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 (CLB) were 6.57 l/hr/kg in rats and 1.61 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 0.031–0.041 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 7.5, 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
human plasma. Tamsulosin could be quantified over the range 1–500 ng/ml in rat plasma, within 13.35% for rat plasma, within 7.36% for dog plasma, and within 13.83% for human plasma. The intra and interday accuracy expressed as relative error for the LLOQ and QC concentration was 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 5% for human plasma. The intra and interday precision expressed as coefficient of variance for LLOQ and QC concentration was within 13.5% for human plasma. The intra and interday precision expressed as coefficient of variance for LLOQ and QC concentration was within 13.5% for rat plasma, within 7.36% for dog plasma, and within 13.83% for human plasma. Tamsulosin could be quantified over the range 1–500 ng/ml in rat and dog plasma 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 RQ 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 0.1-ml 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 (t 1/2α), β-half-life (t 1/2β), apparent volume of distribution (Vd), area under the plasma concentration-time curve (AUC), and total plasma clearance (Cl). The total blood clearance (Cl) was calculated as Cl = Rd/Rp. Plasma tamsulosin concentrations after oral dosing were subject to noncompartmental analysis. The maximum concentration (C max ) and time to C max (T max ) 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. The elimination half-life (t 1/2) was calculated as λ/2.303/λ. The AUC extrapolated to infinity (AUCinf) 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 AUCinf after oral dosing to that after iv dosing corrected for the difference in dose levels. Oral clearance (Cloral) was calculated as dose/AUCinf. The percentage bound and the unbound fraction (fu) were calculated using the following equations:

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

\[ fu = C_f/C_t \]

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 t 1/2 were 0.32 and 1.13 hr, respectively, indicating that tamsulosin was eliminated rapidly in rats in comparison with dogs. Vd, Cl, and t 1/2 were 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. $F_u$ 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. $CL_{fu}$ 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
TABLE 2
Pharmacokinetic parameters of tamsulosin after oral administration to rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>6.5</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.125</td>
</tr>
<tr>
<td>AUC0-∞ (ng·hr/ml)</td>
<td>8.8a</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>1.32</td>
</tr>
<tr>
<td>CLtot (l/hr/kg)</td>
<td>113.6c</td>
</tr>
<tr>
<td>F (%)</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Values represent the mean of three (1 and 3 mg/kg) or four (10 mg/kg) rats.

* 0–4 hr value (AUC0–4hr).
* Not calculable due to insufficient data points.
* Calculated using the AUC0–4hr.

TABLE 3
Pharmacokinetic parameters of tamsulosin after oral administration to dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>37 ± 3</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.13 ± 0.00</td>
</tr>
<tr>
<td>AUC0-∞ (ng·hr/ml)</td>
<td>78 ± 9</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>1.44 ± 0.11</td>
</tr>
<tr>
<td>CLtot (l/hr/kg)</td>
<td>3.99 ± 0.44</td>
</tr>
<tr>
<td>F (%)</td>
<td>29.8 ± 3.3</td>
</tr>
</tbody>
</table>

Values represent the mean ± SEM of four (0.3 and 1 mg/kg) or five (3 mg/kg) dogs.

Fig. 5. Plasma concentration-time profiles of unchanged tamsulosin in human male volunteers. Each point represents the mean ± SD of four volunteers. (■) 0.05 mg; (●) 0.1 mg; (▲) 0.2 mg.

dosing in the present study was 1.3 l/hr/kg in rats and 0.11 l/hr/kg in dogs, suggesting a small contribution to CLtot (16% and 9%, respectively). These findings indicate that the elimination of tamsulosin in rats and dogs is attributable to nonrenal elimination, such as hepatic metabolism. CLH values in rats and dogs calculated as CLtot/RB were 6.57 l/hr/kg and 1.61 l/hr/kg, respectively, being larger than hepatic blood flow rate (Qh) in rats, and smaller than Qh in dogs (Qh: 3.5 l/hr/kg and 2.6 l/hr/kg, respectively) (Dedrick et al., 1973; Greenway and Stark, 1971). These data indicate that the clearance of tamsulosin is “hepatic blood flow-limited” in rats and “intermediate flow-dependent” in dogs. Although data for intravenous dosing to humans were not obtained in the present clinical study, CLH value in a previous study in humans was 0.037 l/hr/kg (2.88 l/hr) (Hoogdalem et al., 1997). This value was much smaller than Qh in humans (94 l/hr) (Greenway and Stark, 1971), indicating that the clearance of tamsulosin is “flow-independent.”

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, CLtotal 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 CLtotal 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 14C-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 interspecies difference is not caused by any difference in absorption. The absolute bioavailability, however, varied widely among the species (rats: 6.9–22.8%, dogs: 29.7–42.0%, humans: approx. 100%). These findings indicate that the interspecies difference in the CLtotal of tamsulosin is a result not only of differences in systemic clearance but also of hepatic availability (Fh).

CLtot, CLH, and Fh are hybrid parameters defined by individually independent parameters, such as organ blood flow, intrinsic clearance, fu, and RB. The CLH of heptically cleared drugs which are well absorbed but not metabolized in the gut wall or by microorganisms in the alimentary tract is generally expressed as the product of fu and
change in $V_{du}$, or $R_B$ (Öie, 1979; Evans et al., 1973). Interspecies differences in $V_{du}$ are often a result of differences in fu (Sawada et al., 1984). The $V_{du}$ of tamsulosin in rats and dogs was 2.86 and 1.74 l/kg, respectively, whereas in humans it was 0.205 l/kg (Hoogdalem et al., 1997), showing a large interspecies difference in $V_{du}$ of tamsulosin. However, distribution volume based on unbound concentration ($V_{du}/fu$) differed little among animal species and humans (Sawada et al., 1984), with $V_{du}/fu$ 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 $R_B$ 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 $R_B$ value result from that in fu.

A species difference in plasma protein binding is also observed for prazosin (Dale and Nilsen, 1984), an $a_1$-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 $a_1$-acid glycoprotein ($a_1$-AGP), an acute phase reactant protein (Kremer et al., 1988). The interspecies difference in fu in prazosin appears to be caused by differences in binding characteristics to $a_1$-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 $a_1$-AGP. It is considered that the interspecies difference in fu of tamsulosin is caused by a difference in the degree of binding to $a_1$-AGP in animal species and humans. In addition, plasma $a_1$-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 concentration 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 orthostatic hypotension was observed in two volunteers when 0.2 mg of tamsulosin was dosed as lactose-triturated powder in the clinical study. Therefore, tamsulosin was developed as sustained release formulation in clinical use to prolong the active duration and to avoid the adverse reactions. Tamsulosin was confirmed to be well tolerated at clinical dose levels (0.4--0.8 mg) when orally dosed as this formulation.

In conclusion, a large interspecies difference in $CL_{oral}$ was observed after oral dosing of tamsulosin to rats, dogs, and humans. This difference seems to have been caused by a difference not only in hepatic metabolism but also in protein binding among these species.

**References**


