PHARMACOKINETICS AND PLASMA PROTEIN BINDING OF TAMSULOSIN HYDROCHLORIDE IN RATS, DOGS, AND HUMANS

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ABSTRACT:

The pharmacokinetics of tamsulosin hydrochloride, a selective α1-adrenoceptor antagonist, was investigated after single iv and oral dosing to rats and dogs, and oral dosing to healthy male volunteers. After iv dosing, plasma tamsulosin concentrations declined in an apparent biexponential manner with terminal half-lives of 0.32 hr in rats and 1.13 hr in dogs. Values for total blood clearance (CLbr) were 6.57 l/hr/kg in rats and 1.01 l/hr/kg in dogs, suggesting “hepatic blood flow-limited” and “intermediate flow-dependent” clearance, respectively. After oral dosing, tamsulosin was rapidly absorbed and reached maximum levels within 1 hr in rats and dogs, and at 1.0–1.8 hr in humans. Values for oral clearance (CLoral) in rats, dogs, and humans were 34.5–113.6, 3.01–3.99, and 0.31–0.041 l/hr/kg, respectively, showing wide variation among these species. The absolute bioavailability (F) increased with dose in rats (from 6.9% at 1 mg/kg to 22.8% at 10 mg/kg), but was almost constant in dogs (29.7–42.0% over the 0.3–3 mg/kg dose range). The plasma protein binding of 14C-tamsulosin in humans was much higher (88.9–99.1%) than that in rats and dogs (79.0–80.6% and 90.2–90.3%, respectively). The ratio of blood to plasma concentrations (RB) value in rats, dogs, and humans decreased in this order (1.2, 0.72, and 0.53, respectively), corresponding to the decrease in plasma unbound fraction (fu) in these species. These results imply that the large interspecies difference in CLoral is attributable to a difference not only in hepatic metabolism but also in protein binding among these species.

Tamsulosin hydrochloride (Harnal, Omnic, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan) is a potent and selective α1-adrenoceptor antagonist (Honda and Nakagawa, 1986; Honda et al., 1987). This drug is used clinically in Japan and several European countries as an oral medication to ameliorate the dysuria associated with prostatic hypertrophy. In vitro study revealed that the selectivity of this drug for prostate α1-adrenoceptor was about 10 times higher than that to aorta (Yamada et al., 1994). Pharmacokinetics and metabolism studies on amosulalol hydrochloride, which is structurally similar to tamsulosin, revealed the existence of an interspecies difference among rats, dogs, monkeys, and humans (Kamimura et al., 1984; Nakashima et al., 1984) and that this difference was attributable to a difference in hepatic metabolism (Kamimura et al., 1985).

However, interspecies variation in the pharmacokinetics of a drug is sometimes caused by a difference in plasma protein binding as well as in hepatic metabolism and/or renal excretion. For an orally administered drug, oral clearance is well correlated to the unbound fraction and hepatic intrinsic clearance if it is well absorbed and primarily metabolized by the liver. Plasma protein binding and hepatic metabolism, therefore, are important determinants in understanding the pharmacokinetics of the drug. Characterization of plasma protein binding and drug metabolism in humans and laboratory animals is necessary for evaluation of toxicological and preclinical studies and for extrapolation of the pharmacokinetics/pharmacodynamics in humans.

In the present study, we investigated the pharmacokinetics of tamsulosin after single dosing to rats, dogs, and humans, and we determined the plasma protein binding of the drug to compare the clearance and the protein binding among these species.

Methods and Materials

Chemicals. Tamsulosin hydrochloride and amosulalol hydrochloride, used as internal standard, were supplied by Yamanouchi Institute for Drug Discovery Research Laboratories. Their chemical structures are shown in fig. 1. 14C-Tamsulosin hydrochloride (specific activity: 3.6 MBq/mg, radiochemical purity: 99% or higher) was synthesized at Amersham International plc (Buckinghamshire, UK) and used for the study after purification by normal phase preparative column chromatography. All other chemicals used in this study were of analytical grade and purchased commercially.

Animal Study.

Intravenous dosing. The method and brief results of iv dosing studies in rats and dogs (1 mg/kg) have been reported (Hoogdalem et al., 1997). Therefore, the present study describes the method for data analysis and the results in detail.

Oral dosing. Male Fischer 344 strain rats (0.15–0.21 kg), and male beagle dogs (11–16 kg) were used after fasting overnight. In the rat study, tamsulosin dissolved in saline was administered at doses of 1, 3, and 10 mg/kg (N = 3–4/time point). Blood (ca. 5 ml/time point) was collected from the inferior vena cava using a heparinized syringe under ether anesthesia predosing, and at 15, 15, and 30 min and 1, 2, 3, 4, 6, and 8 hr after dosing. In the dog study, tamsulosin was administered at doses of 0.3, 1, and 3 mg/kg (N = 4–5). Blood
(ca. 5 ml/time point) was collected from the forelimb vein predosing, and at 7.5, 15, and 30 min and 1, 2, 3, 4, 6, 8, and 10 hr after dosing. The same dogs were used in the iv and oral dosing studies except for the 3-mg/kg oral dosing study, following a washout period of at least 1 week. The 3-mg/kg oral dosing study was conducted on five different dogs. Plasma was separated by centrifugation at 1000g for 15 min and stored at −20°C until analysis. Dose levels in these animal studies were selected to measure the plasma tamsulosin concentrations with sufficient sensitivity.

**Clinical Study.** Eight Japanese healthy male volunteers (20–24 yr old, 52–74 kg, 161.2–181 cm) were enrolled in the study. Subjects were divided into groups A and B with four subjects in each group. Group A was orally dosed with tamsulosin in a capsule form (lactose-triturated powder) at a dose of 0.2 mg and group B at doses of 0.05 and 0.1 mg. Blood was collected from the antecubital vein using a heparinized syringe predosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 15, and 24 hr after dosing. After centrifugation, plasma was separated and stored at −20°C until analysis.

**Sample Analysis.** An aliquot of plasma (1.5 ml) was buffered with 1 ml of saturated sodium bicarbonate solution and extracted with 5 ml of ethyl acetate after addition of 100 μl of internal standard aqueous solution (250 ng of amosulalol). The extract was removed and then 2.5 ml of 0.4N HCl was added. The mixture was shaken, centrifuged, and the organic layer was discarded. The water layer was buffered with 2 ml of saturated sodium bicarbonate solution and extracted again with 5 ml of ethyl acetate. The extract was removed and evaporated to dryness under reduced pressure. The residue was dissolved in 50 μl of 0.1 M NaHCO3, and 500 μg of dansylchloride dissolved in acetone (100 μl) was added. Reaction was performed for 90 min at 35°C. After addition of 5 ml of distilled water, the reaction mixture was extracted with 5 ml of diethyl ether. The extract was removed and evaporated to dryness in a water bath at 45°C. The residue was reconstituted in 60 μl of the mobile phase (benzene/methanol 100:1 v/v), and a small aliquot (20–50 μl) of the sample was injected onto the HPLC system. Tamsulosin and amosulalol, which were dansylated, were detected after elution from a normal phase column (Nucleosil SI100-5, 4 mm i.d., Chemco, Osaka, Japan) by use of a fluorescence detector (RF-535, Shimadzu, Kyoto, Japan) with excitation at 352 nm and emission at 450–550 nm. The low limit of quantitation (LLOQ) was 0.5 ng/ml for human plasma and 0.05 ng/ml for rat and dog plasma. The intra and interday precision expressed as coefficient of variance for LLOQ and each quality control (QC) concentration (3, 250, and 400 ng/ml for rats and dogs and 1.5, 40, and 60 ng/ml for humans) was within 13.41% for rat plasma, within 8.7% for dog plasma, and within 13.88% for human plasma. The intra and interday accuracy expressed as relative error for the LLOQ and QC concentration was within −24.48% for human plasma, and within 13.88% for human plasma. The intra and interday precision expressed as coefficient of variance for LLOQ and each quality control (QC) concentration (3, 250, and 400 ng/ml for rats and dogs and 1.5, 40, and 60 ng/ml for humans) was within 13.41% for rat plasma, within 8.7% for dog plasma, and within 13.88% for human plasma. Tamsulosin could be quantified over the range 1–500 ng/ml in rat and dog plasma and 0.5–80 ng/ml in human plasma.

**Determination of the Ratio of Blood to Plasma Concentrations (Rb).** Heparinized blood of rats, dogs, and humans was used. To 2.95-ml aliquots of blood, 0.05-ml aliquots of phosphate buffered isotonic solution (pH 7.4) containing 14C-tamsulosin were added to make concentrations of 50 ng/ml in rat and dog blood and 200 ng/ml in human blood (N = 3 for each species). After incubation for 30 min at 37°C, a 0.05-ml aliquot was taken from each blood sample to measure the blood concentration, and the remaining sample was centrifuged for 15 min at 1000g. After centrifugation, a 0.05-ml aliquot of plasma was taken to measure the plasma concentration. This 0.05-ml aliquot of plasma was diluted to 1 ml with distilled water, and 10 ml of liquid scintillator (Aquasol-2, New England Nuclear, Boston, MA) was added. The 0.05-ml aliquot of blood was added to the mixture of 0.5 ml of tissue solubilizer (Solene 350, Packard Instrument, Meriden, CT) and 0.5 ml of isopropanol to solubilize red blood cells, and then 30% hydrogen peroxide solution was added for decolorization. After overnight incubation at 4°C, 10 ml of liquid scintillator (Hionic fluore, Packard) was added to this mixture. Samples were counted using a liquid scintillation counter (LS 6000TA, Beckman Instruments, Inc., Fullerton, CA), and Rb values were determined comparing the concentration of 14C-tamsulosin in blood and plasma.

**Protein Binding Study.** To 2-ml aliquots of rat, dog, and human plasma, 0.1-ml aliquots of phosphate buffered isotonic solution containing 14C-tamsulosin were added to make concentrations of 200 ng/ml and 600 ng/ml, except for human plasma at the concentration of 200 ng/ml which was prepared by adding 0.3-ml aliquots of 14C-tamsulosin solution to 6-ml aliquots of plasma (N = 3 for each species). After incubation for 30 min at 37°C, a 0.2-ml aliquot was taken from each plasma sample to measure the total plasma concentration, and the unused portion was transferred to an ultrafiltration tube (Ultracent-10, Tosoh, Tokyo, Japan). Unused human plasma containing 200 ng/ml of 14C-tamsulosin were divided into the three tubes. The tubes were centrifuged for 15 min (1000g, 37°C), and a 0.2-ml aliquot of filtrate was taken for the measurement of unbound plasma concentration. The filtrates from the divided human plasma were pooled and a 0.6-ml aliquot was taken for measurement. The aliquots of plasma and filtrate were diluted to 1 ml with distilled water, and 10 ml of liquid scintillator (Aquasol-2) was added. Samples were counted using a liquid scintillation counter (2000CA, Packard).

**Data Analysis.** Plasma tamsulosin concentrations after iv dosing were fitted to a two-compartment model using the nonlinear least squares regression program NONLIN 84 (Statistical Consultants Co., Apex, NC) to calculate the following pharmacokinetic parameters: α half-life (t1/2α). β half-life (t1/2β), apparent volume of distribution (Vα), area under the plasma concentration-time curve (AUC), and total plasma clearance (CLα). The total plasma clearance (CLα) was calculated as CLα/Rb. Plasma tamsulosin concentrations after oral dosing were subject to noncompartmental analysis. The maximum concentration (Cmax) and time to Cmax (Tmax) were observed values. The terminal elimination rate constant (λ) was determined by least squares regression analysis of terminal log-linear portions of the plasma concentration-time profile (λ = −2.303 × slope). The elimination half-life (t1/2λ) was calculated as 0.693/λ. The AUC extrapolated to infinity (AUC∞) was determined by the trapezoidal rule up to the last time point and thereafter extrapolated to infinity on the basis of λ. Pharmacokinetic parameters in rats were calculated using the mean plasma concentrations because they were sacrificed at their sampling time, whereas those in dogs and humans were calculated individually. The absolute bioavailability of tamsulosin after oral administration (F) was calculated from the ratio of AUC∞ after oral dosing to that after iv dosing, corrected for the difference in dose levels. Oral clearance (CLoral) was calculated as dose/AUC∞. The percentage bound and the unbound fraction (fu) were calculated using the following equations:

\[
\% \text{ bound} = \left( 1 - \frac{C_u}{C_t} \right) \times 100
\]

\[
f_u = \frac{C_f}{C_t}
\]

where \( C_t \) is the total 14C-tamsulosin concentration and \( C_u \) the unbound 14C-tamsulosin concentration in plasma.

**Results**

**Intravenous Dosing to Rats and Dogs.** Plasma concentration-time profiles of tamsulosin in rats and dogs after iv dosing are shown in fig. 2. The plasma concentrations declined in an apparent biexponential manner. The mean t1/2αβ in rats and dogs were 0.32 and 1.13 hr, respectively, indicating that tamsulosin was eliminated rapidly in rats in comparison with dogs. \( V_{ss} \) and CLtot in rats were 2.86 l/kg and 7.88 l/hr/kg, and those in dogs were 1.74 l/kg and 1.16 l/hr/kg,
respectively. $V_{dss}$ and $CL_{tot}$ in dogs were smaller than those in rats (table 1).

**Oral Dosing to Rats and Dogs.** After oral dosing, plasma tamsulosin concentrations rapidly increased and reached maximum levels at 7.5 min in rats and 7.5–30 min in dogs (figs. 3 and 4, tables 2 and 3). The plasma concentrations decreased with $t_{1/2}$ of 0.99–1.15 hr in rats and 1.27–1.68 hr in dogs, showing no dose dependency. $CL_{oral}$ values were 34.5–113.6 l/hr/kg in rats and 3.01–3.99 l/hr/kg in dogs. Increase in $C_{max}$ and $AUC_{0-\infty}$ in rats was greater than proportional to doses over the 1–10 mg/kg dose range, whereas that in dogs was proportional to doses over the 0.3–3 mg/kg dose range. Thus, absolute bioavailability in rats increased with increases in dose from 6.9% at 1 mg/kg to 22.8% at 10 mg/kg, whereas that in dogs was 29.7–42.0%, remaining constant within the dose range studied.

**Clinical Study.** After oral dosing to healthy male volunteers, plasma tamsulosin concentrations increased and reached maximum levels at 1.0–1.8 hr after dosing and thereafter decreased gradually with $t_{1/2}$ of 5.25–6.79 hr, showing no dose dependency (fig. 5, table 4). Elimination of tamsulosin in humans was slower than that in rats and dogs. $CL_{oral}$ values were 0.031–0.041 l/hr/kg (1.85–2.61 l/hr). Increase in $C_{max}$ and $AUC_{0-\infty}$ was proportional to the dose over the 0.05–0.2 mg dose range. Moderate orthostatic hypotension was observed in two volunteers at a dose of 0.2 mg.

**Plasma Protein Binding and $R_B$ Values.** The results of plasma protein binding and $R_B$ values in rats, dogs, and humans are shown in table 5. Percentage bound of $^{14}C$-tamsulosin in rats, dogs, and humans was 79.0–80.6%, 90.2–90.3% and 98.9–99.1%, respectively, indicating that tamsulosin was highly bound to human plasma protein. Protein binding was almost constant regardless of the increase in concentration from 200 to 600 ng/ml in all species. $Fu$ in rats (0.194–0.210) and dogs (0.097–0.098) was 20 and 10 times higher than that in humans (0.009–0.011), respectively. $R_B$ values in rats, dogs, and humans were 1.2, 0.72, and 0.53, respectively, appearing to decrease with increases in the plasma protein binding among these species. $CL_B$ values calculated using these $R_B$ values were 6.57 l/hr/kg in rats and 1.61 l/hr/kg in dogs (table 1). $CL_{oral}/fu$ values calculated to estimate the hepatic intrinsic clearance ($CL_{int}$) of tamsulosin were 164–586 l/hr/kg in rats, 31–41 l/hr/kg in dogs, and 2.8–4.6 l/hr/kg in humans. Distribution volume based on unbound tamsulosin ($V_{dss}/fu$) was 13.6–14.7 l/kg in rats and 17.6–17.9 l/kg in dogs (table 6).

**Discussion**

After oral dosing of $^{14}C$-tamsulosin at a dose of 1 mg/kg in rats and dogs, urinary excretion of unchanged tamsulosin over 24 hr was 1.18% and 2.72%, respectively (Soeishi et al., 1996a). Renal clearance ($CL_u$) estimated using these values and AUC after intravenous administration to rats and dogs at the dose of 1 mg/kg was:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rats ($N = 3$)</th>
<th>Dogs ($N = 4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2\alpha}$ (hr)</td>
<td>0.035</td>
<td>0.134 ± 0.034</td>
</tr>
<tr>
<td>$t_{1/2\beta}$ (hr)</td>
<td>0.32</td>
<td>1.13 ± 0.07</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (mg/hr/ml)</td>
<td>127</td>
<td>873 ± 65</td>
</tr>
<tr>
<td>$V_{dss}$ (l/kg)</td>
<td>2.86</td>
<td>1.74 ± 0.16</td>
</tr>
<tr>
<td>$CL_{oral}$ (l/hr/kg)</td>
<td>7.88</td>
<td>1.16 ± 0.08</td>
</tr>
<tr>
<td>$CL_u$ (l/hr/kg)</td>
<td>6.57</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Values represent the mean ± SEM.

$CL_u = CL_{oral}/R_B$. 

![Fig. 2. Plasma concentration-time profiles of unchanged tamsulosin in rats and dogs after intravenous dosing at a dose of 1 mg/kg. Each point represents the mean ± SD of three rats (■) or four dogs (●).](image2)

![Fig. 3. Plasma concentration-time profiles of unchanged tamsulosin in rats after oral dosing. Each point represents the mean ± SD of three (1 and 3 mg/kg) or four (10 mg/kg) rats. (■) 1 mg/kg; (●) 3 mg/kg; (▲) 10 mg/kg.)](image3)

![Fig. 4. Plasma concentration-time profiles of unchanged tamsulosin in dogs after oral dosing. Each point represents the mean ± SD of four (0.3 and 1 mg/kg) or five (3 mg/kg) dogs. (■) 0.3 mg/kg; (●) 1 mg/kg; (▲) 3 mg/kg.](image4)
Interspecies variation in the pharmacokinetics of tamsulosin was observed among rats, dogs, and humans after oral dosing. Plasma concentrations in dogs and humans increased proportionally with an increase in dose, whereas those in rats increased nonlinearly over the dose range studied. In addition, CL<sub>oral</sub> values in rats and dogs were about 100 times and 1000–3000 times higher than that in humans, respectively, thus showing a large interspecies difference. Probable causes of the interspecies differences in CL<sub>oral</sub> include differences in the amount of absorption, systemic clearance, or presystemic extraction in the liver. The amount of radioactivity absorbed in rats and dogs after oral dosing of <sup>14</sup>C-tamsulosin at a dose of 1 mg/kg under fasting conditions was more than 99% and ca. 90% over 72 hr, respectively (unpublished data), and absolute bioavailability in humans was approximately 100% (Hoogdalem et al., 1997), suggesting that the clearance of tamsulosin is “flow-independent.”

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was about 1/20 and 1/10 of that in rats and dogs, respectively, indicating
interspecies difference in CLoral of tamsulosin is attributable to the
fu in humans, moreover, was about 1/20 and 1/10 of that in rats and dogs, respectively, indicating
that the interspecies difference in the CLoral of tamsulosin is largely
attributable to the difference in fu.

Plasma protein binding is an important concept in understanding the pharmacokinetics of a drug. The protein binding of a drug often changes because of changes in the plasma protein levels (Grossman et al., 1982; Jackson et al., 1982), the presence of endogenous inhibitors (McNamara et al., 1981; Sjöholm et al., 1976) or exogenous compounds such as concomitant drugs (Dahlqvist et al., 1979; Anggeler et al., 1967; McElnay and O’Arcy, 1980). In such a case, inter- and intra-subject variations in pharmacokinetics appear to have occurred. Moreover, changes in protein binding may cause changes in unbound drug concentration in plasma, generating problems such as changes in pharmacological effects and/or the development of adverse reactions. As for orally administered drugs that are heptatically cleared, however, plasma unbound concentrations are thought to be less affected by changes in protein binding. The reason for this is that, as based on the Well-stirred model (Wilkinson and Shand, 1975), unbound oral clearance expressed as CLoral/fu reflects CLhint. The estimated CLhint of tamsulosin, calculated as CLoral/fu, in rats, dogs, and humans was 164–586, 31–41 and 2.8–4.6 l/hr/kg, respectively, suggesting that the interspecies difference in CLoral of tamsulosin is attributable to the difference not only in fu but also in CLhint. In fact, our preliminary study demonstrated that metabolic activity in microsomal enzymes was a few times higher in dogs and 20 to 30 times higher in rats than in humans.

In our previous work, five metabolites were confirmed to exist as the primary metabolites of tamsulosin (fig. 6) (Soeishi et al., 1996a,b). Tamsulosin is mainly metabolized to M-1 and M-4 in rats and to M-1 and AM-1 in dogs and humans. Studies on human hepatic microsomes and human lymphoblastoid cells expressing P450 cDNAs revealed that CYP3A4 was the isoform responsible for tamsulosin metabolism to M-1 and AM-1 and that CYP2D6 was responsible for M-3 and M-4 (unpublished data). These data suggest that the interspecies differences in the metabolism of tamsulosin reflect the differences in the rate of metabolism to M-1 and M-4 in these species.

Changes in protein binding may sometimes alter the distribution of a drug to systemic components. Such alteration is observed as a change in Vdss or RB (Oie, 1979; Evans et al., 1973). Interspecies differences in Vdss are often a result of differences in fu (Sawada et al., 1984). The Vdss of tamsulosin in rats and dogs was 2.86 and 1.74 l/kg, respectively, whereas in humans was 0.205 l/kg (Hoogdaem et al., 1997), showing a large interspecies difference in Vdss of tamsulosin. However, distribution volume based on unbound concentration (Vdss/fu) differed little among animal species and humans (Sawada et al., 1984), with Vdss/fu values for tamsulosin in rats, dogs, and humans closely similar at 13.6–14.7, 17.6–17.9 and 18.6–22.8 l/kg, respectively.

The RB value in rats, dogs, and humans decreased in this order, corresponding to the decrease in fu. If the interspecies difference in red blood cell uptake (red blood cell concentration to unbound plasma concentration) of tamsulosin does not exist, the concentration ratio of red blood cell to plasma would be reduced because of an increase in plasma protein binding. This result suggests that interspecies differences in the RB value result from that in fu.

A species difference in plasma protein binding is also observed for prazosin (Dale and Nilsen, 1984), an α1-adrenoceptor antagonist like tamsulosin, which is used in the treatment of hypertension. Percentage bound of prazosin to serum protein in rats and humans was 81.4% and 93.4%, respectively, showing a similar species difference to that for tamsulosin. Many basic drugs, including prazosin, are known to be highly bound to α1-acid glycoprotein (α1-AGP), an acute phase reactant protein (Kremers et al., 1988). The interspecies difference in fu appears to be caused by differences in binding characteristics to α1-AGP in animal species and humans. Like prazosin, tamsulosin is a basic drug and was shown in our preliminary study to be highly bound to α1-AGP. It is considered that the interspecies difference in fu of tamsulosin is caused by a difference in the degree of binding to α1-AGP in animal species and humans. In addition, plasma α1-AGP levels tend to increase in aged men. It is also considered, therefore, that plasma protein binding of tamsulosin may increase in patients with benign prostatic hypertrophy since it is a common problem of aging.

Tamsulosin is rapidly absorbed, and also its plasma concentrations rapidly increases when orally dosed as solution or powder. This rapid increase is undesirable because it may lead to some adverse reactions, such as orthostatic hypotension and dizziness. In fact, moderate or

References


Fig. 6. Scheme for the primary metabolism of tamsulosin in rats, dogs, and humans.


