Relationships between Pharmacokinetics and Blockade of Agonist-Induced Prostatic Intracathral Pressure and Mean Arterial Pressure in the Conscious Dog After Single and Repeated Daily Oral Administration of Terazosin

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ABSTRACT
The purpose of this study was to determine the potency and selectivity of the alpha-1 adrenergic receptor antagonist terazosin based on relationships between plasma concentrations and blockade of intracathral pressure (IUP) and mean arterial pressure (MAP) responses. When IUP and MAP blockade effects were plotted against terazosin plasma concentration, direct relationships were observed that were well described by the sigmoidal maximal effect model and resulted in IUP and MAP IC50 values of 48.6 and 12.2 ng/ml, respectively. Repeated daily dosing resulted in little accumulation of terazosin in plasma and demonstrated consistent blockade responses over 7 days. MAP blockade was observed up to 23 hr after terazosin administration, whereas IUP blockade returned to control levels before 23 hr. Combined pharmacokinetic/pharmacodynamic analysis showed no selective antagonism of IUP by terazosin but may provide a useful way to show uroselectivity of novel agents.

Terazosin is an alpha-1-selective adrenergic antagonist initially developed as an oral antihypertensive agent with subsequent indications for treatment of symptomatic BPH (Duzendofer, 1989; Fabricius et al., 1990; Lepor et al., 1992; Wilde et al., 1993). The compound reduces blood pressure and alleviates BPH symptomology through blockade of alpha-1 receptor-mediated vasoconstriction and contraction of smooth muscle in the lower urinary tract, respectively (Timmarsh and Monk, 1987; Wilde et al., 1993). Although terazosin is an effective agent for the treatment of symptomatic BPH, there remain concerns about the cardiovascular side effects, particularly syncope and excessive hypotension in elderly patients (Kaplan et al., 1995; Wilde et al., 1993). The potential for the development of uroselective alpha-1-selective adrenergic antagonists having reduced vascular effects is, therefore, of considerable therapeutic interest. For the purposes of characterizing terazosin as a reference compound and providing a basis for comparison with novel uroselective alpha-1-selective adrenergic antagonists, a conscious canine model has been developed to simultaneously assess blockade of agonist-induced IUP and MAP responses (Brune et al., 1996). The concomitant measurement of terazosin plasma concentrations has been incorporated to investigate the relationships between pharmacokinetics and blockade of agonist-induced IUP and MAP responses. The experimental model described herein has been used to simultaneously evaluate the pharmacokinetic and pharmacodynamic properties of terazosin, an alpha-1-selective adrenergic antagonist. Fur-
thermore, establishing the pharmacokinetic/pharmacodynamic relationship for terazosin provides a benchmark for evaluating differential cardiovascular and urological effects of novel alpha-1 antagonists and allows for the identification of these compounds as uroselective agents for the safe and effective treatment of symptomatic BPH.

Materials and Methods

Animals

Male beagle dogs (Marshall Farms, North Rose, NY) >2 years of age and weighing between 10 and 15 kg were used in this study. For single dosing studies, dogs were fasted 20 hr before dosing. For the repeated daily dosing study, dogs were allowed access to food (1600 Canine Chow, Agway Inc., Syracuse, NY) from 12:30 to 3:30 p.m. from 10 days before the first dose until study completion. Water was available ad libitum. Dogs were cared for according to National Institutes of Health guidelines on canine care, and all experimental protocols described herein were reviewed and approved by the Institutional Animal Care and Use Committee of Abbott Laboratories.

Instrumentation

At least 1 week before any antagonist dosing, dogs were instrumented for the chronic, continuous measurement of arterial blood pressure by implantation of a telemetry transducer/transmitter (TA11PA-C40, Data Sciences International, St. Paul, MN) into a carotid artery. On test day, dogs were placed in sling restraints, and an Abbocath-T i.v. catheter (18-G, Abbott Laboratories, North Chicago, IL) was inserted into a cephalic vein for blood sampling and for the administration of agonist. The telemetry receiver (RA1310, Data Sciences International, St. Paul, MN), placed near the head of each dog, was connected to an analog output adapter (R11C1PA, Data Sciences International), which was in turn interfaced to a computerized data acquisition system (Modular Instruments, Inc., Mulverno, PA), allowing continuous, calibrated recording of the arterial pressure wave form. MAP was obtained by electronically filtering this signal. A 7F Swan-Ganz balloon catheter (41224–01, Abbott Laboratories) was lubricated with a water-soluble jelly (PDI Lubricating Jelly, Professional Disposables, Orangeburg, NY), inserted into the urethral orifice and advanced ~40 cm until the balloon tip was placed well inside the bladder. The balloon was then inflated with 1 ml of room air, and the catheter was slowly withdrawn just past the first resistance that was felt at the bladder neck. Preliminary experiments in which dogs were killed after such placement confirmed that this technique resulted in consistent positioning of the balloon within the prostatic urethra. The balloon port of the catheter was connected to an Abbott Transpac pressure transducer (42556–01) interfaced to the same computerized data acquisition system for the continuous measurement of IUP.

Chemicals

Terazosin was synthesized at Abbott Laboratories. Prazosin and PE were purchased from Sigma Chemical Co. (St. Louis, MO). HPLC-grade TFA, acetonitrile, ethyl acetate and hexane were purchased from EM Sciences (Gibbstown, NJ). Normal dog plasma in EDTA was from Pel Freez (Rogers, AR). Other reagents used in the study were analytical grade.

Study Design

Single dosing. Three groups of dogs were administered three different oral doses of terazosin2 at 0.1 (n = 5), 0.3 (n = 4) and 1 (n = 5) mg/kg. In addition, effect data were collected for a vehicle-treated group (n = 7) to assess effects unrelated to terazosin administration. Before dosing, baseline IUP and MAP responses were measured after single i.v. bolus injections of PE3 (saline vehicle) at 32 μg/kg in a volume of 0.1 ml/kg b.wt. Dogs then received oral doses of terazosin at 0.1, 0.3 or 1 mg/kg (water vehicle) by gavage in a volume of 1 ml/kg. Before and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hr after terazosin administration, 4-ml blood samples were collected for measurement of plasma terazosin concentrations. At 1, 2, 4, 6, 12 and 24 hr after terazosin dosing, IUP and MAP responses were measured after i.v. bolus PE challenges at 32 μg/kg.

Repeated daily dosing. Two dose groups (n = 4) were given oral doses of terazosin (water vehicle) at 0.3 and 1.0 mg/kg by gavage once a day at precise 24-hr intervals for 7 consecutive days at a dosing volume of 1 ml/kg. Blood samples for subsequent determination of terazosin plasma concentrations, and the IUP and MAP pressor responses to 32 μg/kg intravenous PE were obtained just before the first dose and at 1, 2 and 23 hr after the first, second, third and various time points after antagonist administration. Increases in IUP and MAP caused by PE were allowed to return to baseline before subsequent challenges. Blood (4 ml) was collected in Vacutainers containing EDTA as an anticoagulant (Becton Dickinson, Franklin Lakes, NJ). Blood samples were centrifuged at 500 × g for 10 min, and the supernatant was collected as the plasma fraction. Plasma samples were stored at −20°C until analysis by HPLC.

Analysis of Terazosin in Plasma

Plasma concentrations of terazosin were measured by a modified HPLC method (Patterson, 1984). Standards were prepared by spiking normal dog plasma with various concentrations of terazosin.1 To 0.2 ml of plasma or plasma standards we added 0.2 ml of 10 ng/ml prazosin2 in 0.1% TFA as an internal standard. Samples were alkalinized with 0.1 ml of 1 N NaOH and extracted once with 5 ml of ethyl acetate/hexane (9:1). The organic layer was collected and concentrated to dryness with a Savant SS22 vacuum-assisted centrifugal evaporator system (Savant Instruments, Farmingdale, NY). The dry residue was reconstituted in 0.2 ml of mobile phase, and 100 μl was injected into the chromatographic system.

The chromatographic system consisted of a model 400 solvent delivery system (Applied Biosystems, Foster City, CA), a model AS-2000 auto sampler (Hitachi Instruments, Chicago, IL), a YMCbasic 150 × 4.6 mm i.d. column (YMC, Wilmington, NC) and a model 980 fluorescence detector (Applied Biosystems, Foster City, CA). Rainin Dynamax software (Rainin, Woburn, MA) was used for data acquisition and peak integration. The column was eluted with 20:80 v/v acetonitrile and 0.1% TFA at a constant flow rate of 0.8 ml/min at room temperature. The effluent from the column was monitored for fluorescence emission using a 350-nm filter before excitation at 250 nm. The retention times were 6.0 and 10.0 min for terazosin and prazosin, respectively. The standard curve was linear from 2 to 200 ng/ml (triplicate samples) with correlation coefficients ≥ .999. Coefficients of variation were determined for triplicate spiked samples at 2, 20 and 200 ng/ml and resulted in values of < 10%. Interday coefficients of variation were also determined for the spiked samples from three separate experiments and resulted in values of < 7%. On the basis of a coefficient of variation of < 20%, the assay had a quantitation limit of 0.5 ng/ml. Analysis of control blank plasma indicated the absence of interfering peaks.
seventh doses. Blood samples and PE challenge responses were also obtained 1 and 2 hr after the fourth dose and 23 hr after the sixth dose.

Analysis of Results

For single-dose studies, elimination half-life values for individual plasma concentration-time data were determined by the iterative curve fitting program NONLIN, VAX Version 3.0 (SCI Software, Lexington, KY), using a one-compartment open model for single oral dosing such that

\[
C = A(e^{-kt} - e^{-kt'}),
\]

where \(C\) is a constant coefficient or intercept, and \(k_a\) and \(k_e\) are first-order rate constants for absorption and elimination, respectively. The elimination rate constant, \(k_e\), was converted to an elimination half-life by the equation \(t_{1/2} = \ln(2)/k_e\). \(C_{\text{max}}\) and \(T_{\text{max}}\) values were determined by inspection of individual concentration-time plots. The \(\text{AUC}_{0-\infty}\) values were calculated by application of the trapezoidal rule such that

\[
\text{AUC}_{0-\infty} = \sum_{i=1}^{n} C_i \Delta t_i + C_{\infty}/k_e,
\]

where \(C_{\infty}\) is the plasma concentration measured at the last time point (Welling, 1986). Oral clearance (CL/F) was calculated with the equation \(\text{CL/F} = \text{dose}/\text{AUC}_{0-\infty}\).

For repeated daily dosing studies, plasma levels were assumed to reach steady state after 5 half-lives or 45 hr (Rowland and Tozer, 1995). Calculation of observed and predicted accumulation indices \((R_{\infty})\) for repeated daily dosing was based on the equation

\[
R_{\infty} = C_{\text{max}}/C_{1,\text{min}} = 1/(1 - e^{-kt}),
\]

where \(C_{\text{max}}\) is the trough plasma concentration at the end of the dosing interval after reaching steady state, and \(C_{1,\text{min}}\) is the plasma concentration at the end of the first dosing interval, \(k_e\) (day\(^{-1}\)) is the elimination rate constant derived from single dosing and \(\tau\) is the dose interval in days (Rowland and Tozer, 1995).

PE-induced IUP and MAP responses measured before and after administration of terazosin were expressed as percent blockade by normalizing postdose attenuation of peak responses to predose or baseline peak responses within individual dogs. \(E_{\text{max}}\) and \(T_{\text{max}}\) values were determined by inspection of individual percent blockade-time plots. The \(\text{AUC}_{0-\infty}\) values, calculated by the trapezoidal rule, were taken to represent the overall IUP and MAP blockade effects of terazosin over time.

Plasma concentrations were related to IUP and MAP percent blockade responses with the \(E_{\text{max}}\) and sigmoidal \(E_{\text{max}}\) models (Holfford and Sheiner, 1981). The PCNONLIN version 4.0 (SCI Software, Lexington, KY) program was used for fitting individual concentration effect data by iterative nonlinear regression according to the following model: \(E = E_{\text{max}} \cdot C_p^{\gamma} / (IC_{50}^{\gamma} + C_p^{\gamma})\), where \(E\) is the observed inhibition, \(E_{\text{max}}\) is the theoretical maximal inhibition that can be obtained, \(C_p\) is the plasma concentration, \(IC_{50}\) is the plasma concentration that produces 50% of the theoretical maximal effect and \(\gamma\) is a shape factor that determines the steepness of the curve around the \(IC_{50}\) value. For the \(E_{\text{max}}\) model, \(\gamma\) was set to a value of 1, whereas \(\gamma\) was a variable for the sigmoidal \(E_{\text{max}}\) model. \(E_{\text{max}}\) values were set to 100% because this is the theoretical maximum for IUP and MAP blockade. The decision to use the sigmoidal \(E_{\text{max}}\) model as opposed to the less complex \(E_{\text{max}}\) model was determined by statistical evaluation of the ability of the models to fit the observed data. Assessment of the goodness of the model to fit the observed data was based on Akaike’s Information Criteria, residual plots, coefficients of determination and S.E.E. values (Akaike, 1978).

One-way ANOVA was applied to determine significant differences between groups and a value of \(P \leq .05\) was used to establish statistical significance. Where only two groups were compared, Student’s \(t\) test was applied, and \(P\) values are reported in the text.

Results

Single dosing (pharmacokinetics). Figure 1 shows the mean plasma concentration-time course for terazosin after oral administration at 0.1, 0.3 and 1 mg/kg. Table 1 lists the mean pharmacokinetic parameters derived from individual animals for each dose group. For all groups, mean \(T_{\text{max}}\) values ranged from 1.0 to 2.1 hr with no significant differences between groups. Mean \(C_{\text{max}}\) values showed dose dependence and were 13, 53 and 194 ng/hr/ml for 0.1, 0.3 and 1 mg/kg doses, respectively. Dose-normalized mean \(\text{AUC}_{0-\infty}\) values were not significantly different between groups with values of 2126 ± 250, 2544 ± 78 and 2661 ± 168 ng/hr/ml for 0.1, 0.3 and 1 mg/kg doses, respectively. Elimination half-life values for individual dogs ranged from 6 to 15 hr, whereas the harmonic means for each group ranged from 8.4 to 8.6 hr and remained roughly constant with respect to dose. Total mean oral clearances for each group ranged from 349 to 457 (ml/hr/kg) with no significant differences between groups.

Single dosing (IUP blockade). Figure 2 shows the mean effect-time course for blockade of 32 \(\mu\)g/kg PE-stimulated IUP responses after single oral administration of terazosin at 0.1, 0.3 and 1 mg/kg or water vehicle. The mean net change in IUP response after stimulation with PE but before oral administration of terazosin (basal response) was 26.7 ± 2.1 mm Hg and ranged from 15 to 37 mm Hg. Peak responses occurred very close to 30 sec after PE injection, and the time to peak was not affected by the antagonist. Analysis of historical IUP base-line responses for individual dogs showed that the S.E.M. values were <10% of the mean (data not shown), indicating consistency of baseline responses from day to day. The vehicle-treated group showed a diminished IUP response to PE at early time points to give an apparent mean blockade that reached a maximum of 17% at 4 hr and gradually declined to 12% at 24 hr. At 0.1 mg/kg, mean blockade reached a maximum of 18% at 1 hr that gradually declined to 4% at
Pharmacokinetic parameters after acute oral administration of terazosin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 (n = 5)</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>1.9</td>
</tr>
<tr>
<td>AUC0–23 (ng/hr/ml)</td>
<td>676 (23)</td>
</tr>
<tr>
<td>AUC0–24 (ng/hr/ml)</td>
<td>2544 (78)</td>
</tr>
<tr>
<td>CL/F (ml/hr/kg)</td>
<td>349 (22)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>4.0 (0.6)</td>
</tr>
</tbody>
</table>

Harmonic mean.

Normalized to 1 mg/kg dose.

Values are mean ± S.E.M.

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**TABLE 2**

Pharmacodynamic parameters for IUP and MAP responses after acute administration of terazosin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle (n = 7)</td>
</tr>
<tr>
<td>IUP Emax (%)</td>
<td>21.5 (3.2)</td>
</tr>
<tr>
<td>IUP TEmax (hr)</td>
<td>5.7 (1.2)</td>
</tr>
<tr>
<td>IUP AUCE (%)</td>
<td>305 (80)</td>
</tr>
<tr>
<td>MAP Emax (%)</td>
<td>36.4 (5.2)</td>
</tr>
<tr>
<td>MAP TEmax (hr)</td>
<td>5.3 (3.1)</td>
</tr>
<tr>
<td>MAP AUC (%)</td>
<td>297 (59)</td>
</tr>
</tbody>
</table>

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6 hr and remained so to 24 hr. Blockade was not significantly (P > .05) different from the apparent blockade observed in the vehicle-treated group for all time points at this dose of terazosin. After a 0.3 mg/kg dose, mean blockade reached a maximum of 64% at 2 hr that gradually declined to vehicle-treated levels at 12 hr. Blockade was significantly (P < .05) greater than the vehicle-treated group for the 2-, 4- and 6-hr time points. After a 1 mg/kg dose, mean blockade reached a maximum value of 97% at 2 hr that gradually declined to 60% at 24 hr. Compared with the vehicle-treated group, blockade was significantly (P < .05) greater in all drug-treated groups and for all time points except for the 1- and 24-hr time points in the 0.1 mg/kg dose group. Table 2 (bottom) summarizes the mean pharmacodynamic parameters derived from the MAP effect-time data for individual animals. Mean MAP AUC0 and MAP Emax values for all dose groups ranged from 162% hr to 1325% hr and 23.1% to 98.1%, respectively, and showed dose dependency over the dose range. Mean IUP AUCE and IUP Emax values for the 0.1 mg/kg dose did not differ markedly from the vehicle-treated group. The range of mean IUP TEmax values (1.6–2.3 hr) for the drug-treated groups was similar to mean plasma Tmax values (1.0–2.1 hr).

**Single dosing (MAP blockade).** Figure 3 shows the mean effect-time course for blockade of PE-stimulated MAP responses after single oral administration of terazosin at 0.1, 0.3 and 1 mg/kg or water vehicle. Base-line PE-induced MAP responses averaged 53 ± 3 mm Hg (n = 20) above prestimulation levels and ranged from 25 to 80 mm Hg. Peak responses most often occurred very close to 30 sec after PE injection, although the MAP pressor peak sometimes occurred a little later (45 sec). In either case, the time to peak was not affected by the antagonist. Analysis of historical MAP baseline responses for individual dogs showed that the S.E.M. values were <12% of the mean (data not shown), indicating consistency of base-line responses from day to day. The vehicle-treated group showed a diminished MAP response to give an apparent blockade value that reached a maximum value of 26% at 2 hr, followed by a gradual decline to 4% at 12 hr and then an increase to 13% at 24 hr. At 0.1 mg/kg, mean blockade reached a maximum value of 54% at 4 hr that gradually declined to 16% at 24 hr. After a 0.3 mg/kg dose of terazosin, mean blockade reached a maximum value of 81% at 2 hr that gradually declined to 37% at 24 hr. After a 1 mg/kg dose, mean blockade reached a maximum value of 98% at 2 hr that gradually declined to 60% at 24 hr. Compared with the vehicle-treated group, blockade was significantly (P < .05) greater in all drug-treated groups and for all time points except for the 1- and 24-hr time points in the 0.1 mg/kg dose group. Table 2 (bottom) summarizes the mean pharmacodynamic parameters derived from the MAP effect-time data for individual animals. Mean MAP AUC0 and MAP Emax values for all dose groups ranged from 855% hr to 1838% hr and 58.9% to 98.1%, respectively, and showed dose dependency over the dose range. The range of mean MAP TEmax values (2.0–2.3 hr) was similar to mean plasma Tmax values (1.0–2.1 hr).

**Daily repeated dosing (pharmacokinetics).** Figure 4 shows concentration-time courses for mean plasma concentrations of terazosin and effect time courses for mean percent blockade of PE-induced IUP and MAP responses after daily repeated oral administration of terazosin at 0.3 and 1 mg/kg over 7 days. For repeated daily dosing of terazosin at 0.3 mg/kg, the mean plasma concentration at 23 hr (C ss,min) after the first dose was 12 ± 1 ng/ml (fig. 4a). At steady state, the mean plasma concentration 23 hr (C ss,min) after dose on...
days 2, 3, 6 and 7, plasma concentrations averaged 16 ± 1 ng/ml and ranged from 11 to 25 ng/ml.

For repeated daily dosing of terazosin at 1.0 mg/kg, the mean plasma concentration 23 hr (C1,min) after the first dose was 43 ± 9 ng/ml (fig. 4b). At steady state, the mean plasma concentration 23 hr (Css,min) after dose on days 2, 3, 6 and 7, was 53 ± 8 ng/ml and ranged from 23 to 122 ng/ml. When calculated from observed Css,min and C1,min values, the accumulation indices (Rss) for the 0.3 and 1 mg/kg dose groups were 1.33 and 1.23, respectively. The observed accumulation indices indicated that accumulation of plasma concentrations after repeated daily dosing was slight. Because Rss = Css,min/C1,min = 1/(1 – e−kτ), the elimination rate constant derived from acute studies (kτ = 1.96 day−1), gave a theoretical accumulation index of 1.16 and was in general agreement with the observed accumulation index. These results show that repeated daily dosing of terazosin resulted in little accumulation and was consistent with the theoretical accumulation predicted from the half-life value as estimated from acute studies and the dosing interval.

**Daily repeated dosing (IUP blockade).** For repeated daily dosing of terazosin at 0.3 mg/kg, mean maximal IUP blockade on days 1 to 4 and 7 averaged 42 ± 3% (fig. 4c). Mean IUP blockade at 23 hr after dose on days 2 to 4, 6 and 7 was at or below blockade levels seen for vehicle-treated animals in the acute studies. For repeated daily dosing of terazosin at 1.0 mg/kg, mean maximal IUP blockade on days 1 to 4 and 7 averaged 64 ± 2% (fig. 4d). Mean IUP blockade at 23 hr after dose on days 2 to 4, 6 and 7 was at or below blockade levels seen for vehicle-treated animals in the acute studies. Statistical analysis of maximal responses by ANOVA did not show significance between days for both doses.

**Daily repeated dosing (MAP blockade).** For repeated daily dosing of terazosin at 0.3 mg/kg, mean maximal MAP blockade on days 1 to 4 and 7 averaged 70 ± 1% (fig. 4e). Mean MAP blockade at 23 hr after dose on days 2 to 4, 6 and 7 averaged 88 ± 1% (fig. 4f). Mean MAP blockade at 23 hr after dose on days 2 to 4, 6 and 7 averaged 60 ± 3%. Statistical analysis of maximal and 23-hr responses by ANOVA did not show significance between days for both doses.

These results show that repeated daily dosing of terazosin at 0.3 or 1 mg/kg was sufficient to block PE-induced MAP responses but not PE-induced IUP responses through 23 hr in conscious dogs. Consistent with the pharmacokinetic data showing little accumulation of plasma terazosin concentrations, both IUP and MAP responses remained unchanged from day to day.

**PK/PD relationships.** Inspection of plasma concentration vs. percent blockade plots for individual subjects did not reveal hysteresis (data not shown) and the mean time courses for blockade and plasma concentration were parallel and concurrent (figs. 1–3). Also, the plasma concentration T_max values (1.0–2.1 hr) were similar to IUP T_E_max values (1.6–2.3 hr) and MAP T_E_max values (2.0–2.3 hr). Taken together, these results are consistent with rapid equilibrium between the effect and sampling compartments and indicates that pharmacodynamic modeling should not require inclusion of a transfer coefficient for the effect compartment. Because blockade of PE-stimulated IUP and MAP responses is receptor mediated, a sigmoidal E_max model was used to describe the PK/PD relationship where the Hill equation applies such that E = E_maxCp/(IC50 + Cp). Figure 5a shows the relationship between plasma terazosin concentrations and blockade of PE-induced IUP responses obtained after single-dose administration. The Hill equation best describing the data was E = 100Cp^1.63/(48.61.63 + Cp^1.63), where IC50 and γ values were determined by iteration with the PCNONLIN program. The mean ± S.E. values for IC50 and γ were 48.6 ± 3.1 ng/ml and 1.63 ± 0.15, respectively. Figure 5b shows the relationship between plasma terazosin concentrations and blockade of PE-induced MAP responses. The Hill equation best describing the data was E = 100Cp^0.87/(12.2^0.87 + Cp^0.87). The mean ± S.E. values for IC50 and γ were 12.2 ± 1.1 ng/ml and 0.87 ± 0.08, respectively. The MAP IC50/IUP IC50 ratio was 12.2/48.6 = 0.25. Terazosin can therefore be characterized as an agent having a 4-fold greater potency for blockade of PE-induced MAP responses vs. PE-induced IUP responses in the conscious dog based on the PK/PD IC50 ratio.

**Discussion**

The oral doses of terazosin given here dose-dependently blocked PE-induced increases in IUP and MAP, consistent with the known alpha-1 antagonist properties of the compound as previously determined by blockade of alpha-1-adrenoceptor-mediated smooth muscle contraction in blood vessels and prostate and consistent with its established utility in the treatment of hypertension and BPH (Hancock et al., 1995; Titmarsh and Monk, 1987; Wilde, et al., 1993). PE-induced increases in MAP were blocked to a greater extent than PE-induced increases in IUP for all doses of terazosin and for all time points. Interestingly, changes in PE-induced IUP and MAP responses were observed in the vehicle-treated groups manifested as apparent blockade despite the absence of antagonist. These IUP and MAP responses varied over time and displayed patterns that differed for either IUP and MAP time courses. The changes in PE-induced IUP and MAP responses observed in the vehicle-treated group may be attributed to environmental and behavioral components such as the time of day, placing or removing animals in their slings, activity of other dogs in the laboratory or other envi-
ronmental cues that may have affected the behavior of the dogs. Alternatively, the varying PE-responses observed in the vehicle-treated group may be consistent with agonist-induced desensitization. Although there is no practical way to avoid this and still obtain frequent measures of PE responses, desensitization was minimized by using PE doses (32 μg/kg) that gave a sufficient signal for measuring blockade but were below doses that gave maximal IUP and MAP responses (128 μg/kg). Furthermore, although it is not possible to assess desensitization in drug-treated groups, the presence of antagonist may have a tendency to reduce receptor-mediated desensitization. In any case, although it is important to characterize these vehicle effects on each parameter, the variations in response were small enough to be relatively unimportant relative to the much stronger antagonist effects and do not influence the overall conclusions as to the selectivity profile of a compound in the model. Moreover, the lack of hysteresis observed for single dosing suggested that the effect compartment was in rapid equilibrium with the central compartment. Consistent with these results was the finding of minimal cumulative effects after repeated daily dosing, which suggested that accumulation of drug in the effect compartment did not occur at any appreciable extent with this dosing regimen. Although the IC₅₀ values for these responses are a measure of potency, the IUP IC₅₀/MAP IC₅₀ ratio can be viewed as a measure of selectivity. Ratios less than unity would result from cardiovascular-selective compounds, ratios greater than unity would result from uroselective compounds and ratios close to unity would result from nonselective compounds. The IUP IC₅₀ and MAP IC₅₀ values for terazosin were 48.6 and 12.2 ng/ml, indicating that terazosin is a potent inhibitor of agonist-induced IUP and MAP responses. The MAP IC₅₀/IUP IC₅₀ ratio for terazosin was 0.25, indicating that terazosin is slightly selective for blockade of PE-induced MAP responses relative to
The blockade of PE-induced IUP responses in this canine model. Moreover, the curves for IUP and MAP described by the $E_{\text{max}}$ model are not parallel, indicating that any other estimate of selectivity is concentration (and therefore dose and time) dependent. In the context of drug development, the ability to characterize the relationship between plasma concentrations of terazosin and IUP/MAP blockade in a single species represents an unique and potentially valuable approach for evaluating novel alpha-1-selective adrenoceptor antagonists and identifying agents with reduced cardiovascular side effects.

The pharmacokinetic results for single dosing showed that terazosin displayed linear pharmacokinetics over the dose range tested as demonstrated by the lack of significant differences between dose groups for rate constants, oral clearances and dose-normalized AUC values. Terazosin has previously been reported to have linear pharmacokinetics in human studies (Patterson, 1985; Sonders, 1986). Results from the 0.3 mg/kg dose group are consistent with results reported previously for a similar dose in dogs (Kyncl et al., 1986) and indicate that coadministration of multiple doses of PE did not alter the pharmacokinetics of terazosin. For repeated daily dosing, the degree of accumulation observed was consistent with that predicted from results derived from the single dosing studies. Results from repeated daily dosing showed that similar to single dosing, the time courses for plasma levels and blockade of PE-induced IUP and MAP responses were in phase and remained so throughout the course of the study. The corresponding effect-time courses for blockade of PE-induced IUP and MAP responses also did not show dependence on dose number and were in harmony with the plasma concentration-time data, which showed little accumulation. Before fully characterizing the relationship between pharmacokinetics and pharmacodynamics for IUP blockade, it was not known whether IUP blockade would be cumulative after repeated daily dosing because the IUP effect compartment could have represented a slowly equilibrating compartment or a site of drug accumulation. Clearly, the pharmacokinetic and pharmacodynamic results are consistent with the idea that the IUP effect compartment is in rapid equilibrium with the central compartment and that drug accumulation for terazosin is minimal.

IUP blockade returned to control levels at 24 hr after single dosing and at 23 hr after repeated daily dosing of terazosin at 1 mg/kg. In men, however, terazosin administered daily at doses ranging from 1 to 10 mg or ~0.014 to 0.14 mg/kg is an effective therapy for treatment of symptomatic BPH. Thus, terazosin appears ~7-fold more potent on a dose-equivalent basis in alleviating the symptoms of BPH in man than in blocking PE-induced IUP responses in the canine. Based on results reported for oral dosing in humans at 1 mg, plasma levels at 24 hr averaged ~3 ng/ml (Jungers et al., 1986). Given the therapeutic dose range of 1 to 10 mg and that terazosin has been reported to have linear pharmacokinetics in man, plasma levels at 24 hr could be expected to range from 3 to 30 ng/ml (in the present study, in which the doses ranged from 0.1 to 1 mg/kg, plasma levels at 24 hr ranged from 3 to 30 ng/ml). Thus, comparison of plasma levels cannot fully reconcile the lack of blockade at 24 hr in dog for single and repeated daily dosing and the therapeutic efficacy observed in humans for once-daily dosing. Perhaps distribution of terazosin into the effect compartment may differ between man and dog such that concentrations of drug in the prostate relative to plasma concentrations could be higher in man. Another explanation for this difference may be the distinction between blockade of exogenous vs. endogenous agonist. Blockade of endogenous agonist may be achieved more readily due to lower physiological levels of norepinephrine release or increased sensitivity to adrenergic blockade at the neuromuscular junction. By contrast, exogenous agonist is administered at pharmacological levels and represents a systemic rather than localized exposure and may stimulate extrasynaptic receptors (Vargas and Gorman, 1995). Alternatively, assessment of symptomatic relief of BPH in man is based on urodynamic as well as subjective measures and may be the basis for the observed differences. IUP measurements in man would be required to understand the relationship between these classic measures and IUP blockade.

Previously, the in vivo uroselectivity of terazosin was evaluated by measuring blockade of IUP responses in the anesthetized cat after electrical stimulation of the hypogastric nerve and the effects of terazosin on arterial blood pressure in unrestrained conscious spontaneously hypertensive rats (Lefevre-Borg et al., 1992). Although this study provided a measure of uroselectivity, the results were based on data from two different species and did not include pharmacokinetic analysis. Other alpha-1 adrenoceptor antagonists have been tested for uroselectivity in anesthetized dog after i.v. or intraduodenal administration but did not include pharmacokinetic analysis. Other alpha-1 adrenoceptor antagonists have been tested for uroselectivity in anesthetized dog after i.v. or intraduodenal administration but did not include pharmacokinetic analysis. Other alpha-1 adrenoceptor antagonists have been tested for uroselectivity in anesthetized dog after i.v. or intraduodenal administration but did not include pharmacokinetic analysis. Other alpha-1 adrenoceptor antagonists have been tested for uroselectivity in anesthetized dog after i.v. or intraduodenal administration but did not include pharmacokinetic analysis. Other alpha-1 adrenoceptor antagonists have been tested for uroselectivity in anesthetized dog after i.v. or intraduodenal administration but did not include pharmacokinetic analysis.
rates and hepatic metabolism may compromise results derived from anesthetized animals. The lack of pharmacokinetic data in all of these studies precludes understanding the temporal relationship between plasma levels and effect and does not take into account the potential for time lag and drug accumulation within the effect compartment.

In conclusion, the experimental model described herein allows for evaluation of the relationship between pharmacokinetics and blockade of PE-induced IUP and MAP responses in the conscious dog after administration of the alpha-1 adrenergic antagonist terazosin. The results of this type of model, in which pharmacokinetic/pharmacodynamic relationships are described for IUP and MAP blockade within a single species, without the use of anesthetics and for oral dosing, appear to be the first of their type in the literature. The MAP IC\textsubscript{50} and IUP IC\textsubscript{50} values for terazosin determined with these studies can be taken as a measure of potency, whereas the MAP IC\textsubscript{50}/IUP IC\textsubscript{50} ratio can be taken as a measure of selectivity. In this way, these results can be used to evaluate novel compounds for uroselectivity with the proviso that the pharmacokinetic/pharmacodynamic relationship can be modeled for the compound under evaluation.

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References


