF, eyes (for SD rats only), large intestine, large intestinal contents, muscle, plasma, small intestine, small intestinal contents, spleen, stomach contents, aorta, bone, fat, lymph nodes, pancreas, pituitary gland, prostate, salivary gland, thymus, thyroid, tongue, trachea, urinary bladder, vena cava, and testes. The total organ or tissue sample was accurately weighed and digested with an appropriate amount of Soluteene-350. An accurately weighed amount of the digested sample was then bleached if necessary, neutralized, and counted as described before. Aqueous humor was counted directly after mixing with the scintillation cocktail. Rat heart, kidneys, liver, and lungs were prepared for scintillation counting by homogenization with water. Eyes of the LE rats and skin of both SD and LE rats were prepared by oxidation. The tissue sample was accurately weighed, transferred to a combustion cone, and digested with an appropriate amount of Soluene-350 (Packard Instrument Company). The total [\( ^{14} \text{C} \)CO\(_2 \)] was collected for scintillation counting. [\( ^{14} \text{C} \)]Avitriptan standards prepared and combusted along with study samples consistently yielded a mean combustion recovery of >95%.

Total radioactivity was measured with a Packard TriCarb scintillation counter using the external standard method. Each fluid or tissue sample was processed in duplicate and counted 3 times for 10 min each or to a 2% sigma error. Each fecal sample from the human study was processed in multiples of 5, and mean values were used in the calculation of recovery of total radioactivity.

For whole-body autoradiography, the frozen rat carcasses were embedded in a 5% aqueous solution of sodium salt of carboxymethylcellulose. Each frozen block was cut in half with a bandsaw before mounting on a cryostat microtome stage (model PMV-2250; LKB, Gaithersburg, MD). The block was shaved until organs of interest were visible. Lateral sections (40 μm) were cut, taken up on adhesive tape, and left to dry inside the cryostat. Dry sections were then used for apposition autoradiography by exposing them on Kodak Xomat AR film (Eastman Kodak Co., Rochester, NY) for up to 32 days. The exposed film was developed in a Kodak M35A Xomat mechanical film processor.

**Analysis of Radioactivity and Pharmacokinetic Data.** Concentrations of radioactivity were expressed as nanograms of avitriptan per milliliter of fluid or per gram of tissue. Control background specimens were prepared from untreated rats for each type of fluid or tissue. The net cpm were determined as the gross cpm minus the average background cpm for that particular type of sample. Samples having a net cpm less than the minimum acceptable value (determined by a counting error >20%) were considered to contain an amount of radioactivity below the LLQ. Radioactivity in urine, bile, feces, and carcass was expressed as a percentage of the administered dose.

**Pharmacokinetic Analysis.** Plasma concentrations vs. time data for avitriptan were analyzed by noncompartmental methods (6) using SAS programs on a IBM 3083 mainframe computer. Plasma concentration-time profiles for total radioactivity were also analyzed by noncompartmental methods. The terminal log-linear phase of the plasma concentration-time curve was identified by least squares linear regression of data points that yielded a minimum mean square error. The AUC\(_{\text{INF}}\) was determined by a combination of trapezoidal and log-trapezoidal methods plus the extrapolated area. The extrapolated area was determined by dividing the observed concentration at the time of last nonzero plasma concentration by the slope (\( \beta \)) of the terminal log-linear phase. The \( t_{1/2} \) of the terminal log-linear phase was calculated as 0.693 divided by the absolute value of \( \beta \). The peak plasma concentration, \( C_{\text{max}} \), and the time at which \( C_{\text{max}} \) occurred, \( t_{\text{max}} \), were obtained from the observed data. Total clearance (\( CL_{\text{p}} \)) and steady-state volume of distribution (\( V_{\text{ss}} \)) were calculated as:

\[
CL_{\text{p}} = \text{Dose(iv)} / \text{AUC}_{\text{INF}}
\]

and

\[
V_{\text{ss}} = \text{Dose(iv)} \times AUMC/(\text{AUC}_{\text{INF}})^2,
\]

where AUMC is the area under the first moment of plasma concentration vs. time curve. The absolute bioavailability of avitriptan (\( F \)) was estimated from the plasma AUC\(_{\text{INF}}\) data of unchanged avitriptan after parenteral and oral treatments.

**Results**

**Excretion of Radioactivity.** Mean percentage recovery of total radioactivity over 168 hr postdose in urine and feces was summarized in table 1. After iv dosing in rats, 22.2% of total radioactivity was recovered in urine. After oral dosing, the recovery of total radioactivity in urine was lower and amounted to 9.83% of the dose in rats. In the first 6 hr postdose, a mean of 18.6% and 7.98% of the total radioactivity was recovered in urine. After iv dosing, a mean of 18.6% and 7.98% of the total radioactivity was recovered in urine after iv and oral dosings, respectively. Fecal excretion accounted for 70.3% after iv dosing and 85.2% after oral dosing, respectively. The majority of the administered dose was recovered in the first 24 hr postdose. Overall, 93% of the total iv dose and 95% of the total oral dose was excreted up to 168 hr postdose in rats.

Biliary excretion of total radioactivity in two rats after iv dosing accounted for 54% of the total dose in 12 hr. The corresponding biliary excretion after oral dosing was 62% of the administered dose.

**TABLE 1**

<table>
<thead>
<tr>
<th>Sample</th>
<th>iv Solution</th>
<th>Oral Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat urine</td>
<td>22.2 (3.06)</td>
<td>9.83 (1.74)</td>
</tr>
<tr>
<td>Rat feces</td>
<td>70.3 (4.58)</td>
<td>85.2 (2.42)</td>
</tr>
<tr>
<td>Rat carcass</td>
<td>0.57 (0.07)</td>
<td>0.51 (0.08)</td>
</tr>
<tr>
<td>Total</td>
<td>93.0 (2.07)</td>
<td>95.5 (1.59)</td>
</tr>
<tr>
<td>Human urine</td>
<td>—</td>
<td>18.0 (4.10)</td>
</tr>
<tr>
<td>Human feces</td>
<td>—</td>
<td>67.4 (16.5)</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>85.9 (17.0)</td>
</tr>
</tbody>
</table>

* The iv dose in the human study was administered as unlabeled avitriptan.
Mean cumulative excretion of total radioactivity in urine over 168 hr postdose was 18.0% of oral dose in the human study. Approximately 90% of the radioactive dose recovered in urine was excreted over the first 24 hr postdose. Fecal excretion in the human accounted for the 67.4% of the dose. Overall, 85.9% of the total radioactivity administered was recovered in urine and feces over 168 hr post-oral dose.

### Plasma Time Course of Total Radioactivity and Pharmacokinetics of Avitriptan

Mean (standard deviation) plasma concentration-time profiles of total radioactivity and unchanged avitriptan after ia and oral dosing are shown in fig. 2. Mean (standard deviation) pharmacokinetic parameters for total radioactivity and avitriptan for rats and humans are summarized in tables 2 and 3, respectively. Plasma concentrations of total radioactivity in rats were considerably lower after oral dosing in comparison with ia dosing. Mean C\text{max} of total radioactivity after oral dosing was one-tenth of the C\text{max} after ia dosing (2,038 ng-eq/ml vs. 21,077 ng-eq/ml), whereas mean AUC\text{INF} after oral dosing was about one-third that after ia dosing (4,273 ng-eq hr/ml vs. 11,567 ng-eq hr/ml). Peak concentrations of total radioactivity occurred at 0.5 hr after oral dosing in all rats. The t\text{1/2} of the total radioactivity was ~8 hr after both routes of administration.

In humans, after oral administration, mean C\text{max} of total radioactivity was 259 ng-eq/ml, and AUC\text{INF} was 1,611 ng-eq hr/ml. Median t\text{max} was 1.5 hr and the mean t\text{1/2} was 5.76 hr. Concentrations of total radioactivity were lower in blood than in plasma. The blood-to-plasma ratio of total radioactivity was ~0.7 (data not shown).

Mean C\text{max} values of unchanged avitriptan after ia and oral dosings in rats were 21,616 ng/ml and 1,493 ng/ml, respectively. Mean AUC\text{INF} values were 6,879 ng · hr/ml after ia dosing and 1,329 ng · hr/ml after oral dosing, with a mean absolute bioavailability of 19.3%. After oral dosing, avitriptan was absorbed rapidly with peak concentrations achieved within 0.5 hr. The decline in plasma avitriptan concentrations was essentially parallel with a mean t\text{1/2} of 5.26 hr after ia dosing and 1.18 hr after oral dosing.

In the human study, mean C\text{max} values after iv and oral treatments were 432 ng/ml and 142 ng/ml, respectively. Mean AUC\text{INF} values were 358 ng · hr/ml and 312 ng · hr/ml, respectively, with a mean absolute bioavailability of 17.2%. Median t\text{max} after oral dosing was 0.5 hr, indicating rapid absorption. Mean t\text{1/2} values were 5.26 and 8.34 hr for iv and oral treatments, respectively, and the decline in plasma avitriptan concentrations seemed to be essentially parallel after the two routes of administration.

Mean total clearance of avitriptan in rats was 48.7 ml/min/kg and mean steady-state volume of distribution was 1.91 liters/kg. Comparison of the AUC\text{INF} of total radioactivity and unchanged avitriptan indicates that ~60% of the total radioactivity in plasma was accounted for by unchanged avitriptan after ia dosing and ~32% after oral dosing. Mean total clearance of avitriptan in humans was 6.44 ml/min/kg, and mean steady-state volume of distribution was 0.875 liters/kg. About 22% of the total circulating radioactivity in human plasma was accounted for by unchanged avitriptan after oral administration.

### Distribution of Radioactivity in Tissues and Fluids

Figures 4 and 5 depict the concentration of total radioactivity in selected tissues in SD rats after oral and iv administrations. The tissues selected represent organs associated with absorption (stomach and small intestine), organs associated with elimination (kidneys, liver, and large intestine), organs associated with likely adverse effects of 5-HT\text{3} agonists (heart) (7, 8), and organs that showed significant concentra-
tions of radioactivity at the last time of measurement (adrenals, bone marrow, testes, thyroid, and lymph nodes).

Highest concentrations of radioactivity after oral dosing were observed at 0.5 hr postdose and 0.08 hr post-iv dose in most tissues, except for the tissues associated with the gastrointestinal tract and urinary bladder. In the large intestine and urinary bladder, the highest concentrations of radioactivity were observed at 8 hr post-oral dose. Peak concentrations of radioactivity post-iv dose occurred at 2 hr in the small intestine and contents, and at 8 hr in the large intestine and contents. Except for aqueous humor, bone, brain, and CSF, all other tissues had higher concentrations of total radioactivity than plasma. Concentrations of total radioactivity were detectable in most tissues up to 24 hr postdose. At 168 hr post-oral dose, radioactivity was detectable in the kidneys, liver, large intestine and contents, and small intestinal contents. At 168 hr post-iv dose, radioactivity was detectable in the adrenals, bone marrow, kidneys, liver, large intestine and contents, lymph nodes, small intestinal contents, testes, and thyroid. Concentrations in all other tissues were below the limit of detection at 168 hr postdose. The approximate half-life for the decline of total radioactivity from plasma was 6.4 hr after iv administration and 6.1 hr

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>t&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AU&lt;sub&gt;INF&lt;/sub&gt;</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>CL&lt;sub&gt;T&lt;/sub&gt;</th>
<th>V&lt;sub&gt;Dss&lt;/sub&gt;</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat ia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21,616 (12,937)</td>
<td>—</td>
<td>6,879 (584)</td>
<td>0.98 (0.26)</td>
<td>48.7 (4.12)</td>
<td>1.91 (0.37)</td>
<td>193</td>
</tr>
<tr>
<td>Human iv&lt;sup&gt;c&lt;/sup&gt;</td>
<td>432 (89.0)</td>
<td>—</td>
<td>358 (64.3)</td>
<td>5.26 (2.40)</td>
<td>6.44 (1.14)</td>
<td>0.875 (0.365)</td>
<td>—</td>
</tr>
<tr>
<td>Rat oral&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1,493 (504)</td>
<td>0.5</td>
<td>1,329 (347)</td>
<td>1.18 (0.65)</td>
<td>—</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Human oral&lt;sup&gt;e&lt;/sup&gt;</td>
<td>142 (70.9)</td>
<td>0.5</td>
<td>312 (128)</td>
<td>8.34 (3.58)</td>
<td>—</td>
<td>17.2 (4.6)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Values reported for t<sub>max</sub> are medians.
<sup>b</sup> Dose: 20 mg/kg.
<sup>c</sup> Dose: 10 mg as a 30-min infusion.
<sup>d</sup> Dose: 20 mg/kg.
<sup>e</sup> Dose: 50 mg.

**Fig. 4.** Concentration of total radioactivity in selected tissues from SD rats after iv (top) and oral (bottom) administrations.
- ○, adrenals; □, plasma; ▼, kidneys; ●, liver; ◇, large intestine; ◊, small intestine; ■, stomach.

**Fig. 5.** Concentration of total radioactivity in selected tissues from SD rats after iv (top) and oral (bottom) administrations.
- ○, bone marrow; ●, heart; □, plasma; ■, testes; ▼, thyroid; ◊, lymph nodes.
Exposure to brain was after oral administration, and was consistent with the $t_{1/2}$ values obtained in the disposition study. The decline in concentration in all tissues except testes seemed to be parallel to the decline in plasma. Concentration of radioactivity in testes seemed to be relatively constant over a 24-hr period postdose but, at the 168 hr time point, was about one-half that concentration post-iv dose and about one-fifth that concentration post-oral dose. The slow elimination of radioactivity from testes was not associated with any toxicological modifications in repeat-dose toxicological studies. Concentrations in all tissues except for those associated with gastrointestinal tract were ~5–10 times higher after iv administration, compared with those after oral administration. AUC$_{i.o.-T}$ for total radioactivity after oral dosing was 22% of that after iv dosing. Exposure to brain was <10% of the exposure in plasma, regardless of the route of administration. Concentrations of radioactivity in blood relative to plasma ranged from 0.62 to 0.98 at various time points. Figure 6 shows the comparison of radioactivity distribution between SD and LE rats in selected tissues after iv and oral administrations. Except for the eye and skin, the total radioactivity concentrations in the tissues from LE rats and SD rats were comparable. At 2 hr postdose, the concentration of total radioactivity in the eyes of the LE rats was nearly 30 times higher in comparison with SD rats. At 168 hr postdose, radioactivity in the eye of LE rats showed a 12% decline after iv administration and a 40% decline after oral administration relative to the concentration at 2 hr postdose. Considerable greater radioactivity remained in the skin of LE rats at 168 hr postdose after both iv and oral doses, compared with the skin of SD rats. The significance of high levels of radioactivity in the eyes of LE rats is difficult to ascertain, because only SD rats were used in repeat-dose toxicology studies.

Whole-Body Autoradiography. Whole-body sections and corresponding autoradiographs obtained at 2 hr post-iv dose in SD and LE rats are shown in fig. 7. The results showed a similar distribution of radioactivity in tissues of SD and LE rats, except for the pigmented tissues of the eye. At 168 hr post-iv dose, only the wall of the eyeball showed significant radioactivity in LE rats. The results of whole-body autoradiography essentially confirmed the results of the distribution of radioactivity in various tissues as determined by liquid scintillation counting.

Discussion

Mean recovery of total radioactivity in urine after oral administration of [14C]avitriptan to rats was ~50% of that after iv administration, suggesting incomplete absorption of the drug. From the bile duct-cannulated rats, ~62% of total radioactivity was recovered in bile and 12% in urine in a 12 hr post-oral dose. This indicates that at least 74% of the oral dose administered was absorbed from the gastrointestinal tract. Despite the high percentage of drug absorbed, absolute bioavailability was ~20%. This suggests a significant portion of the orally administered dose is subject to first-pass metabolism. A major portion of the dose was excreted in the urine and feces within 24 hr postdose, and >90% of the total dose was recovered in 168 hr postdose, regardless of the route of administration. Because the majority of the iv dose was recovered in feces, it seems that biliary excretion is the major route of excretion of avitriptan and its metabolites in rats.

Results of urinary and fecal excretion of [14C]avitriptan in rats are consistent with those observed in healthy normal subjects. Due to accumulation and slow decline of total radioactivity from the pigmented tissues of the eye, [14C]avitriptan was not administered intravenously to healthy subjects. After oral administration, only 18% of the total radioactive dose in feces was recovered in urine over 168 hr postdose, and the majority of the dose was recovered in feces. Because avitriptan administered by the iv route was not radiolabeled, it is not possible to ascertain as to what fraction of the radioactivity in feces is the unabsorbed dose and what fraction is the dose excreted in bile. However, based on rat data, it may be speculated that a significant portion of the radioactive dose in feces is coming via the biliary route. Biliary excretion seems to be a predominant route for avitriptan elimination. This is unlike the antimigraine drug sumatriptan that is mainly renally excreted as the parent drug and its indole acetic acid metabolite (9). Metabolism of avitriptan in rats and humans has been characterized and will be the topic of a future publication.

Absorption of avitriptan in rats and humans after oral administration was rapid, with peak plasma concentrations occurring in 0.5 hr postdose. The <100% absorption of [14C]avitriptan in rats after oral administration is also evident from the dissimilarity in the plasma concentration-time profiles of total radioactivity after oral and ia administrations. Maximum plasma concentration of avitriptan in rats after oral dosing was ~10-fold lower, compared with that after ia dosing, with an absolute bioavailability of 19.3%. Because the pharmacokinetics of avitriptan in rats is concentration-dependent, it may be argued that the systemic clearance at 10-fold higher concentrations after ia dosing is lower than the systemic clearance after oral dosing, and thus absolute bioavailability is underestimated. However, the apparent elimination half-life for the parent drug between the ia and oral dosings is similar, and there is no obvious indication that the systemic clearance between the two routes of administration is dif-
Different. Absolute bioavailability of avitriptan in humans was 17.2% and was similar to that observed in rats. Total clearance corrected for body weight was ~8 times higher, and the steady-state volume of distribution was ~2 times higher in rats, compared with the corresponding values in humans.

Comparison of total radioactivity and unchanged drug in rat and human plasma indicates that there are one or more circulating metabolites of the drug in plasma. In rats, the $t_{1/2}$ for the total radioactivity was longer, compared with the parent drug. However, in humans, the $t_{1/2}$'s for total radioactivity and unchanged avitriptan were similar.

After oral and iv administrations, radioactivity associated with $[^{14}C]$avitriptan and metabolites was extensively distributed in various rat tissues. Concentrations of radioactivity in tissues associated with the gastrointestinal tract were higher after oral dosing, but all other tissues had lower radioactivity after oral dosing compared with iv dosing; thus suggesting incomplete absorption of the drug. Significant radioactivity in intestinal tissues and contents after iv administration also supports biliary excretion of drug. Penetration across the blood-brain barrier was low, as seen from low concentrations of radioactivity in the brain relative to plasma. Moderate penetration of the drug-related material was observed in the cellular elements of blood.

LE rats were used in the tissue distribution study to assess the distribution of radioactivity in pigmented tissues. Except for the eyes and skin, the distribution of radioactivity was similar in all tissues of the LE and SD rats. Concentrations in the eye of LE rats were 30 times higher at 2 hr postdose, compared with SD rats and declined very slowly over 168 hr postdose. The radioactive material seemed to be concentrated in the melanin-containing uveal tract. This finding is similar to sumatriptan, which also was found to be concentrated in the uveal tract of the eye and measurable levels of radioactivity remained in the eye 7 days after dose (9). Further histopathological evaluation confirmed that the radioactivity was associated with the iris, ciliary body, and the choroid and retinal pigmented epithelia of the eye, but not in the lens or other components of the eye. The amount of radioactive material associated with the eye of LE rats was minimal and accounted for <0.1% of the dose at 168 hr postdose.

In summary, a number of similarities were observed in the disposition of avitriptan in rats and humans. $[^{14}C]$Avitriptan was rapidly absorbed after oral administration in both species, with absolute bioavailability of ~20%. The drug is subject to significant first-pass metabolism after oral administration, and a major portion of the plasma radioactivity is associated with metabolites of avitriptan. Biliary excretion is the predominant route of elimination and a majority of the administered dose undergoes excretion in feces. $[^{14}C]$Avitriptan shows extensive distribution in tissues with a tendency for accumulation in the melanin-containing tissues.

Acknowledgments. We are grateful to C. Ita, R. M. Fancher, D. A. D’Aprix, and K. Liao for their technical assistance, and G. M. Luke for the synthesis of radiolabeled avitriptan.

References


