Pharmacological Effect of Tamsulosin in Relation to Dog Plasma and Tissue Concentrations: Prostatic and Urethral Retention Possibly Contributes to Uroselectivity of Tamsulosin

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ABSTRACT
In the present study the pharmacokinetics and pharmacodynamics of tamsulosin were investigated in anesthetized male dogs. Hypogastric nerve stimulation elevated the intraurethral pressure (IUP), which was inhibited dose dependently by intraduodenal administration of tamsulosin (3–30 μg/kg). The inhibition peaked about 90 min after dosing and lasted up to 240 min. The basal mean blood pressure did not change significantly during the observation period. The plasma, prostatic, and urethral concentrations of tamsulosin were determined by the liquid chromatography-mass spectrometry/mass spectrometry method. The plasma concentration reached the maximal level within 30 min after dosing and gradually declined thereafter. The maximal total plasma concentration of tamsulosin (C_{\text{max, \text{t}}}) and its unbound concentration (C_{\text{max, u}}) correlated with the maximal effect on IUP response (P = 0.015, n = 15) and P = 0.04 (P = 0.01, n = 15, respectively). Each individual unbound plasma concentration did not correlate, however, with its associated inhibition of IUP response (P = 0.04, n = 126). Although the plasma concentration of tamsulosin decreased nearly to the lower limit of quantitation 240 min after dosing, the prostatic and urethral concentrations remained high, i.e., 13 to 44 times greater than the plasma concentration. Our data demonstrate that the maximal inhibition by tamsulosin of IUP response is well correlated with the maximal plasma concentration in the early phase. The sustained effect of tamsulosin on IUP response that follows may be related to prostatic and urethral retention of tamsulosin.

Prostatic and urethral smooth muscle tone is maintained by stimulation of postjunctional α1-adrenoceptors through the release of noradrenaline from the adrenergic nerves in both animals and humans (Andersson and Sjögren, 1982; Gosling, 1983). Benign prostatic hyperplasia is associated with a bladder outlet obstruction that has been postulated to occur via both mechanical compression exerted by the increased bulk of the prostate and alterations in the neural control of the prostatic smooth muscle. In recent years, therefore, α1-adrenoceptor antagonists have been increasingly used for the symptomatic treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (Chapple, 1998). α1-Adrenoceptor antagonists, originally developed as antihypertensives, generally show poor selectivity for lower urinary tract over vascular-related adverse events, however, which limits their tolerance and clinical utility. There is therefore great interest in the design of α1-adrenoceptor antagonists with a high uroselective profile.

Molecular and pharmacological studies have led to the division of α1-adrenoceptors into three subtypes: α_{1A}, α_{1B}, and α_{1D}-adrenoceptors (Hieble et al., 1995; Michel et al., 1995). The α_{1A}-adrenoceptor subtype has been described as predominant in the human prostate and urethra (Price et al., 1993; Nasu et al., 1998) and plays a prevalent role in mediating the contractile response of human prostate (Forray et al., 1994). These findings suggest that an α_{1A}-adrenoceptor subtype-selective antagonist may equally improve LUTS and curtail adverse circulatory events in comparison with non-α_{1}-adrenoceptor subtype-selective antagonists.

Tamsulosin is an α_{1}-adrenoceptor antagonist developed primarily for LUTS treatment. In in vitro studies tamsulosin...
shows a 12- to 20-fold and 2- to 3-fold greater affinity for \( \alpha_1 \)-adrenoceptors than for \( \alpha_2 \)- and \( \alpha_3 \)-adrenoceptors, respectively (Foglar et al., 1995; Leonardi et al., 1997; Taguchi et al., 1997) and an approximately 12-fold greater affinity for \( \alpha_1 \)-adrenoceptors in the human prostate than in the human aorta (Yamada et al., 1994a). In phase III double-blind, placebo-controlled studies, tamsulosin had improved LUTS with a minimal decrease in blood pressure and a low incidence of circulatory adverse events, e.g., dizziness, orthostatic hypotension, and tachycardia (Chapple et al., 1996; Lepor, 1998; Narayan et al., 1998), indicating that tamsulosin shows uroselectivity clinically. It has been postulated that the uroselectivity of tamsulosin is based on both \( \alpha_1 \)-selectivity (Brune et al., 1996) and modified release formulation (Takanaka et al., 1995). These hypotheses are still controversial, however.

Although tamsulosin is widely used clinically, the relationship between the pharmacokinetics and pharmacodynamics of the drug has not been studied. We therefore investigated the relationship between the pharmacokinetics of tamsulosin and its inhibitory activity on hypogastric nerve stimulation (HNS)-induced prostatic intraurethral pressure (IUP) elevation in anesthetized male dogs. This canine model allows us to measure the effect of tamsulosin at shorter intervals than an \( \alpha_1 \)-agonist-induced, e.g., phenylephrine-induced, IUP elevation model, because the urethral response to HNS returns to the basal level more quickly in contrast to a model with phenylephrine-induced IUP elevation. In addition to the determination of the total concentration of tamsulosin, the unbound concentration, which is more responsible for efficacy than the total concentration, was also calculated by measuring plasma protein binding. Interestingly, our study revealed that an inhibitory effect on IUP response lasted after the plasma concentration decreased to close to the lower limit of quantitation (LLOQ), suggesting that the drug may possibly be retained by the target tissue. The concentrations of tamsulosin were therefore also determined in the urethra and prostate. Our pharmacokinetics data suggest that lower urinary tract retention of tamsulosin possibly contributes to not only a sustained effect on IUP response in dogs but also to its clinically observed uroselectivity.

**Materials and Methods**

**Functional Experiment.** The animal experiments in the present study were performed in compliance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical. Male beagle dogs (9.5–13.0 kg) were fasted overnight and anesthetized with pentobarbital sodium (30 mg/kg i.v. and 3–5 mg/kg/h i.v.). After endotracheal intubation, the animals were artificially ventilated with room air (respirator: SN-480-3; Shinano Seisakusyo, Tokyo, Japan; tidal volume: 20 ml/kg; respiration rate: 20 breaths/min). After a stabilizing period following the surgical procedure, the animal experiments in the present study were performed in compliance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical. Male beagle dogs (9.5–13.0 kg) were fasted overnight and anesthetized with pentobarbital sodium (30 mg/kg i.v. and 3–5 mg/kg/h i.v.). After endotracheal intubation, the animals were artificially ventilated with room air (respirator: SN-480-3; Shinano Seisakusyo, Tokyo, Japan; tidal volume: 20 ml/kg; respiration rate: 20 breaths/min). After a stabilizing period following the surgical procedure, the animals were artificially ventilated with room air (respirator: SN-480-3; Shinano Seisakusyo, Tokyo, Japan; tidal volume: 20 ml/kg; respiration rate: 20 breaths/min). After a stabilizing period following the surgical procedure, the animals were artificially ventilated with room air (respirator: SN-480-3; Shinano Seisakusyo, Tokyo, Japan; tidal volume: 20 ml/kg; respiration rate: 20 breaths/min).

**In Vitro Protein Binding.** Plasma samples obtained from anesthetized dogs before and 240 min after administration of tamsulosin were used in vitro. In vitro protein binding was examined by the equilibrium dialysis method (Matsushima et al., 1997) as follows. Briefly, in vitro bound or unbound fraction was measured in the plasma containing tamsulosin by means of a \(^{14} C \) tamsulosin. To a 1-ml aliquot of the plasma, a 50-\( \mu l \) aliquot of \(^{14} C \) tamsulosin solution (phosphate-buffered isotonic solution, pH 7.4) was added to give a rather high concentration of 50 ng/ml to achieve a reliable determination. The solution was then dialyzed with an equal volume of the phosphate-buffered isotonic solution at \( 37^\circ C \) for 4 h in an equilibrium dializer (Spectra/Por equilibrium dializer; Spectrum Co., Houston, TX). One milliliter of the dialysate fluid and 0.2 ml of plasma after dialysis were used to measure the unbound and total \(^{14} C \) tamsulosin concentrations. These samples were mixed with 10 ml of scintillation cocktail (Aquasol 2; New England Nuclear, Boston, MA). The total (\( C_t \)) and unbound (\( C_u \)) plasma concentrations were calculated from the radioactivity of \(^{14} C \) tamsulosin. The fraction of unbound drug in plasma (\( f_u \)) and the protein binding (\% binding) of tamsulosin were also calculated as follows:

\[
\% \text{ binding} = (1 - f_u)100
\]

**Calculation of Pharmacokinetic Parameters.** The maximal total plasma concentration (\( C_{\text{max},t} \)) and time to \( C_{\text{max},t} \) (\( T_{\text{max},t} \)) were observed values. The area under the total plasma concentration-time curve up to the last measurable time point (\( \text{AUC}_{\text{last},t} \)) was analyzed using a noncompartmental technique (log-linear trapezoidal method). The elimination half-life (\( t_{1/2} \)) was determined by least-squares regression analysis of the terminal log-linear portions of the plasma concentration-time profile. The \( C_{\text{max}} \) and \( \text{AUC}_{\text{last}} \) of unbound tamsulosin (\( C_{\text{max},u} \) and \( \text{AUC}_{\text{last},u} \)) were calculated by the following equations using the \( f_u \) value obtained from the in vitro binding study:

\[
\begin{align*}
C_{\text{max},u} &= C_{\text{max},t} \times f_u \\
\text{AUC}_{\text{last},u} &= \text{AUC}_{\text{last},t} \times f_u
\end{align*}
\]
Drugs. Tamsulosin hydrochloride was synthesized at Yamanouchi Pharmaceutical Co., Ltd. Epinephrine was purchased from Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan) and [14C]tamsulosin (specific activity: 3.6 Bq/ng, radiochemical purity: 99% or higher) was specially synthesized by Amersham (Tokyo, Japan). Tamsulosin was dissolved and diluted with distilled water.

Statistical Analysis. Two-way repeated-measures ANOVA followed by Dunnett’s multiple range test was used to compare the degree of the inhibition of HNS-induced IUP response or mean blood pressure (MBP) effects at each time point during the time course of the experiment. Differences were considered significant at $p < 0.05$.

ED50, a dose inducing 50% inhibition of the IUP response was computed by the linear regression method. The time course of inhibition of the IUP response was plotted with the plasma concentration for analyzing the relationship between efficacy and tamsulosin concentrations. The relationship between the pharmacokinetic parameters and inhibition of IUP response was analyzed by linear regression analysis.

Results

Functional Experiment. Figures 1 and 2 show the time course of tamsulosin effects on HNS-induced increases in prostatic IUP and basal MBP in anesthetized dogs. Tamsulosin (3–30 μg/kg i.d.) dose dependently inhibited HNS-induced IUP elevation. The effect peaked at about 90 min after dosing and lasted at least 240 min. An ED50 value (the dose required to produce a 50% inhibition of HNS-induced IUP response) of 7.2 μg/kg i.d. was estimated. Tamsulosin had no significant effect on basal MBP during the observation period.

Plasma Concentrations. Figure 3 shows the plasma concentration time course of tamsulosin after intraduodenal administration at 3, 10, and 30 μg/kg. Table 1 lists the pharmacokinetic parameters derived from individual animals for each dose group. The plasma concentration of tamsulosin reached the maximal level ($C_{\text{max}, t}$: 0.25, 1.51, and 4.18 ng/ml) at 10 to 30 min after dosing and declined with a $t_{1/2}$ of 81 to 98 min. The AUClast, t values showed linear dose dependence and were 22, 104, and 259 ng · min/ml for 3, 10, and 30 μg/kg i.d., respectively. At 240 min after dosing, the plasma concentration declined to below LLOQ (0.05 ng/ml), 0.092, and 0.262 ng/ml at 3, 10, and 30 μg/kg i.d., respectively.

Plasma Protein Binding and Unbound Tamsulosin Concentration. The degree of plasma protein binding did not change before or after tamsulosin dosing. It exhibited a mean ratio of 71.7 to 77.6% with no major difference between groups (Table 2), a result indicating that the degree of plasma protein binding was stable in this experiment. The $C_{\text{max}, u}$ and AUClast, u were calculated as 68 to 967 pg/ml and 5.9 to 61.2 ng · min/ml, respectively (Table 3).

Relationship between Plasma Concentration and Efficacy. The correlation coefficients ($r^2$) between $C_{\text{max}, t}$ and AUClast, t, and maximal effect ($E_{\text{max}}$) on IUP response in anesthetized dogs were 0.81 ($p < 0.01, n = 15$) and 0.83 ($p < 0.01, n = 15$), respectively (Fig. 4). $C_{\text{max}, u}$ and AUClast, u also showed a good correlation with $E_{\text{max}}$ [Fig. 5, $r^2 = 0.84$ ($p < 0.01, n = 15$) and $r^2 = 0.85$ ($p < 0.01, n = 15$), respectively]. Each individual plasma concentration did not correlate with its associated inhibition of IUP response, however (data not shown; $r^2 = 0.04, n = 126$). The inhibitory effect of tamsulosin on IUP response was plotted against the plasma tamsulosin concentration in Fig. 6. The resulting curves exhibited a counterclockwise hysteresis loop at every tested dose.

Tissue Concentrations. Figure 7 shows the plasma, prostatic, and urethral concentrations of tamsulosin (10 and 30 μg/kg i.d.) at 240 min after dosing in anesthetized dogs. The prostatic concentrations were 44 and 21 times higher.

(A) Control

(B) Tamsulosin

Fig. 1. Typical trace of HNS (4–10 V, 10 Hz, 2-ms duration, for 5 s)-induced IUP elevation before and after administration of distilled water (control) (A) and tamsulosin (30 μg/kg i.d.) (B) in anesthetized dogs.
than the plasma concentrations (4.03 ng/g versus 0.092 ng/ml at 10 μg/kg i.d. and 5.49 ng/g versus 0.262 ng/ml at 30 μg/kg i.d., respectively). The urethral concentrations were also 29 and 13 times greater than the plasma concentrations.

### Discussion

In the present study the relationship between the pharmacological effect and the associated plasma and tissue concentrations of tamsulosin was investigated in anesthetized dogs. Furthermore, the unbound plasma concentration, which is presumably related to efficacy more than the total concentration, was determined by measurement of the in vitro protein binding of tamsulosin.

Tamsulosin dose dependently inhibited the HNS-induced IUP elevation, whereas $C_{\text{max}}$ also increased in a dose-dependent manner in anesthetized dogs. The correlation coefficient of $C_{\text{max}, \text{t}}$ or $C_{\text{max}, \text{u}}$ versus $E_{\text{max}}$ of IUP response showed high values ($r^2 = 0.81$ and $r^2 = 0.84$, respectively), indicating that the maximal effect of tamsulosin on IUP response correlates with the maximal plasma concentration. It should be noted that $E_{\text{max}}$ was observed about 90 min after dosing, whereas the plasma concentration of tamsulosin quickly increased with a $T_{\text{max}}$ of 10 to 30 min. When the inhibitory effect of tamsulosin on IUP response was plotted against the plasma tamsulosin concentration, the resulting curves exhibited a counterclockwise hysteresis loop, a result indicating a time lag between the plasma concentration and the pharmacological effect. Although there is no good explanation for the time lag, this gap between the pharmacokinetics and pharmacodynamics may correspond to the time required to deliver tamsulosin to the target organ and initiate action.

Interestingly, the pharmacological effect of tamsulosin on IUP response lasted up to 240 min with no attenuation, although the plasma concentration started to decline within 30 min after administration at every dose. Three possible reasons for this are 1) the contribution of metabolites, 2) an irreversible blocking effect, and 3) tissue retention. Although several active metabolites of tamsulosin have been reported (Taguchi et al., 1997), the ratio of metabolites was low in dogs (Soeishi et al., 1996), suggesting that active metabolites are not involved. A comparison of high performance liquid chromatography and radioreceptor assay analysis of tamsulosin pharmacokinetics in humans also did not show evidence of relevant concentrations of active metabolites (Taguchi et al., 1998). The binding of $[\text{H}]$tamsulosin in human prostate membranes after achieving a steady state could be dissociated time dependently by an excess of phentolamine (Yamada et al., 1994b). In radioligand binding experiments, $[\text{H}]$tamsulosin competed with several $\alpha$-adrenoceptor agonists and antagonists using cloned $\alpha_1$-adrenoceptor subtypes (Fukasawa et al., 1998) and membranes of the rat hippocampus and spleen (Yazawa et al., 1992). These results suggest that irreversible antagonism by tamsulosin can also be ruled out. In our study, the prostatic and urethral concentrations at 240 min after dosing were comparative to plasma $C_{\text{max}, \text{t}}$ and were 13 to 44 times higher than the plasma concentration at the 240 min time point. In rats, tamsulosin produced sustained occupancy of $\alpha_1$-adrenoceptors in the prostate after a marked reduction in the plasma concentration (Ohkura et al., 1998). Taken together, these data indicate that tamsulosin appeared to be retained in its target organs, i.e., the prostate and urethra, longer than in the plasma and that it showed a sustained urethral effect.

As shown in Table 1 and Fig. 4, the values of $C_{\text{max}, \text{t}}$ and $\text{AUC}_{\text{last}, \text{t}}$ for tamsulosin in anesthetized dogs were lower than those of $C_{\text{max}, \text{t}}$ (9.1 ng/ml) and $\text{AUC}_t$ (6480 ng · min/ml.
(=108 ng·h/ml) after oral administration of tamsulosin (0.2 mg) to healthy human volunteers (Koiso et al., 1996). As shown in Table 3 and Fig. 5, however, $C_{\text{max}, \text{u}}$ (68–967 pg/ml) and AUC$_{\text{last}, \text{u}}$ (5.9–61.2 ng·min/ml) for tamsulosin in anesthetized dogs were of the same order of magnitude compared with $C_{\text{max}, \text{u}}$ (80 pg/ml) and AUC$_{\text{u}}$ [53.9 ng·min/ml (=899 pg·h/ml)] in healthy human volunteers (Koiso et al., 1996). In comparison to the pharmacokinetic profile of an orally administered 0.4-mg dose of tamsulosin in humans (Wolzt et al., 1998), the $C_{\text{max}}$ and AUC in anesthetized dogs were also similar, not in terms of total plasma concentration but in terms of unbound plasma concentration. These observations appear to be explained by a higher protein binding of tamsulosin in humans (99%) (Matsushima et al., 1998) than in dogs (71.7–77.6%) in this study. These data confirm the importance of considering the differences in protein binding of drugs between species when plasma concentrations at the effective doses are compared. Moreover, the unbound concentration of tamsulosin in dogs was similar to that in humans, suggesting that the effective concentrations of tamsulosin in dogs and humans are comparable.

Tamsulosin is the first $\alpha_1$-adrenoceptor antagonist that was proved to ameliorate LUTS without showing relevant hypotensive effects in phase III placebo-controlled studies (Chapple et al., 1996; Lepor, 1998; Narayan et al., 1998). In placebo-controlled clinical trials with doxazosin or terazosin (Djavan and Marberger, 1999), non-$\alpha_1$-subtype-selective antagonists, larger incidences of cardiovascular side effects than those observed with tamsulosin have been reported. Although the reasons for the uroselective profile of tamsulosin are still controversial, slower absorption and depressed $C_{\text{max}}$ by a modified release oral formulation and $\alpha_1$-A-subtype selectivity may be involved (Takenaka et al., 1995; Brune et al., 1996). Alfuzosin, a non-$\alpha_1$-subtype-selective antagonist, showed functional uroselectivity, which may be related to the higher prostatic concentration of alfuzosin in the prostate.

### Table 1
Pharmacokinetic parameters of tamsulosin after intraduodenal administration in anesthetized male dogs
The values are the means ± S.E.M. The number of animals is shown in parentheses.

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>$C_{\text{max}, \text{t}}$ (ng/ml)</th>
<th>$T_{\text{max}}$ (min)</th>
<th>AUC$_{\text{last}, \text{t}}$ (ng·min/ml)</th>
<th>$t_{1/2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.25 ± 0.05 (5)</td>
<td>30 ± 8 (5)</td>
<td>22 ± 3 (5)</td>
<td>84 ± 10</td>
</tr>
<tr>
<td>10</td>
<td>1.51 ± 0.24 (5)</td>
<td>12 ± 2 (5)</td>
<td>104 ± 16 (5)</td>
<td>81 ± 5</td>
</tr>
<tr>
<td>30</td>
<td>4.18 ± 0.92 (5)</td>
<td>10 ± 2 (5)</td>
<td>209 ± 49 (5)</td>
<td>98 ± 9</td>
</tr>
</tbody>
</table>

* One of five animals could not be analyzed.

### Table 2
Plasma protein binding of tamsulosin after intraduodenal administration in anesthetized male dogs
The values are the means ± S.E.M.

<table>
<thead>
<tr>
<th>Plasma Protein Binding</th>
<th>Before</th>
<th>After</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 µg/kg (n = 5)</td>
<td>70.2 ± 2.6</td>
<td>73.1 ± 1.5</td>
<td>71.7 ± 2.0</td>
</tr>
<tr>
<td>10 µg/kg (n = 5)</td>
<td>76.7 ± 2.6</td>
<td>78.4 ± 1.1</td>
<td>77.6 ± 1.3</td>
</tr>
<tr>
<td>30 µg/kg (n = 5)</td>
<td>74.2 ± 2.2</td>
<td>75.7 ± 2.2</td>
<td>75.3 ± 2.1</td>
</tr>
</tbody>
</table>

### Table 3
Pharmacokinetic parameters of unbound tamsulosin after intraduodenal administration in anesthetized male dogs
The values are the means ± S.E.M. of five animals.

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>$C_{\text{max}, \text{u}}$ (pg/ml)</th>
<th>AUC$_{\text{last}, \text{u}}$ (ng·min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>68 ± 9</td>
<td>5.9 ± 0.5</td>
</tr>
<tr>
<td>10</td>
<td>328 ± 29</td>
<td>23.0 ± 3.2</td>
</tr>
<tr>
<td>30</td>
<td>967 ± 159</td>
<td>61.2 ± 9.3</td>
</tr>
</tbody>
</table>

Fig. 4. Relationship between $C_{\text{max}, \text{t}}$ (A) and AUC$_{\text{last}, \text{t}}$ (B) of tamsulosin (3–30 µg/kg i.d.) and maximal effect ($E_{\text{max}}$) on HNS-induced IUP responses in anesthetized dogs. The vertical bold line in the column and its width represent the mean ± S.D. of $C_{\text{max}, \text{t}}$ (A) and AUC$_{\text{t}}$ (B) after administration of tamsulosin (0.2 mg p.o.) to healthy volunteers (Koiso et al., 1996).

$E_{\text{max}}$ by a modified release oral formulation and $\alpha_1$-A-subtype selectivity may be involved (Takenaka et al., 1995; Brune et al., 1996). Alfuzosin, a non-$\alpha_1$-subtype-selective antagonist, showed functional uroselectivity, which may be related to the higher prostatic concentration of alfuzosin in the prostate.
than in plasma (Martin et al., 1998). Although several antagonists showing a high degree of uroselectivity in animal models have been identified, their clinical superiority over currently available \( \alpha_1 \)-adrenoceptor antagonists has not yet been demonstrated (Hieble and Ruffolo, 1997). Our results indicate that high tissue retention of tamsulosin may also contribute to the clinically observed uroselectivity of tamsulosin, but further study would be necessary to confirm this hypothesis.

In conclusion, tamsulosin dose dependently inhibited the IUP response and its maximal effect correlated well with the maximal plasma concentration in anesthetized male dogs. The time course of tamsulosin’s effect on IUP response did not correlate with the plasma concentration. The sustained pharmacological effect of tamsulosin after the concentration in the plasma declined may be related to the high level of prostatic and urethral concentrations of tamsulosin.

Fig. 5. Relationship between \( C_{\text{max},u} \) (A) and \( \text{AUC}_{\text{last},u} \) (B) of tamsulosin (3–30 \( \mu \)g/kg i.d.) and maximal effect (\( E_{\text{max}} \)) on HNS-induced IUP responses in anesthetized dogs. The vertical bold line in the column and its width represent the mean \( \pm \) S.D. of \( C_{\text{max},u} \) (A) and \( \text{AUC}_{\text{last},u} \) (B) after administration of tamsulosin (0.2 mg p.o.) to healthy volunteers (Koiso et al., 1996).

Fig. 6. Relationship between plasma concentration and the inhibitory effect on HNS-induced IUP responses after intraduodenal administration of tamsulosin (●, 3 \( \mu \)g/kg; ▲, 10 \( \mu \)g/kg; ■, 30 \( \mu \)g/kg) in anesthetized dogs. The symbols correspond to the mean data obtained in Figs. 2 and 3.

Fig. 7. Plasma, prostatic, and urethral concentrations of tamsulosin at 240 min after dosing in anesthetized dogs. The plasma concentrations shown in Fig. 2 at 240 min after 10- and 30-\( \mu \)g/kg doses of tamsulosin were selected for comparison. Each column represents the mean \( \pm \) S.E.M.

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