

# Modeling of Relationships between Pharmacokinetics and Blockade of Agonist-Induced Elevation of Intraurethral Pressure and Mean Arterial Pressure in Conscious Dogs Treated with $\alpha_1$ -Adrenoceptor Antagonists

DAVID G. WITTE, MICHAEL E. BRUNE, SWETA P. KATWALA, IVAN MILICIC, DEANNE STOLARIK, YU-HUA HUI, KENNAN C. MARSH, JAMES F. KERWIN, JR., MICHAEL D. MEYER, and ARTHUR A. HANCOCK

*Pharmaceutical Products Discovery, Neurological Urological Disease Research, Abbott Laboratories, Abbott Park, Illinois*

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## ABSTRACT

Fiduxosin is a new  $\alpha_1$ -adrenoceptor antagonist targeted for the treatment of symptomatic benign prostatic hyperplasia. The purpose of this study was to determine and compare the potencies of the  $\alpha_1$ -adrenoceptor antagonists terazosin, doxazosin, tamsulosin, and fiduxosin, based on relationships between plasma drug concentrations and blockade of phenylephrine (PE)-induced intraurethral (IUP) and mean arterial pressure (MAP) responses after single oral dosing in conscious male beagle dogs. Magnitude of blockade and plasma concentrations were evaluated at selected time points over 24 h. All drugs produced dose-dependent antagonism of PE-induced IUP and MAP responses. When IUP and MAP blockade effects were plotted against drug plasma concentrations, direct relationships were observed that were well described by the sigmoidal maximal effect model. IUP  $IC_{50}$  values for terazosin, doxazosin, tamsulosin, and fiduxosin were 48.6, 48.7, 0.42, and 261 ng/ml,

respectively. MAP  $IC_{50}$  values were 12.2, 13.8, 1.07, and 1904 ng/ml, respectively. Uroselectivity index values, defined as MAP  $IC_{50}$ /IUP  $IC_{50}$ , were 0.25, 0.28, 2.6, and 7.3, respectively. These results extend previous observations with terazosin in this model, showing that doxazosin exhibits a uroselectivity index comparable to terazosin, consistent with the lack of  $\alpha_1$ -adrenoceptor subtype selectivity or uroselectivity of these drugs. Tamsulosin, an  $\alpha_{1a}$ / $\alpha_{1d}$ -subtype selective agent, had an index value approximately 10-fold greater than the nonselective drugs. Based on its pharmacokinetic profile and a relative uroselectivity 29-fold greater than the nonselective drugs, fiduxosin is expected to exhibit greater selectivity for urethral compared with vascular  $\alpha_1$ -adrenoceptors in human and should be a novel, long-acting, uroselective  $\alpha_1$ -adrenoceptor antagonist.

$\alpha_1$ -Adrenoceptor antagonists represent first-line therapy for the pharmacological treatment of benign prostatic hyperplasia (BPH), in part by relaxing prostatic smooth muscle (Lowe, 1999). Fiduxosin (ABT-980) is a novel  $\alpha_1$ -adrenoceptor antagonist. Compared with other clinical agents, such as terazosin, doxazosin, and tamsulosin, fiduxosin exhibits a somewhat different  $\alpha_1$ -adrenoceptor subtype selectivity profile. Radioligand binding potencies at human  $\alpha_{1a}$ ,  $\alpha_{1b}$ , and  $\alpha_{1d}$ -adrenoceptors are reported to be 1.81, 1.16, and 0.67 nM for terazosin; 0.79, 0.80, and 0.81 nM for doxazosin; 0.03, 0.60, and 0.06 nM for tamsulosin; and 0.16, 24.89, and 0.92 nM for fiduxosin, respectively (Hancock et al., 1998b, 2002),

showing fiduxosin to be selective for  $\alpha_{1a}$ - and  $\alpha_{1d}$ -adrenoceptors compared with  $\alpha_{1b}$ -adrenoceptors to a greater extent than tamsulosin.

Accumulating data suggest that extraprostatic  $\alpha_1$ -adrenoceptors in bladder, spinal cord, ganglia, or nerve terminals may also contribute to ameliorating the irritative and voiding symptoms of BPH (Fitzpatrick, 2000; Schwinn and Michelotti, 2000). Three subtypes of  $\alpha_1$ -adrenoceptors are known to exist,  $\alpha_{1A}$ ,  $\alpha_{1B}$ , and  $\alpha_{1D}$ -adrenoceptors (Bylund et al., 1994). The findings of enrichment of  $\alpha_{1A}$ -adrenoceptors in human prostate gland stimulated interest in identifying  $\alpha_{1A}$ -selective, and by extrapolation "prostate-selective", antago-

**ABBREVIATIONS:** BPH, benign prostatic hyperplasia; fiduxosin (ABT-980), (3-[4-((3aR,9bR)-cis-9-methoxy-1,2,3,3a,4,9b-hexa-hydro-[1]benzopyrano[3,4-c]pyrrol-2-yl)butyl]-8-phenyl-pyrazino[2',3':4,5]thieno-[3,2-d]pyrimidine-2,4(1H,3H)-dione)); REC 15/2739, (N-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide); PE, phenylephrine; MAP, mean arterial pressure; IUP, intra-urethral pressure; PK, pharmacokinetics; PD, pharmacodynamics; TFA, trifluoroacetic acid; A-86192 (N-[2-benzofuran-6-yl]ethyl)-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetra-hydronaphthalen-1-ylmethyl]-N-methylamine mathanesulfonate); A-131701 (3-[2-((3aR,9bR)-cis-6-methoxy-2,3,3a,4,5,9b,hexa-hydro-[1H]-benz[e]isoindol-2-yl)ethyl]pyrido[3',4':4,5]thieno[3,2-d]-pyrimidino-2,4(1H,3H)-dione); LC-MS, liquid chromatography-mass spectrometry; RSD, relative standard deviation; CL/F, oral plasma clearance/oral bioavailability; ANOVA, analysis of variance;  $AUC_{0-\infty}$ , area under the plasma concentration-time curve;  $AUC_E$ , area under the effect against time curve.

nists to ameliorate BPH symptoms and to reduce adverse effects (e.g., decreased blood pressure, postural hypotension, or syncope) observed with nonsubtype-selective  $\alpha_1$ -antagonists such as doxazosin or terazosin (Lowe, 1999). However, REC 15/2739, a compound showing high  $\alpha_{1A}$ -adrenoceptor selectivity, failed to ameliorate BPH symptoms in clinical trials (Lowe, 1999), perhaps the result of poor pharmacokinetic properties (A. A. Hancock and S. A. Buckner, unpublished data). Thus, the hypothesis of  $\alpha_{1A}$ -selectivity correlating to clinical uroselectivity remains unproved.<sup>1</sup>

Interest in the role of  $\alpha_{1D}$ -adrenoceptors in the lower urinary tract has increased based on studies showing that this subtype predominates in human bladder (Lowe, 1999; Schwinn and Michelotti, 2000) and may play a role in detrusor instability (Fitzpatrick, 2000; Schwinn and Michelotti, 2000), a frequent and major component of BPH symptomatology (DeMey, 1999).

Cardiovascular sequelae of  $\alpha_1$ -adrenoceptor blockade are generally attributed to actions primarily at  $\alpha_{1B}$ -adrenoceptors, because neither  $\alpha_{1A}$ - nor  $\alpha_{1D}$ -adrenoceptors appear to predominate in any vascular bed (DeMey 1999). Although selective  $\alpha_{1A}$ -adrenoceptor antagonists have been shown to potently block increases of noradrenaline-induced resistance in isolated preparations, effects on MAP are observed only with very high doses, suggesting some non- $\alpha_{1A}$ -adrenoceptors regulate blood pressure control. (Hieble and Ruffolo, 1997). In addition, the ratio of  $\alpha_{1A}$ - to  $\alpha_{1B}$ -adrenoceptors decreases with age in blood vessels (Fitzpatrick, 2000), suggesting that vascular function could be maintained in the absence of blockade of  $\alpha_{1B}$ -adrenoceptors (Fitzpatrick, 2000). Thus, compounds that are highly selective for the  $\alpha_{1A}$ -/ $\alpha_{1D}$ -subtypes relative to  $\alpha_{1B}$ -adrenoceptors could have the potential for enhanced clinical uroselectivity compared with available  $\alpha_1$ -adrenoceptor antagonists (DeMey, 1999; Fitzpatrick, 2000; Schwinn and Michelotti, 2000).

A challenge for experimental therapeutics is to establish models of uroselectivity predictive for clinical BPH. Several animal models have been previously used toward this end, having the benefit of using intact animals to include extraprostatic influence on efficacy measurements, with the most appropriate functional models based on the dog. Canine prostate surrounds and impinges upon the urethra with advancing age as seen in human (DeKlerk et al., 1979), and the pharmacology of canine  $\alpha_1$ -adrenoceptors also resembles human (Hieble et al., 1986; Lepor et al., 1992). First attempts in the anesthetized dog measured the potency of  $\alpha_1$ -antagonists to block agonist-induced increases in blood and intraurethral pressures (Kenny et al., 1994; Brune et al., 1995). Limitations of these methods include the acute nature of the experiments, the necessity for intravenous drug administration, and the inability to incorporate pharmacokinetic considerations into the experimental design. These factors may have contributed to the difficulty in demonstrating functional selectivity of  $\alpha_1$ -antagonists evaluated therein (Kenny et al., 1994; Brune et al., 1995).

Subsequently, a conscious dog model was developed (Brune et al., 1996), featuring oral administration of compounds and

evaluation of the antagonism of vascular and urethral  $\alpha_1$ -adrenoceptors with stimulation by phenylephrine (PE) over time. Analysis of mean arterial (MAP) and intraurethral pressure (IUP) responses, coupled with quantification of plasma levels of terazosin provided a pharmacokinetic (PK) and pharmacodynamic (PD) profile consistent with the clinical attributes of this nonsubtype-selective  $\alpha_1$ -adrenoceptor antagonist (Witte et al., 1997). More recently, however, pharmacodynamic analysis of data from the conscious canine model has been used to evaluate the potential uroselectivity of novel  $\alpha_1$ -adrenoceptor antagonists (Hancock et al., 1998). In the present study we compared the PK and PD properties of four  $\alpha_1$ -adrenoceptor antagonists. These included the nonselective antagonists terazosin and doxazosin; the  $\alpha_{1A}$ -/ $\alpha_{1D}$ -adrenoceptor-selective antagonist tamsulosin, reported in comparative studies to show uroselectivity (Lee and Lee, 1997; Schäfers et al., 1999; Tsujii, 2000); and a novel  $\alpha_{1A}$ -/ $\alpha_{1D}$ -adrenoceptor-selective antagonist fiduxosin. PK/PD modeling of these data provide a basis for evaluating the potential uroselectivity of fiduxosin compared with nonselective  $\alpha_1$ -antagonists.

## Materials and Methods

### Animals

Male beagle dogs (Marshall Farms, North Rose, NY) greater than 2 years of age and weighing between 12 and 15 kg were used in this study. Dogs were cared for as previously described (Witte et al., 1997) and in accordance to National Institutes of health guidelines on canine care. All experimental protocols described herein were reviewed and approved by the Institutional Animal Care and Use Committee of Abbott Laboratories.

### Instrumentation

Dogs were instrumented for the continuous measurement of MAP and periodic measurement of IUP as previously described (Witte et al., 1997). Briefly, a telemetry transducer/transmitter (TA11PA-C40; Data Sciences International, St. Paul, MN) was implanted into a carotid artery for measurement of MAP and a 7F Swan-Ganz balloon catheter (41224-01; Abbott Laboratories, North Chicago, IL) was inserted into the urethral orifice and connected to an Abbott Transpac pressure transducer (42556-01) for the measurement of IUP.

### Chemicals

Fiduxosin, terazosin, doxazosin, tamsulosin [R(-)], A-86192, and A-131701 were synthesized at Abbott Laboratories. Prazosin and PE were purchased from Sigma Chemical (St. Louis, MO). High-performance liquid chromatography grade trifluoroacetic acid (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.

### Measurement of IUP/MAP Responses and Collection of Plasma Samples

The pressor effects of 32  $\mu\text{g}/\text{kg}$  i.v. PE on IUP and MAP were compared before and at various time points after p.o. doses of the  $\alpha_1$ -adrenoceptor antagonists fiduxosin, terazosin, doxazosin, and tamsulosin as previously described (Witte et al., 1997). PE doses of 8 and 16  $\mu\text{g}/\text{kg}$  were also measured and showed that pressor effects were dose-dependent and linear over the 8- to 32- $\mu\text{g}/\text{kg}$  range. Higher doses of PE were not tested because of the potential for adverse effects that could compromise the safety and long-term use of dogs used in this study. Data from 32  $\mu\text{g}/\text{kg}$  PE were chosen for analysis because of the larger response and greater signal-to-noise

<sup>1</sup> In this article, nomenclature used to differentiate among the subtypes of  $\alpha_1$ -adrenoceptors uses uppercase subscripted letters to describe tissue-sourced receptors and lowercase subscripts to define cloned receptors (Bylund et al., 1994).

ratio with this dose. Blood samples were collected at the same time points and processed as previously described (Witte et al., 1997).

### Analysis of Drugs in Plasma

For fiduxosin, standards were prepared by spiking normal dog plasma with concentrations of fiduxosin ranging from 100 to 4000 ng/ml.<sup>2</sup> To 0.5 ml of unknown or standard samples was added 0.2 ml of 1000 ng/ml A-86192 in 0.1% TFA as an internal standard. Samples were alkalized with 1 ml of 0.5 M Na<sub>2</sub>CO<sub>3</sub> 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  $\mu$ l was injected into the chromatographic system and the eluant was monitored for UV absorption at a wavelength of 205 nm. Fiduxosin and the internal standard were resolved on a YMCbasic column with a mobile phase of 35:65 (v/v) acetonitrile and 0.1% TFA at a constant flow rate of 1.6 ml/min at room temperature. Retention times were 14.0 and 10.4 min for fiduxosin and A-86192, respectively. The plasma drug concentration of each sample was calculated by least-squares linear regression analysis of the peak area ratio (fiduxosin area/internal standard area) of the spiked plasma standards versus concentration. The standard curve was linear from 100 to 4000 ng/ml (triplicate samples) with correlation coefficients  $\geq 0.999$ . Coefficients of variation were determined for triplicate spiked samples at 10, 50, 200, and 2000 ng/ml and resulted in values lower than 10%. Interday coefficients of variation were also determined for the spiked samples from three separate experiments and resulted in values lower than 10%. On the basis of a coefficient of variation less than 20%, the assay had a detection limit of 5 ng/ml. Analysis of control blank plasma indicated the absence of interfering peaks.

The chromatographic system consisted of a model 400 solvent delivery system (Applied Biosystems, Foster City, CA), a model AS-2000 autosampler (Hitachi Instruments, Chicago, IL), a 150  $\times$  4.6-mm i.d. YMCbasic column (YMC, Wilmington, NC), and a model 785A UV detector (Applied Biosystems). Rainin Dynamax software (Rainin, Woburn, MA) was used for data acquisition and peak integration. Plasma concentrations of terazosin and doxazosin were measured as previously described (Patterson, 1984; Witte et al., 1997).

For tamsulosin, standards were prepared by spiking normal dog plasma with concentrations of tamsulosin<sup>2</sup> ranging from 0.26 to 1220 ng/ml. To 0.5 ml of unknown or standard samples was added 0.2 ml of 150 ng/ml A-131701<sup>2</sup> in acetonitrile/water (30:70) as an internal standard. Tamsulosin was selectively removed from the plasma by using liquid-liquid extraction with 5 ml of ethyl acetate after alkalization with 0.5 ml of 0.5 M Na<sub>2</sub>CO<sub>3</sub>. The organic layer was evaporated to dryness and reconstituted in 0.2 ml of acetonitrile/aqueous 0.1% TFA (40:60, v/v) for LC-MS. An API III+ LC-MS-MS System (PerkinElmer Sciex Instruments, Thornhill, ON, Canada) was used for quantification of tamsulosin in plasma.

Tamsulosin and its internal standard (A-131701) were separated on a 10-cm  $\times$  3-mm, 5- $\mu$ m Kromasil C18 column (Higgins Analytical, Inc., Mountain View, CA) with a 40% acetonitrile in 0.1% TFA mobile phase at a flow rate of 0.5 ml/min by using a model 500D syringe pump (ISCO, Lincoln, NE). A heated nebulizer (450°C, 70 psi) with an atmospheric pressure chemical ionization source was used as the interface between LC and MS-MS systems. MS detection of the analytes was at MRM mode (tamsulosin channel 409.1  $\rightarrow$  147.2 and IS channel 449.0  $\rightarrow$  246.0).

The plasma drug concentration of each sample was calculated by least-squares linear regression analysis of the peak area ratio (tamsulosin area/internal standard area) of the spiked plasma standards versus concentration. The intraday precision and accuracy of the method were evaluated by triplicate analysis of spiked plasma stan-

dards at each of three separate concentrations. The assay precision was based on the calculation of the relative standard deviation (RSD). An indication of accuracy was based on the relative error of the samples, i.e., [(F - T)/T]  $\times$  100, in which the deviation between the found concentration (F) and the theoretical concentration (T) was calculated. The interday precision for the plasma analysis was assessed from the results of intraday assays on two separate days.

The assay for the quantification of tamsulosin in plasma samples by using liquid-liquid extraction followed by LC-MS detection provided excellent linearity and reproducibility. Tamsulosin provided a correlation coefficient  $> 0.99$  for all assays over a concentration range of 0 to 1220 ng/ml. The RSDs for the analysis of triplicate samples at 142, 64.5, and 1.29 ng/ml averaged 6.02, 8.13, and 0.88%, respectively, with relative error (accuracy) ranging from -19.3 to 4.7% of theoretical. The mean interday precision, as evaluated from triplicate analysis of spiked standards on two separate days, averaged 18.3, 18.2, and 1.8% (RSD) at concentrations of 142, 64.5, and 1.29 ng/ml, respectively. The lower limit of quantification was 0.1 ng/ml.

### Study Design

Thirteen groups of dogs ( $N = 4-6$ ) were administered oral doses of terazosin (0.1, 0.3, and 1 mg/kg), doxazosin (0.1, 0.3, and 1 mg/kg), tamsulosin (0.001, 0.01, and 0.1 mg/kg), or fiduxosin (0.1, 0.3, 1, and 3 mg/kg).<sup>3</sup> Vehicle for terazosin, doxazosin, and tamsulosin was 0.9% saline and vehicle for fiduxosin was 20% ethanol, 30% polyethylene glycol, and 50% of D5W (v/v); the vehicles are designated vehicle 1 and vehicle 2, respectively. In addition, effect data were collected for a vehicle-treated group to assess effects unrelated to test compound administration. Before administration of test compound or vehicle, baseline IUP and MAP responses were measured after i.v. bolus injections of PE<sup>3</sup> (saline vehicle) at 32  $\mu$ g/kg in a volume of 0.1 ml/kg of body weight. Dogs then received oral doses of test compound or vehicle by gavage in a volume of 0.1 ml/kg. Before and at 0.5, 1, 2, 4, 6, 8, 12, and 24 h after test compound administration, 4-ml blood samples were collected for measurement of whole plasma concentrations. Although the use of whole plasma drug concentrations does not allow for estimation of drug potencies that can be directly compared with in vitro drug potencies, assessment of uroselectivity does not require the use of free plasma drug concentrations. At 1, 2, 4, 6, 12, and 24 h after test compound dosing, IUP and MAP responses were measured following i.v. bolus PE challenges at 32  $\mu$ g/kg.

### Analysis of Results

**PK/PD.** PK parameters were estimated from individual plasma concentration-time data with the iterative curve-fitting program NONLIN, VAX version 3.0 (SCI Software, Lexington, KY), by using a one-compartment open model for single oral dosing as previously described (Witte et al., 1997). IUP and MAP effects, expressed as percentage of blockade, were used to estimate PD parameters from individual effect-time data as previously described (Witte et al., 1997). Plasma concentrations were related to effect with the sigmoidal  $E_{\max}$  model (Holford and Sheiner, 1981). The PCNONLIN version 4.0 (SCI Software) program was used for fitting individual concentration-effect data by iterative nonlinear regression according to the following model:  $E = E_{\max} \cdot C_p^\gamma / (IC_{50}^\gamma + C_p^\gamma)$ , where  $E$  is the observed inhibition,  $E_{\max}$  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.  $E_{\max}$  values were set to 100% because this is the theoretical maximum for IUP and MAP blockade as described previously (Witte et al., 1997). Correlations and associated  $P$  values to assess dose dependence for PK parameters ( $AUC_{0-\infty}$  and  $C_{\max}$ ) were determined by linear regression analysis (JMP, version 2.04; SAS Institute Inc., Cary, NC). One-way analysis of variance with a

<sup>2</sup> Solutions of compound(s) were prepared based upon the free-base weight.

<sup>3</sup> Dose solutions of compound(s) were prepared based upon the salt weight.

Tukey-Kramer post hoc test at the 95% confidence limit was applied to determine statistically significant differences between dose groups for PK parameters ( $k_e$ , CL/F, and  $T_{max}$ ) as well as IUP and MAP responses (StatView, version 1.04; Abacus Concepts, Berkeley, CA).

## Results

**Pharmacokinetics.** Figure 1, a to d, shows the mean plasma concentration-time courses for terazosin, doxazosin, tamsulosin, and fiduxosin, respectively, after oral administration at the indicated doses. Table 1 lists the mean pharmacokinetic parameters derived from individual animals for each drug and dose group. Within each drug group, elimination rates ( $k_e$ ) were roughly constant over the dose ranges tested and did not differ significantly (ANOVA). Mean  $AUC_{0-\infty}$  and  $C_{max}$  values were directly proportional to dose for all drug groups ( $R^2 \geq 0.992$ ,  $P < 0.05$ ), whereas total mean oral clearance values were roughly constant over the dose ranges tested within each drug group and did not differ significantly (ANOVA). Mean  $T_{max}$  values within all drug groups ranged from 1.0 to 3.3 h, whereas mean  $T_{max}$  values did not differ significantly between dose groups (ANOVA). These results show that all drugs displayed linear pharmacokinetics over the dose ranges tested.

**IUP Blockade.** Figure 2, a to d, shows mean effect-time courses for blockade of 32  $\mu\text{g}/\text{kg}$  PE-stimulated IUP responses after single oral administration of terazosin, doxazosin, tamsulosin, fiduxosin, or vehicle, at the indicated doses. The mean net change in IUP response after stimulation with PE but before oral administration of drug was  $26.7 \pm 2.1$  mm Hg and ranged from 15 to 37 mm Hg. Inspection of mean effect-time courses for all drugs showed dose-dependent blockade of PE-induced IUP responses.

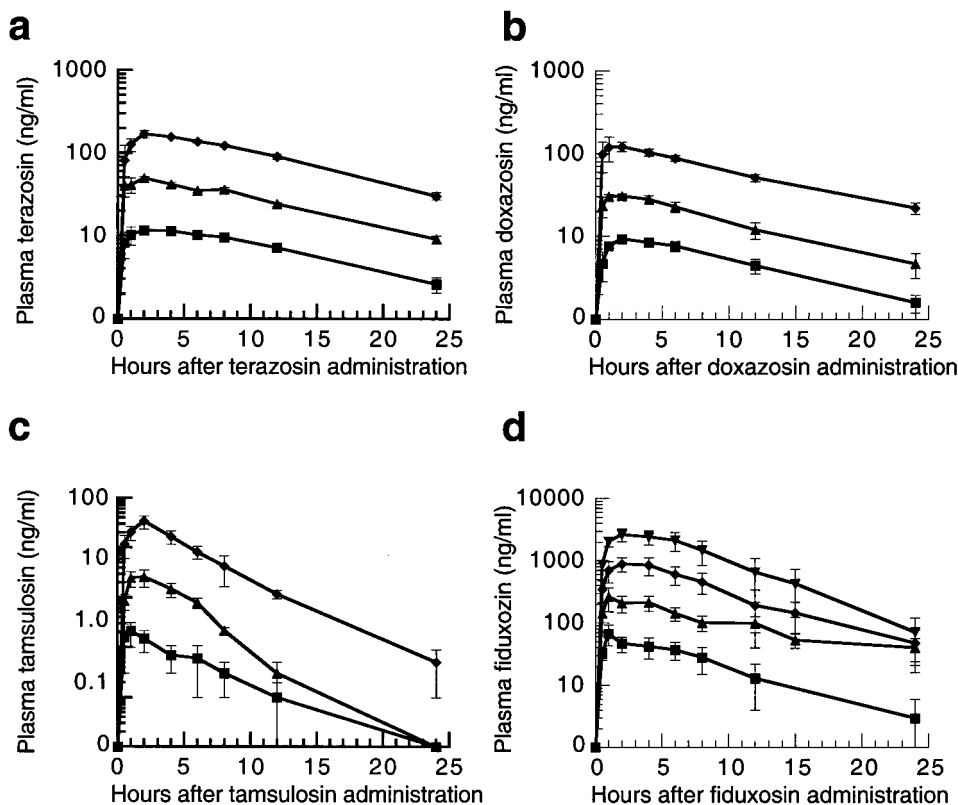
Table 2 summarizes the mean IUP pharmacodynamic pa-

rameters derived from IUP effect-time data for individual animals. Within each drug group, mean IUP  $E_{max}^{obs}$  and IUP  $AUC_E$  values were dose-dependent over the dose ranges tested. Moreover, mean IUP  $E_{max}^{obs}$  and IUP  $AUC_E$  values for the highest doses tested within each drug group were similar and ranged from 80.0 to 99.0 and 1202 to 1494%  $\cdot$  h, respectively. The range of mean IUP  $T_{Emax}$  values (1.0–3.3 h) for all drug-treated groups was similar to the range observed for mean plasma  $T_{max}$  values (1.0–3.3 h).

**MAP Blockade.** Figure 3, a to d, shows mean effect-time courses for blockade of PE-stimulated MAP responses after single oral administration of terazosin, doxazosin, tamsulosin, and fiduxosin, respectively, at the indicated doses, or water vehicle. Baseline PE-induced MAP elevations averaged  $53 \pm 3$  mm Hg above prestimulation levels and ranged from 25 to 80 mm Hg. Inspection of mean effect-time courses for all drugs showed dose-dependent blockade of PE-induced MAP responses.

Table 3 summarizes the mean MAP pharmacodynamic parameters derived from MAP effect-time data for individual animals. Within each drug group, mean MAP  $E_{max}^{obs}$  and MAP  $AUC_E$  values were dose-dependent over the dose ranges tested. MAP  $E_{max}^{obs}$  and MAP  $AUC_E$  values were similar for terazosin, doxazosin, and tamsulosin and ranged from 86.1 to 98.1 and 1208 to 1838%  $\cdot$  h, respectively, whereas the values for fiduxosin were somewhat less (72.1 and 827%  $\cdot$  h). The range of mean MAP  $T_{Emax}$  values (1.3–5.5 h) for all drug-treated groups was similar to the range of mean plasma  $T_{max}$  values (1.0–3.3 h).

**PK/PD Relationships.** IUP and MAP blockade responses were highly correlated with plasma drug concentrations (Figs. 4 and 5, respectively). Inspection of plasma concentration versus percentage of blockade plots for individual sub-

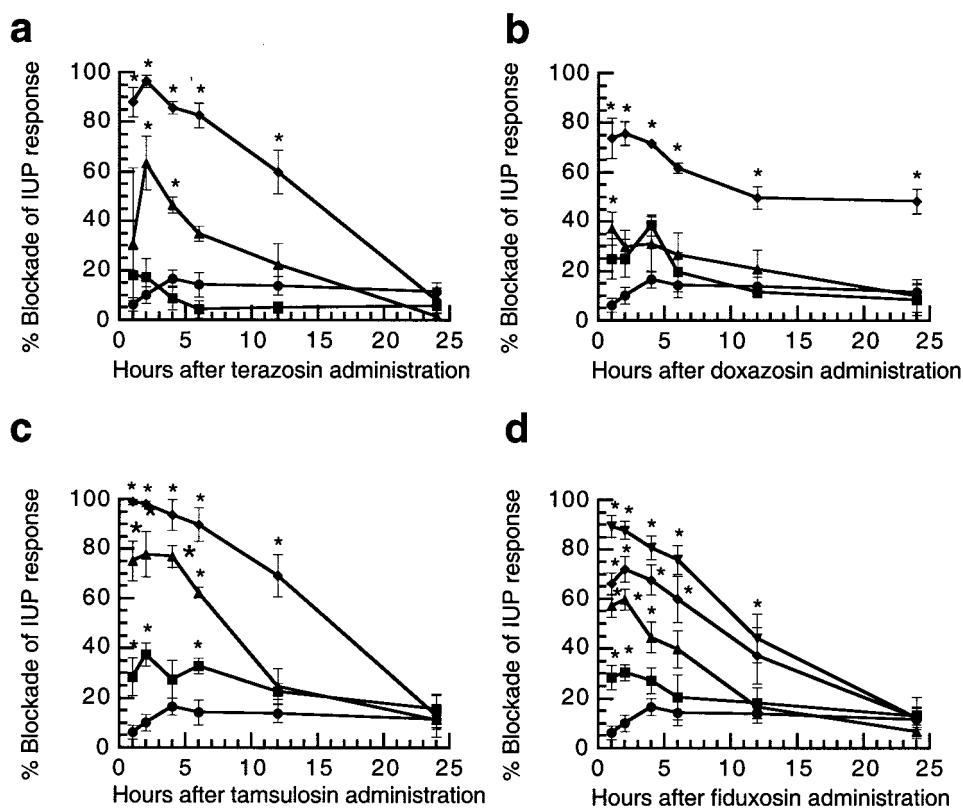


**Fig. 1.** Plasma concentration-time course for compounds in dogs after oral administration of \*terazosin at 0.1 (■), 0.3 (▲), and 1.0 (◆) mg/kg (a); doxazosin at 0.1 (■), 0.3 (▲), and 1.0 (◆) mg/kg (b); tamsulosin at 0.001 (■), 0.01 (▲), and 0.1 (◆) mg/kg (c); and fiduxosin at 0.1 (■), 0.3 (▲), 1.0 (◆), and 3.0 (▼) mg/kg (d). Data are expressed as the mean  $\pm$  S.E.M. \*Terazosin data from Witte et al. (1997), with permission.

TABLE 1

Mean ( $\pm$ S.E.M.) pharmacokinetic parameters following oral administration of  $\alpha$ -adrenoceptor antagonists

Drug	Dose	<i>N</i>	<i>k</i> <sub>e</sub>	<i>t</i> <sub>1/2<math>\beta</math></sub> <sup>a</sup>	AUC <sub>0-∞</sub>	AUC <sub>0-∞</sub> <sup>b</sup>	CL/F <sup>c</sup>	<i>C</i> <sub>max</sub>	<i>C</i> <sub>max</sub> <sup>b</sup>	<i>T</i> <sub>max</sub>
	mg/kg		h <sup>-1</sup>	h	ng · h/ml	ng · h/ml	ml/h · kg	ng/ml	ng/ml	h
Terazosin <sup>d</sup>	0.1	5	0.083 (0.015)	8.4	213 (25)	2126 (250)	457 (60)	13 (1)	128 (11)	2.1 (0.8)
	0.3	4	0.074 (0.002)	9.4	763 (23)	2544 (78)	360 (12)	53 (3)	177 (8)	1.0 (0.4)
	1.0	5	0.082 (0.007)	8.4	2661 (168)	2661 (168)	349 (22)	194 (13)	194 (13)	1.9 (0.6)
Doxazosin	0.1	4	0.085 (0.009)	8.2	139 (24)	1389 (244)	739 (139)	9 (1)	93 (9)	1.8 (0.3)
	0.3	4	0.102 (0.016)	6.8	419 (75)	1397 (251)	734 (133)	34 (1)	112 (2)	1.9 (0.8)
	1.0	4	0.086 (0.009)	8.1	1741 (198)	1741 (198)	553 (62)	145 (26)	145 (26)	1.1 (0.3)
Tamsulosin	0.001	6	0.363 (0.105)	1.9	1.2 (0.8)	1202 (780)	1920 (610)	0.3 (0.2)	343 (154)	2.5 (0.7)
	0.01	5	0.342 (0.027)	2.0	11 (3)	1060 (324)	1110 (310)	2.8 (0.9)	275 (92)	1.5 (0.3)
	0.1	4	0.292 (0.032)	2.4	146 (40)	1460 (400)	1330 (790)	36 (10)	357 (99)	1.4 (0.4)
Fiduxosin	0.1	4	0.158 (0.037)	4.4	575 (209)	5750 (2093)	358 (220)	73 (23)	730 (230)	1.8 (0.8)
	0.3	4	0.125 (0.027)	5.6	2660 (495)	8867 (1649)	125 (34)	302 (92)	1008 (307)	1.8 (0.8)
	1.0	4	0.173 (0.031)	4.0	9025 (2982)	9025 (2982)	219 (130)	979 (240)	979 (240)	2.3 (0.6)
	3.0	4	0.166 (0.024)	4.1	25047 (8647)	8349 (2882)	188 (85)	2807 (603)	936 (201)	3.3 (1.1)

<sup>a</sup> Harmonic mean.<sup>b</sup> Parameters normalized to 1 mg/kg.<sup>c</sup> CL/F based upon free base weight.<sup>d</sup> Terazosin data from Witte et al., 1997, with permission.

**Fig. 2.** Response time course for blockade of PE-induced IUP responses in dogs after oral administration of vehicle (●) or †terazosin at 0.1 (■), 0.3 (▲), and 1.0 (◆) mg/kg (a); doxazosin at 0.1 (■), 0.3 (▲), and 1.0 (◆) mg/kg (b); tamsulosin at 0.001 (■), 0.01 (▲), and 0.1 (◆) mg/kg (c); and fiduxosin at 0.1 (■), 0.3 (▲), 1.0 (◆), and 3.0 (▼) mg/kg (d). Data are expressed as the mean  $\pm$  S.E.M. (\**P* < 0.05, one-way ANOVA). †Terazosin data from Witte et al. (1997), with permission.

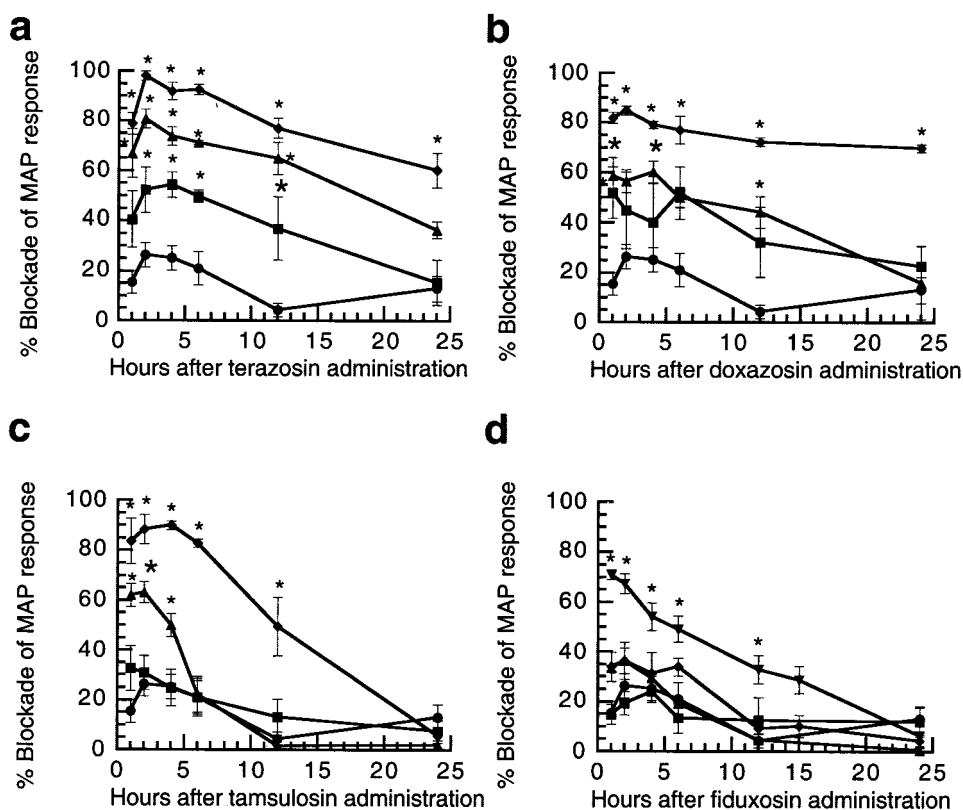
jects in all dose groups revealed no hysteresis (data not shown). Moreover, the mean time-courses for blockade and plasma concentrations were parallel and concurrent (Figs. 1–3), and plasma concentration  $T_{\max}$  values were similar to IUP  $T_{E_{\max}}$  values and MAP  $T_{E_{\max}}$  values (Tables 1–3). Taken together, these results are consistent with rapid equilibrium between the effect and sampling compartments and indicate that PK/PD modeling should not require inclusion of a transfer coefficient for the effect compartment. To reinforce this assumption, PK/PD modeling was carried out with a transfer coefficient as an additional variable, but the resulting curve fit showed no improvement in correlation over modeling without a transfer coefficient. 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  $E = E_{\max} \cdot C_p^\gamma / (IC_{50}^\gamma + C_p^\gamma)$ . Figure 4, a to d, shows the relationship between plasma drug concentrations and blockade of PE-induced IUP responses obtained after antagonist administration, as well as the theoretical dose-response curve best fit by the sigmoidal  $E_{\max}$  model, whereas Table 4 summarizes the estimated PK/PD parameters. For terazosin, estimated values for  $IC_{50}$  and  $\gamma$  were  $48.6 \pm 3.1$  ng/ml and  $1.6 \pm 0.2$ , respectively. For doxazosin, estimated values for  $IC_{50}$  and  $\gamma$  were  $48.7 \pm 5.8$  ng/ml and  $0.8 \pm 0.1$ , respectively. For tamsulosin, estimated values for  $IC_{50}$  and  $\gamma$  were  $0.42 \pm 0.08$  ng/ml and  $0.9 \pm 0.2$ , respectively, whereas estimated

TABLE 2

Mean ( $\pm$ S.E.M.) pharmacodynamic parameters for blockade of IUP responses following oral administration of  $\alpha$ -adrenoceptor antagonists

Drug	Dose	N	$E_{\max}$	$T_{E_{\max}}$	AUC <sub>E</sub>
	mg/kg		%	h	% · h
Vehicle		7	21.5 (3.2)	5.7 (1.2)	305 (80)
Terazosin <sup>a</sup>	0.1	5	23.1 (8.4)	2.0 (0.5)	162 (63)
	0.3	4	66.8 (9.3)	2.3 (0.6)	548 (55)
	1.0	5	96.5 (2.4)	1.6 (0.2)	1325 (133)
Doxazosin	0.1	4	39.5 (4.7)	2.5 (0.9)	373 (75)
	0.3	4	39.6 (7.3)	2.5 (0.9)	498 (177)
	1.0	4	80.0 (3.2)	2.0 (0.7)	1316 (78)
Tamsulosin	0.001	3	40.2 (4.9)	2.0 (0.5)	572 (78)
	0.01	5	81.7 (8.4)	2.2 (0.5)	889 (76)
	0.1	4	99.0 (0.0)	1.0 (0.0)	1494 (155)
Fiduxosin	0.1	4	33.6 (3.8)	3.3 (1.1)	454 (140)
	0.3	4	59.7 (4.2)	1.5 (0.3)	584 (66)
	1.0	4	73.6 (4.2)	1.8 (0.3)	954 (171)
	3.0	4	90.4 (4.1)	1.3 (0.3)	1202 (169)

<sup>a</sup> Terazosin data from Witte et al., 1997, with permission.

**Fig. 3.** Response time course for blockade of PE-induced MAP responses in dogs after oral administration of vehicle (●) or <sup>†</sup>terazosin at 0.1 (■), 0.3 (▲), and 1.0 (◆) mg/kg (a); doxazosin at 0.1 (■), 0.3 (▲), and 1 (◆) mg/kg (b); tamsulosin at 0.001 (■), 0.01(▲), and 0.1 (◆) mg/kg (c); and fiduxosin at 0.1 (■), 0.3 (▲), 1.0 (◆), and 3.0 (▼) mg/kg (d). Data are expressed as the mean  $\pm$  S.E.M. (\* $P$  < 0.05, one-way ANOVA). <sup>†</sup>Terazosin data from Witte et al. (1997), with permission.

values for  $IC_{50}$  and  $\gamma$  were  $261 \pm 34$  ng/ml and  $0.6 \pm 0.1$ , respectively, for fiduxosin.

Figure 5, a to d, shows the relationship between plasma concentrations of terazosin, doxazosin, tamsulosin, and fiduxosin and blockade of PE-induced MAP responses obtained after antagonist administration, as well as the theoretical dose-response curve best fit by the sigmoidal  $E_{\max}$  model, whereas Table 4 summarizes the estimated PK/PD parameters. For terazosin, estimated values for  $IC_{50}$  and  $\gamma$  were  $12.2 \pm 1.1$  ng/ml and  $0.9 \pm 0.1$ , respectively. For doxazosin, estimated values for  $IC_{50}$  and  $\gamma$  were  $13.8 \pm 2.0$  ng/ml and  $0.6 \pm 0.1$ , respectively. For tamsulosin, estimated values for  $IC_{50}$  and  $\gamma$  were  $1.07 \pm 0.26$  ng/ml and  $0.8 \pm 0.2$ , respectively, whereas estimated values for  $IC_{50}$  and  $\gamma$  were  $1904 \pm 418$  ng/ml and  $0.5 \pm 0.1$ , respectively, for fiduxosin. The IUP and MAP  $IC_{50}$  values for these drugs can be expressed as a

ratio (IUP  $IC_{50}$ /MAP  $IC_{50}$ ) to give an index of selectivity for IUP blockade versus MAP blockade in the conscious dog. Thus, the selectivity indices for terazosin, doxazosin, tamsulosin, and fiduxosin are 0.25, 0.28, 2.55, and 7.30, respectively (Table 4). Relative to terazosin (relative index), doxazosin is equally nonselective, whereas tamsulosin and fiduxosin are 10- and 29-fold more selective for blockade of IUP responses compared with MAP responses, respectively (Table 4).

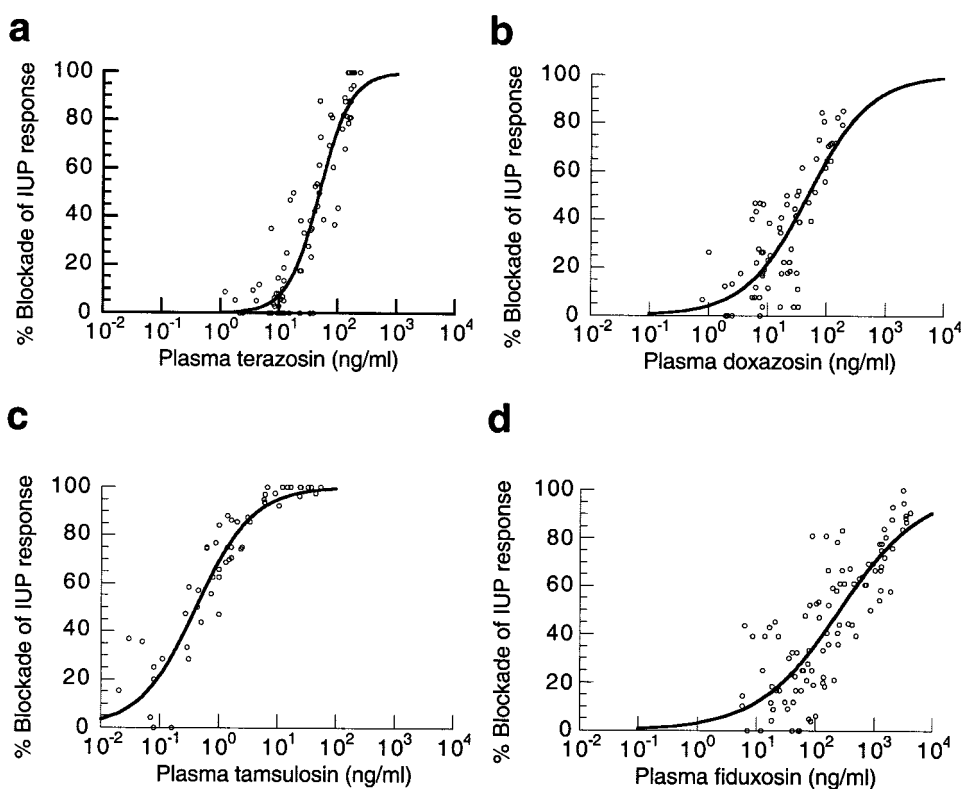
## Discussion

In this study we compared PK/PD relationships of fiduxosin to three  $\alpha_1$ -adrenoceptor antagonists in clinical use for BPH. All four  $\alpha_1$ -adrenoceptor antagonists displayed linear pharmacokinetics, where dose was highly correlated with

TABLE 3

Mean ( $\pm$ S.E.M.) pharmacodynamic parameters for blockade of MAP responses following oral administration of  $\alpha$ -adrenoceptor antagonists

Drug	Dose	N	$E_{\max}$	$T_{E_{\max}}$	AUC <sub>E</sub>
	mg/kg		%	h	% · h
Vehicle		7	36.4 (5.2)	5.3 (3.1)	297 (59)
Terazosin <sup>a</sup>	0.1	5	58.9 (4.2)	2.2 (0.5)	855 (187)
	0.3	4	81.8 (3.7)	2.3 (0.6)	1444 (52)
	1.0	5	98.1 (1.9)	2.0 (0.0)	1838 (73)
Doxazosin	0.1	4	54.9 (10.7)	2.3 (1.3)	833 (279)
	0.3	4	64.7 (4.2)	2.0 (0.7)	958 (172)
	1.0	4	86.1 (2.7)	2.3 (1.3)	1746 (35)
Tamsulosin	0.001	3	37.6 (8.1)	2.6 (1.0)	378 (143)
	0.01	5	66.3 (3.8)	1.4 (0.2)	373 (34)
	0.1	4	93.8 (3.0)	2.3 (0.6)	1208 (120)
Fiduxosin	0.1	4	29.1 (3.3)	5.5 (2.2)	330 (90)
	0.3	4	40.9 (4.5)	1.5 (0.3)	271 (36)
	1.0	4	37.6 (4.3)	1.3 (0.3)	408 (85)
	3.0	4	72.1 (2.2)	1.3 (0.3)	827 (76)

<sup>a</sup> Terazosin data from Witte et al., 1997, with permission.

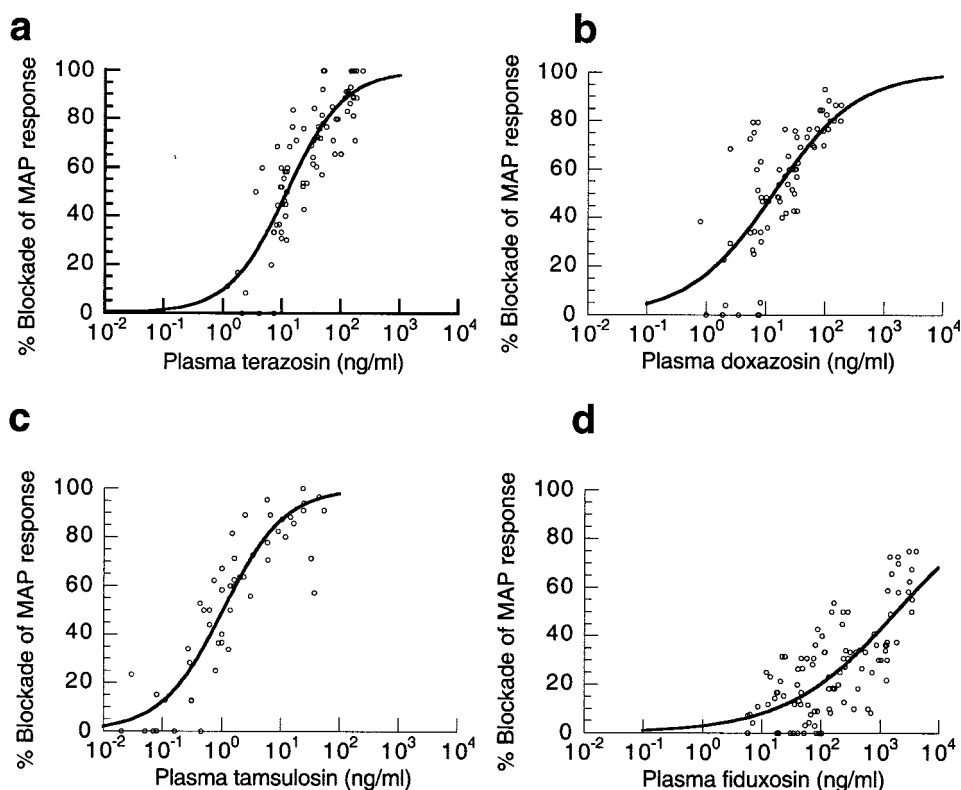
**Fig. 4.** Relationship between plasma drug concentrations and blockade of PE-induced IUP responses in dogs after oral administration of \*terazosin (a), doxazosin (b), tamsulosin (c), and fiduxosin (d). Each point represents a single plasma concentration value and its associated blockade value. The total data set is from all dogs and all dose groups. \*Terazosin data from Witte et al. (1997), with permission.

$C_{\max}$  and AUC<sub>0-∞</sub> values, whereas  $k_e$  and CL/F values remained roughly constant over the dose ranges tested.

Based on PK/PD-derived IC<sub>50</sub> values, the nonsubtype selective  $\alpha_1$ -adrenoceptor antagonists terazosin and doxazosin were 4-fold more effective in blocking PE-induced MAP responses compared with PE-induced IUP responses. Conversely, tamsulosin, a drug having selectivity for  $\alpha_{1a}$ - and  $\alpha_{1d}$ - versus  $\alpha_{1b}$ -receptors, was 2.55-fold more effective in blocking PE-induced IUP responses compared with PE-induced MAP responses. Fiduxosin, a novel antagonist having enhanced selectivity for  $\alpha_{1a}$ - and  $\alpha_{1d}$ - versus  $\alpha_{1b}$ -adrenoceptors, was 7.30-fold more effective in blocking PE-induced IUP responses compared with PE-induced MAP responses. Notably, in comparison with the other antagonists, the potency of fiduxosin for blockade of IUP and MAP responses is markedly higher than would be expected from binding potencies.

However, the apparent low potency of fiduxosin can be attributed to high plasma protein binding (>99.8%; data not shown) compared with that of the other drugs (98–60%; data not shown), leading to large differences in free drug plasma concentrations. Indeed, potential effects of pharmacokinetics on potency underscore the importance of intact animal studies that incorporate efficacy with consideration of pharmacokinetic parameters. Whereas comparisons of in vitro potencies with in vivo potencies may not be appropriate due to pharmacokinetic issues, the model described herein allows for the estimation of uroselectivity. In contrast to absolute measures of potency, which are dependent upon free drug plasma concentrations, uroselectivity is based on relative potencies, a measure that is valid when using total drug plasma concentrations.

Terazosin and doxazosin PK and PD parameters, obtained



**Fig. 5.** Relationship between plasma drug concentrations and blockade of PE-induced MAP responses in dogs after oral administration of \*terazosin (a), doxazosin (b), tamsulosin (c), and fiduxosin (d). Each point represents a single plasma concentration value and its associated blockade value. The total data set is from all dogs and all dose groups. \*Terazosin data from Witte et al. (1997), with permission.

**TABLE 4**  
Mean ( $\pm$ S.E.M.) PK/PD parameters for IUP and MAP blockade of PE-induced responses

Drug	IUP			MAP			MAP/IUP Indices	
	IC <sub>50</sub>	Slope	Corr.	IC <sub>50</sub>	Slope	Corr.	Selectivity Index <sup>a</sup>	Relative Index <sup>b</sup>
	ng/ml			ng/ml				
Terazosin <sup>c</sup>	48.6 (3.1)	1.6 (0.2)	0.92	12.2 (1.1)	0.9 (0.1)	0.87	0.25	1.0
Doxazosin	48.7 (5.8)	0.8 (0.1)	0.80	13.8 (2.0)	0.6 (0.1)	0.73	0.28	1.1
Tamsulosin	0.42 (0.08)	0.9 (0.2)	0.94	1.07 (0.26)	0.8 (0.2)	0.93	2.55	10.2
Fiduxosin	261 (34)	0.6 (0.1)	0.82	1904 (418)	0.5 (0.1)	0.74	7.30	29.2

<sup>a</sup> Selectivity index defined as  $\text{MAP} - \text{IC}_{50}/\text{IUP} - \text{IC}_{50}$ .

<sup>b</sup> Relative index defined as selectivity index of drug/selectivity index of terazosin.

<sup>c</sup> Terazosin data from Witte et al., 1997, with permission.

from identical doses, compared very well, a result attributable to similarities in structure, physicochemical properties, distribution, elimination, and potencies at the three  $\alpha_1$ -adrenoceptor subtypes. These results are consistent with clinical data in which terazosin and doxazosin have been shown to be similarly potent and similarly efficacious agents for the treatment of symptomatic BPH, but with a similar frequency of cardiovascular side effects (Djavan and Merberger, 1999). Interestingly, clinical studies for tamsulosin indicated reduced incidence of cardiovascular side effects compared with terazosin and doxazosin (Lee and Lee, 1997; Djavan and Merberger, 1999; Schäfers et al., 1999; Tsujii, 2000). These observations support the hypothesis that cardiovascular side effects are primarily associated with blockade of  $\alpha_{1b}$ -adrenoceptors, whereas improvement of BPH symptoms is primarily associated with blockade of  $\alpha_{1a}$ -, and perhaps  $\alpha_{1d}$ -adrenoceptors (Testa et al., 1994; Take et al., 1998). It is difficult to say whether the reduced cardiovascular side effects for tamsulosin can be attributed to factors other than subtype selectivity, such as reduced peak to trough plasma concentrations (through modified release formulation) or dosing at submaxi-

mal efficacy (Wyllie, 1999). Indeed, the relative contribution of specific subtypes to efficacy and safety remains unclear (Hieble and Ruffolo, 1997; de May, 1999; Lowe, 1999). Therefore, controlled head-to-head comparative clinical studies with existing as well as new  $\alpha_1$ -adrenoceptor antagonists with unique subtype selectivity profiles will be needed to prove or disprove this hypothesis (Debruyne and Van der Poel, 1999). Nevertheless, the findings for tamsulosin in this study validate the utility of the conscious dog model as a tool for measuring and perhaps predicting uroselectivity and efficacy of novel  $\alpha_{1a}$ -/ $\alpha_{1d}$ -selective adrenoceptor antagonists such as fiduxosin in human.

Although PD data alone can be used to readily discriminate uroselectivities of nonsubtype- versus subtype-selective adrenoceptor antagonists (Hancock et al., 1998a), it is more difficult to assess the relative uroselectivity for compounds having similar subtype selectivity profiles. This difficulty largely arises from the time dependence of blockade data, and consequently the time dependence of uroselectivity estimates. To understand the pharmacological profile of compounds with distinct structures, and physicochemical and

pharmacokinetic properties, one must take into account the temporal relationships between functional blockade of the effect compartment (PD) and plasma concentrations (PK). This is important because it is not possible to know a priori the extent of time-dependent distribution of drug from the central compartment to the effect compartment. By incorporating PK data into a study, it becomes possible to investigate the potential involvement of time lag via inspection of PK/PD time course data as well as PK/PD modeling. PK/PD analysis showed that for the panel of compounds tested,  $T_{\max}$  values for plasma concentration and  $T_{E_{\max}}$  values for efficacy were roughly equivalent. Comparisons of goodness of fit for PK/PD modeling, with and without a time lag, also showed no marked differences for these compounds. Taken together, these observations suggest that both IUP and MAP effect compartments are in rapid equilibrium with the central compartment for these compounds. Moreover, because a sigmoidal  $E_{\max}$  model, in which the slope is a variable, was chosen over the simpler  $E_{\max}$  model, where the slope is fixed to unity (based on goodness of fit), uroselectivity estimates from dose-effect data alone become dose-dependent, albeit to a slight degree. The rank order of uroselectivity estimated from PK/PD analysis was fiduxosin > tamsulosin > terazosin = doxazosin with IUP/MAP selectivity indices of 7.30, 2.55, 0.25, and 0.28, respectively. When uroselectivity indices are normalized to terazosin (relative index), doxazosin is similar, tamsulosin is 10-fold more uroselective, and fiduxosin is 29-fold more uroselective. Based on this analysis, fiduxosin is a uroselective compound that would be expected to have reduced cardiovascular side effects compared with terazosin and doxazosin, and perhaps tamsulosin as well.

Various methods of assessing in vivo uroselectivities of  $\alpha_1$ -adrenoceptor antagonists are well represented in the literature (Lefevre-Borg et al., 1992; Shibasaki et al., 1992; Kenny et al., 1994; Testa et al., 1994; Takenaka et al., 1995), but do not include PK/PD modeling. The anesthetized canine model described by Kenny et al. (1994) does not incorporate PK factors, and as such, does not take into account potential time lags for distribution of drug from the central compartment to the effect compartment. In addition, the paradigm uses i.v. dosing of test compound because oral absorption would be confounded by anesthesia-induced inhibition of gastrointestinal motility. Furthermore, the anesthetic effects on cardiac function and vascular tone via increased sympathetic outflow, hepatic metabolism and clearance of test compound, as well as central nervous system-mediated contributions, could potentially confound results. Other assessments of uroselectivity have involved cross-species comparisons (Lefevre-Borg et al., 1992; Testa et al., 1994). Although these paradigms have been used to assess uroselectivity, the paradigm herein described is believed to represent a methodological advance, because it affords a more discriminatory assessment of uroselectivity by allowing for oral dosing of compound and estimation of efficacy and potency for blockade of urethral and cardiovascular responses within the same species. Moreover, the dependence of such measures on agonist dosage and potential time lags between the central and effect compartments are taken into account, whereas confounding effects of anesthetic are avoided.

However, limitations of the conscious dog PK/PD model should not be ignored. First, antagonism is measured by blockade of exogenous agonist, which could differ from block-

ade of the endogenous neurotransmitter not only in terms of the use of PE compared with norepinephrine but also in terms of the relative local concentrations of synaptically released neurotransmitter. Second, the use of exogenous agonist could activate extrasynaptic adrenergic receptors, which may not have relevance in a clinical setting. Third, although drug effects on basal MAP can be measured, the responses are small for nonselective  $\alpha_1$ -adrenoceptor antagonists (terazosin and doxazosin) and even smaller for the  $\alpha_{1a}$ -/ $\alpha_{1d}$ -selective adrenoceptor antagonists, such that there is little correlation between plasma concentration and effect, precluding PK/PD analysis (data not shown). However, the changes in basal MAP may have considerable clinical importance, particularly with regard to potential adverse cardiovascular events. Fourth, the current method for measuring IUP with a balloon catheter does not allow for the accurate measurement of changes in basal IUP. Balloon measurements of IUP are possible after hypogastric nerve stimulation, which could have the advantage of antagonizing the endogenous neurotransmitter released at the synapse. However, it is possible that extrasynaptic receptors might also be stimulated in this pharmacological experiment, and anesthetized animals are required, with the consequent disadvantages previously described for such models. Finally, maximal inhibition of agonist-evoked MAP responses is difficult to measure for compounds having low potency for blockade of agonist-induced hypertension (e.g., fiduxosin) resulting in incomplete PK/PD curves.

In summary, the conscious dog model provided PK and PD data for oral administration of terazosin, doxazosin, tamsulosin, and the novel  $\alpha_1$ -adrenoceptor antagonist fiduxosin, by the concurrent measurement of plasma drug concentrations and blockade of PE-induced IUP and MAP responses. PK/PD modeling allowed for estimation of drug potencies for blockade of these responses. Inhibitory potencies were then used to assess uroselectivities (selectivity index) of the panel of drugs tested. The nonsubtype-selective  $\alpha_1$ -adrenergic antagonists terazosin and doxazosin were roughly 4-fold selective for MAP versus IUP blockade. Conversely, the  $\alpha_{1a}$ -/ $\alpha_{1d}$ -selective adrenoceptor antagonist tamsulosin was 2.55-fold selective for IUP versus MAP blockade. Fiduxosin, a compound having improved selectivity for  $\alpha_{1a}$ -/ $\alpha_{1d}$ -adrenoceptors, was 7.30-fold selective for blockade of IUP versus MAP responses. Expressing uroselectivity relative to that of terazosin (relative index), doxazosin was equally uroselective, tamsulosin was 10-fold more uroselective, whereas fiduxosin was 29-fold more uroselective. These results suggest that fiduxosin could be effective as a pharmacotherapy for the treatment of symptomatic BPH in human, with reduced cardiovascular side effects.

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**Address correspondence to:** David Witte, D-47MN, AP9A/2, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064-6123. E-mail: david.g.witte@abbott.com

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