

## 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  $\alpha_1$ -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 ( $CL_B$ ) 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 ( $CL_{oral}$ ) 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  $^{14}C$ -tamsulosin in humans was much higher (98.9–99.1%) than that in rats and dogs (79.0–80.6% and 90.2–90.3%, respectively). The ratio of blood to plasma concentrations ( $R_B$ ) 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  $CL_{oral}$  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  $\alpha_1$ -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  $\alpha_1$ -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 metab-

olism, 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.  $^{14}C$ -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 (Hoogdaem *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

<sup>1</sup> Abbreviations used are: LLOQ, low limit of quantitation; QC, quality control; AUC, area under the plasma concentration-time curve;  $t_{1/2}$ , elimination half-life;  $V_{dss}$ , apparent volume of distribution;  $Cl_{tot}$ , total plasma clearance;  $CL_B$ , total blood clearance;  $C_{max}$ , maximum concentration;  $T_{max}$ , time to maximum concentration; fu, unbound fraction.

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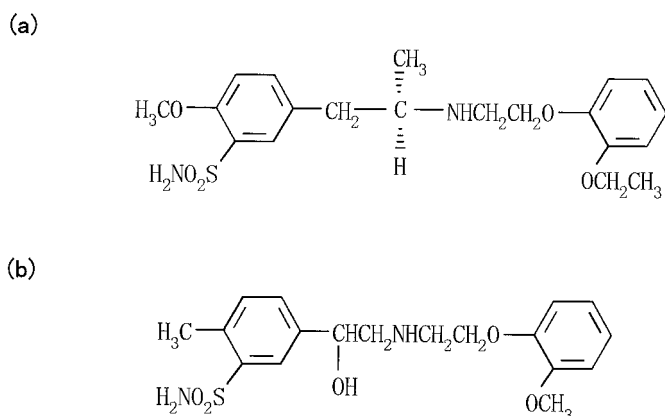


FIG. 1. Chemical structure of tamsulosin (a) and amosulalol (b).

(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  $-20^{\circ}\text{C}$  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  $-20^{\circ}\text{C}$  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  $\mu\text{l}$  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  $\mu\text{l}$  of 0.1 M  $\text{NaHCO}_3$ , and 500  $\mu\text{g}$  of dansylchloride dissolved in acetone (100  $\mu\text{l}$ ) was added. Reaction was performed for 90 min at  $35^{\circ}\text{C}$ . 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  $45^{\circ}\text{C}$ . The residue was reconstituted in 60  $\mu\text{l}$  of the mobile phase (benzene/methanol 100:1 v/v), and a small aliquot (20–50  $\mu\text{l}$ ) 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 SII100-5, 250 mm  $\times$  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 500 nm. The low limit of quantitation (LLOQ)<sup>1</sup> was 0.5 ng/ml for human plasma and 1.0 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 13.35% 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 0.5–80 ng/ml in human plasma.

**Determination of the Ratio of Blood to Plasma Concentrations ( $R_B$ ).** 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  $^{14}\text{C}$ -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  $37^{\circ}\text{C}$ , 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  $4^{\circ}\text{C}$ , 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  $R_B$  values were determined comparing the concentration of  $^{14}\text{C}$ -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  $^{14}\text{C}$ -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  $^{14}\text{C}$ -tamsulosin solution to 6-ml aliquots of plasma ( $N = 3$  for each species). After incubation for 30 min at  $37^{\circ}\text{C}$ , 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  $^{14}\text{C}$ -tamsulosin were divided into the three tubes. The tubes were centrifuged for 15 min (1000g,  $37^{\circ}\text{C}$ ), 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:  $\alpha$  half-life ( $t_{1/2\alpha}$ ),  $\beta$  half-life ( $t_{1/2\beta}$ ), apparent volume of distribution ( $V_{\text{dss}}$ ), area under the plasma concentration-time curve (AUC), and total plasma clearance ( $\text{CL}_{\text{tot}}$ ). The total blood clearance ( $\text{CL}_B$ ) was calculated as  $\text{CL}_{\text{tot}}/R_B$ . Plasma tamsulosin concentrations after oral dosing were subject to noncompartmental analysis. The maximum concentration ( $C_{\text{max}}$ ) and time to  $C_{\text{max}}$  ( $T_{\text{max}}$ ) were observed values. The terminal elimination rate constant ( $\lambda$ ) was determined by least squares regression analysis of terminal log-linear portions of the plasma concentration-time profile ( $\lambda = -2.303 \times \text{slope}$ ). The elimination half-life ( $t_{1/2}$ ) was calculated as  $0.693/\lambda$ . The AUC extrapolated to infinity ( $\text{AUC}_{0-\infty}$ ) was determined by the trapezoidal rule up to the last time point and thereafter extrapolated to infinity on the basis of  $\lambda$ . 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  $\text{AUC}_{0-\infty}$  after oral dosing to that after iv dosing, corrected for the difference in dose levels. Oral clearance ( $\text{CL}_{\text{oral}}$ ) was calculated as  $\text{dose}/\text{AUC}_{0-\infty}$ . The percentage bound and the unbound fraction ( $f_u$ ) were calculated using the following equations:

$$\% \text{ bound} = (C_t - C_u)/C_t \times 100$$

$$f_u = C_u/C_t$$

where  $C_t$  is the total  $^{14}\text{C}$ -tamsulosin concentration and  $C_u$  the unbound  $^{14}\text{C}$ -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  $t_{1/2\beta}$  in rats and dogs were 0.32 and 1.13 hr, respectively, indicating that tamsulosin was eliminated rapidly in rats in comparison with dogs.  $V_{\text{dss}}$  and  $\text{CL}_{\text{tot}}$  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,

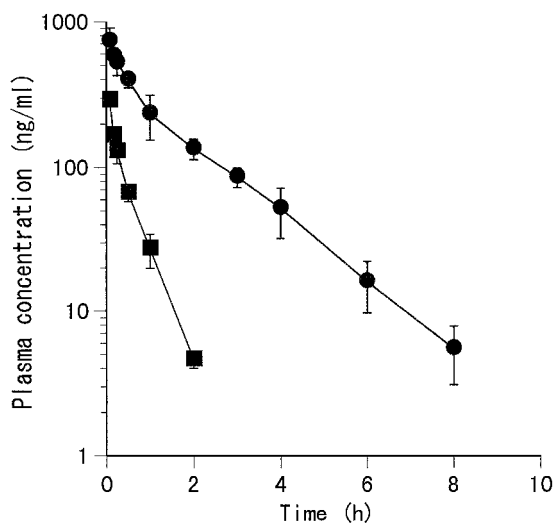


FIG. 2. Plasma concentration-time profiles of unchanged tamsulosin in rats and dogs after intravenous dosing at a dose of 1 mg/kg. Each point represents the mean  $\pm$  SD of three rats (■) or four dogs (●).

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.  $CL_B$  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).  $CL_{oral}/F_u$  values calculated to estimate the hepatic intrinsic clearance ( $CL_{hint}$ ) 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 ( $V_{dss}/F_u$ ) was 13.6–14.7 l/kg in rats and 17.6–17.9 l/kg in dogs (table 6).

TABLE 1

Pharmacokinetic parameters of tamsulosin after intravenous administration to rats and dogs at the dose of 1 mg/kg

Parameter	Rats (N = 3)	Dogs (N = 4)
$t_{1/2\alpha}$ (hr)	0.035	0.134 $\pm$ 0.034
$t_{1/2\beta}$ (hr)	0.32	1.13 $\pm$ 0.07
$AUC_{0-\infty}$ (ng·hr/ml)	127	873 $\pm$ 65
$V_{dss}$ (l/kg)	2.86	1.74 $\pm$ 0.16
$CL_{tot}$ (l/hr/kg)	7.88	1.16 $\pm$ 0.08
$CL_B$ (l/hr/kg)	6.57	1.61

Values represent the mean ( $\pm$  SEM).

$CL_B = CL_{tot}/R_B$ .

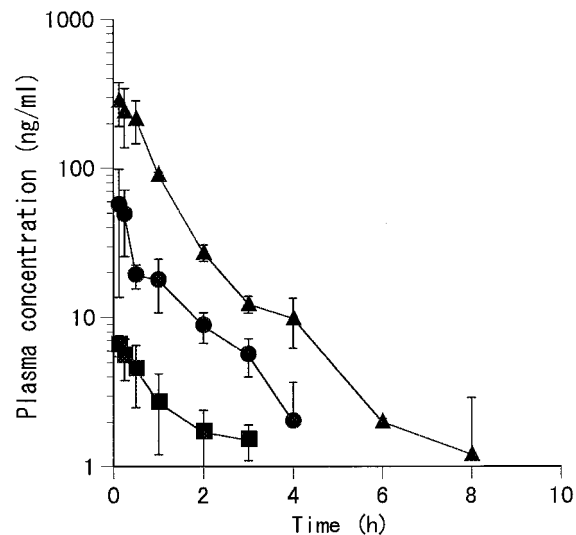


FIG. 3. Plasma concentration-time profiles of unchanged tamsulosin in rats after oral dosing. Each point represents the mean  $\pm$  SD of three (1 and 3 mg/kg) or four (10 mg/kg) rats. (■) 1 mg/kg; (●) 3 mg/kg; (▲) 10 mg/kg.

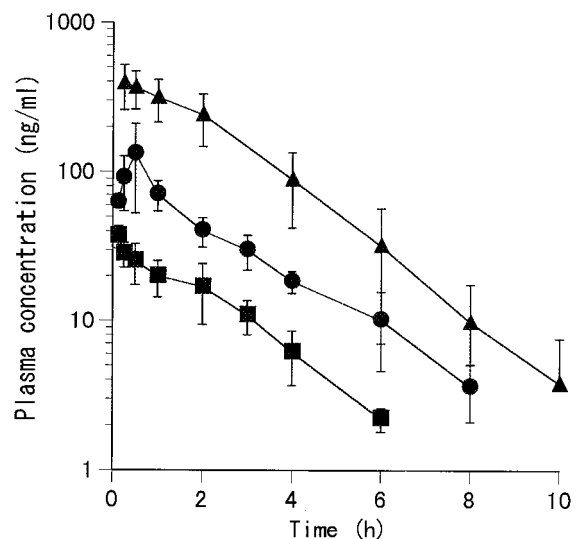


FIG. 4. Plasma concentration-time profiles of unchanged tamsulosin in dogs after oral dosing. Each point represents the mean  $\pm$  SD of four (0.3 and 1 mg/kg) or five (3 mg/kg) dogs. (■) 0.3 mg/kg; (●) 1 mg/kg; (▲) 3 mg/kg.

## 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 ( $CL_r$ ) estimated using these values and AUC after intravenous

TABLE 2

Pharmacokinetic parameters of tamsulosin after oral administration to rats

Parameter	Dose (mg/kg)		
	1	3	10
C <sub>max</sub> (ng/ml)	6.5	56.1	283.9
T <sub>max</sub> (hr)	0.125	0.125	0.125
AUC <sub>0-∞</sub> (ng·hr/ml)	8.8 <sup>a</sup>	55	290
t <sub>1/2</sub> (hr)	— <sup>b</sup>	0.99	1.15
CL <sub>oral</sub> (l/hr/kg)	113.6 <sup>c</sup>	54.5	34.5
F (%)	6.9 <sup>c</sup>	14.4	22.8

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

<sup>a</sup> 0–4 hr value (AUC<sub>0-4 h</sub>).

<sup>b</sup> Not calculable due to insufficient data points.

<sup>c</sup> Calculated using the AUC<sub>0-4 hr</sub>.

TABLE 3

Pharmacokinetic parameters of tamsulosin after oral administration to dogs

Parameter	Dose (mg/kg)		
	0.3	1	3
C <sub>max</sub> (ng/ml)	37 ± 3	146 ± 36	433 ± 50
T <sub>max</sub> (h)	0.13 ± 0.00	0.34 ± 0.10	0.50 ± 0.10
AUC <sub>0-∞</sub> (ng·hr/ml)	78 ± 9	259 ± 22	1100 ± 171
t <sub>1/2</sub> (h)	1.44 ± 0.11	1.68 ± 0.10	1.27 ± 0.05
CL <sub>oral</sub> (l/hr/kg)	3.99 ± 0.44	3.94 ± 0.32	3.01 ± 0.48
F (%)	29.8 ± 3.3	29.7 ± 2.5	42.0 ± 6.5

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

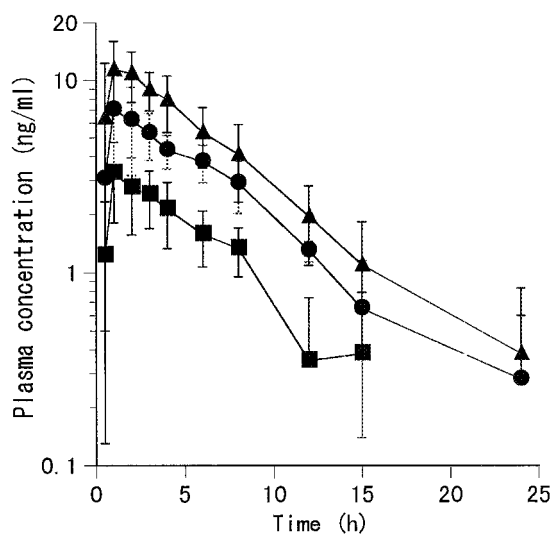


FIG. 5. Plasma concentration-time profiles of unchanged tamsulosin in human male volunteers. Each point represents the mean ± SD of four volunteers. (■) 0.05 mg; (●) 0.1 mg; (▲) 0.2 mg.

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 CL<sub>tot</sub> (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. CL<sub>B</sub> values in rats and dogs calculated as CL<sub>tot</sub>/R<sub>B</sub> were 6.57 l/hr/kg and 1.61 l/hr/kg, respectively, being larger than hepatic blood flow rate (Q<sub>h</sub>) in rats, and smaller than Q<sub>h</sub> in dogs (Q<sub>h</sub>: 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, CL<sub>tot</sub> value in a previous study in humans was 0.037 l/hr/kg (2.88 l/hr) (Hoogdalem *et al.*,

TABLE 4

Pharmacokinetic parameters of tamsulosin after oral administration to humans

Parameter	Dose (mg)		
	0.05	0.1	0.2
C <sub>max</sub> (ng/ml)	3.3 ± 0.7	7.2 ± 1.8	12.8 ± 2.2
T <sub>max</sub> (h)	1.0 ± 0.0	1.8 ± 0.5	1.6 ± 0.6
AUC <sub>0-∞</sub> (ng·hr/ml)	27.5 ± 4.2	57.0 ± 7.7	85.5 ± 15.8
t <sub>1/2</sub> (h)	6.33 ± 0.54	6.79 ± 1.05	5.25 ± 0.93
CL <sub>oral</sub> (l/hr)	1.95 ± 0.31	1.85 ± 0.23	2.61 ± 0.49
(l/hr/kg)	0.033 ± 0.005	0.031 ± 0.003	0.041 ± 0.009

Values represent the mean ± SEM of four volunteers.

TABLE 5

Plasma protein binding and R<sub>B</sub> value of tamsulosin in rats, dogs, and humans

	Drug concentrations <sup>a</sup> (ng/ml)	Rats	Dogs	Humans
		% bound (fu)	200	80.6 (0.194)
R <sub>B</sub>	600	79 (0.210)	90.3 (0.097)	99.1 (0.009)
	50	1.20	0.72	ND
	200	ND	ND	0.53

Values represent the mean of triplicate determinations.

ND, Not determined.

<sup>a</sup> Nominal concentration of <sup>14</sup>C-tamsulosin in plasma or blood before centrifugation.

TABLE 6

Estimated pharmacokinetic parameters based on the plasma unbound tamsulosin in rats, dogs, and humans

Estimated parameter	Rats	Dogs	Humans
CL <sub>oral</sub> /fu (l/hr/kg)	164–586	31–41	2.8–4.6
V <sub>dss</sub> /fu (l/kg)	13.6–14.7	17.6–17.9	18.6–22.8 <sup>a</sup>

CL<sub>oral</sub>/fu: unbound oral clearance; V<sub>dss</sub>/fu, distribution volume based on unbound tamsulosin.

Estimations use fu values determined using <sup>14</sup>C-tamsulosin at the plasma concentration of 200 and 600 ng/ml.

<sup>a</sup> Mean value for V<sub>dss</sub> in humans is 0.205 l/kg (Hoogdalem *et al.*, 1997).

1997). This value was much smaller than Q<sub>h</sub> 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, 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 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 CL<sub>oral</sub> of tamsulosin is a result not only of differences in systemic clearance but also of hepatic availability (F<sub>h</sub>).

CL<sub>oral</sub>, CL<sub>tot</sub>, and F<sub>h</sub> are hybrid parameters defined by individually independent parameters, such as organ blood flow, intrinsic clearance, fu, and R<sub>B</sub>. The CL<sub>oral</sub> of hepatically 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

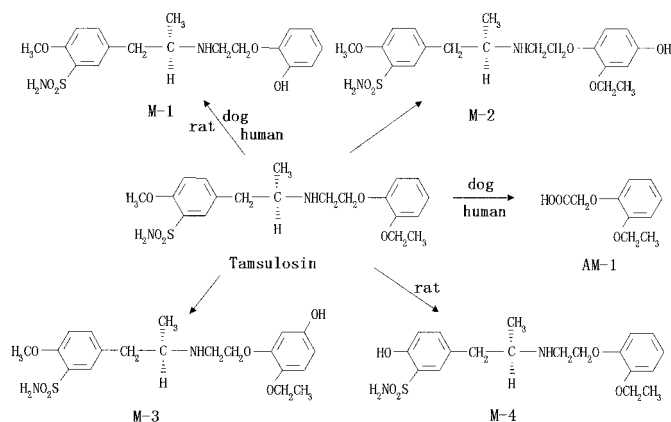


FIG. 6. Scheme for the primary metabolism of tamsulosin in rats, dogs, and humans.

$CL_{\text{hint}}$ , based on the assumption of the Well-stirred model (Pang and Rowland, 1977). This means that the plasma drug concentration after oral dosing is affected by change in  $f_u$  as well as by that in  $CL_{\text{hint}}$ . The  $CL_{\text{oral}}$  of tamsulosin in humans was much lower ( $1/100$ – $1/3000$ ) than that in rats and dogs as mentioned above. The  $f_u$  in humans, moreover, was about  $1/20$  and  $1/10$  of that in rats and dogs, respectively, indicating that the interspecies difference in the  $CL_{\text{oral}}$  of tamsulosin is largely attributable to the difference in  $f_u$ .

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; Aggeler *et al.*, 1967; McElroy and O'Arcy, 1980). In such a case, inter and intrasubject 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 hepatically 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  $CL_{\text{oral}}/f_u$  reflects  $CL_{\text{hint}}$ . The estimated  $CL_{\text{hint}}$  of tamsulosin, calculated as  $CL_{\text{oral}}/f_u$ , 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  $CL_{\text{oral}}$  of tamsulosin is attributable to the difference not only in  $f_u$  but also in  $CL_{\text{hint}}$ . 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  $V_{\text{dss}}$  or  $R_B$  (Øie, 1979; Evans *et al.*, 1973). Interspecies differences in  $V_{\text{dss}}$  are often a result of differences in  $f_u$  (Sawada *et al.*, 1984). The  $V_{\text{dss}}$  of tamsulosin in rats and dogs was 2.86 and 1.74 l/kg, respectively, whereas that in humans was 0.205 l/kg (Hoogdaem *et al.*, 1997), showing a large interspecies difference in  $V_{\text{dss}}$  of tamsulosin. However, distribution volume based on unbound concentration ( $V_{\text{dss}}/f_u$ ) differed little among animal species and humans (Sawada *et al.*, 1984), with  $V_{\text{dss}}/f_u$  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  $f_u$ . 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  $f_u$ .

A species difference in plasma protein binding is also observed for prazosin (Dale and Nilsen, 1984), an  $\alpha_1$ -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  $\alpha_1$ -acid glycoprotein ( $\alpha_1$ -AGP), an acute phase reactant protein (Kremer *et al.*, 1988). The interspecies difference in  $f_u$  appears to be caused by differences in binding characteristics to  $\alpha_1$ -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  $\alpha_1$ -AGP. It is considered that the interspecies difference in  $f_u$  of tamsulosin is caused by a difference in the degree of binding to  $\alpha_1$ -AGP in animal species and humans. In addition, plasma  $\alpha_1$ -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 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  $CL_{\text{oral}}$  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.

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