Preclinical Pharmacology of Fiduxosin, a Novel \( \alpha_1 \)-Adrenoceptor Antagonist with Uroselective Properties

ARTHUR A. HANCOCK, STEVEN A. BUCKNER, MICHAEL E. BRUNE, TIMOTHY A. ESSENSHAKE, LYNNE M. IRELAND, SWETA KATWALA, IVAN MILICIC, MICHAEL D. MEYER, JAMES F. KERWIN, JR., and MICHAEL WILLIAMS

Neurological and Urological Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois

Received July 24, 2001; accepted October 19, 2001 This paper is available online at http://jpet.aspetjournals.org

ABSTRACT

Benign prostatic hyperplasia (BPH), common in aging males, is often treated with \( \alpha_1 \)-adrenoceptor antagonists. To minimize hypotensive and other side effects, compounds with selective antagonist activity at \( \alpha_{1A} \) and \( \alpha_{1D} \) (compared with \( \alpha_{1B} \)) adrenoceptors were evaluated that would block lower urinary tract \( \alpha_{1B} \)-adrenoceptors in preference to cardiovascular \( \alpha_{1D} \)-adrenoceptors. Fiduxosin (3-[4-((3aR,9bR)-cis-9-methoxy-1,2,3,3a,4,9b-hexahydro-[1]-benzopyran-8-yl)pyrazino[2',3':4,5]thieno[3,2-d]pyrimidin-2-4-(1H,3H)-dione; ABT-980) was tested in radioligand binding assays, isolated tissue bioassays, intraurethral pressure (IUP) tests in isoflurane-anesthetized dogs, and blood pressure analyses in spontaneously hypertensive rats (SHR). Fiduxosin had higher affinity for cloned human \( \alpha_{1A} \) (0.16 nM) and \( \alpha_{1D} \)-adrenoceptors (0.92 nM) in radioligand binding studies compared with \( \alpha_{1B} \)-adrenoceptors (25 nM) or in isolated tissue bioassays [pA\(_2\) values of 8.5–9.6 for \( \alpha_{1A} \)-receptors in rat vas deferens or canine prostate strips, 8.9 at \( \alpha_{1D} \)-adrenoceptors (rat aorta), compared with 7.1 at \( \alpha_{1B} \)-adrenoceptors (rat spleen)]. Furthermore, the compound antagonized putative \( \alpha_{1L} \)-adrenoceptors in the rabbit urethra (pA\(_2\) value of 7.58). Fiduxosin blocked epinephrine-induced increases in canine IUP (pseudo-pA\(_2\) value of 8.12), eliciting only transient decreases in mean arterial blood pressure (MAP) in SHR. The area under the curve (AUC\(_{0-\infty}\)) for the hypotensive response was dose related with a log index value for fiduxosin of 5.23, indicating a selectivity of 770-fold comparing IUP to MAP effects. Preferential antagonism of \( \alpha_{1A} \) and \( \alpha_{1D} \) versus \( \alpha_{1B} \)-adrenoceptors in vitro, blockade of putative \( \alpha_{1L} \)-sites in vitro, and selective effects on lower urinary tract function versus blood pressure in vivo by fiduxosin suggest the potential utility of this compound for the treatment of BPH.


ABBREVIATIONS: BPH, benign prostatic hyperplasia; REC 15/2739, (\( N-[3-4-(2-methoxyphenyl)-1-piperazinyl]propyl\)-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide); Ro-70-0004, 3-[3-[4-(fluoro-2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl)-propyl]-5-methyl-1H-pyrimidine-2,4-dione mono hydrochloride; fiduxosin (ABT-980), [3-[4-((3aR,9bR)-cis-9-methoxy-1,2,3,3a,4,9b-hexahydro-[1]-benzopyran-8-yl)pyrazino[2',3':4,5]thieno[3,2-d]pyrimidin-2-4-(1H,3H)-dione; DMSO, dimethyl sulfoxide; PE, phenylephrine; IUP, intraurethral pressure; EPI, epinephrine; SHR, spontaneously hypertensive rats; MAP, mean arterial blood pressure; AUC, area under the curve; pED\(_{50}\), negative logarithm of the molar dose of compound required to elicit a reduction in blood pressure for 60 min to a point midway between hypertensive and normotensive; ANOVA, analysis of variance; \( K_i \), inhibition constant as a measure of drug affinity for a receptor, equivalent to the concentration of compound required to occupy 50% of receptors; pKB, negative logarithm of the dissociation constant; pA\(_2\), negative logarithm of the concentration of compound required to elicit a 2-fold shift of an agonist concentration-response curve in isolated tissues; A-131701, [3-[4-((3aR,9bR)-cis-6-methoxy-3,3a,4,5,9b, hexahydro-[1H]-benz[e]isoindol-2-yl]pyrido[3',4':5,4]thieno[3,2-d]pyrimidine-2,4-(1H,3H)-dione]; CL, confidence limit; B8805-033, ([\( \pm \)]-1,3,5-trimethyl-6-[3-[4-((2,3-dihydro-2-hydroxymethyl)-1,4-benzodioxin-5-yl]-1-piperazinyl]propyl]amino)-2,4(1H,3H)-pyrimidin-one); WB-4101, [2-(2,5-dimethoxyphenoxymethyl)aminomethyl-1,4-benzodioxane; BMY-7378, [8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-1,7,9-dione]; RWJ-38063, [N-[2-[4-((2-methylthoxy)phenyl)piperazinyl]ethyl-2-2-oxopiperadinenyl]acatamide]; RWJ-69736, [N-[3-[4-(2-methylthoxy)phenyl)piperazinyl]propyl-2-2-oxopiperadinenyl]acetamide].
nisms, more than the “static” component related to the volume of glandular tissue. Over the past decade, α1-receptor antagonists have transformed BP therapy from surgical to pharmacological intervention (Altwein, 1995), resulting in reduced adverse events (Barry and Roehrborn, 1997). However, several approved medications (e.g., terazosin and doxazosin) were originally identified as antihypertensive agents (for review, see Hancock, 1996), which may explain cardiovascular side effects associated with these compounds.

Since the discovery of subtypes of α1-receptors1 and of the enrichment of the α1A-subtype in the human prostate gland (Price et al., 1993), investigators have pursued α1A-subtype-selective (Hancock, 1996) and, by extrapolation, “prostate-selective” antagonists. These compounds were designed to ameliorate BPH symptoms with fewer adverse effects (e.g., decreased blood pressure or postural hypotension and syncope) observed with nonselective α1-blockers. Quinazoline-type α1-antagonists (e.g., terazosin and doxazosin) with potent hypotensive and other cardiovascular effects have in some instances been shown to have slightly greater affinity for α1H compared with α1A-receptors in functional and radioligand binding studies (Hancock, 1996), although this is not universally observed. Moreover, mice deficient in the α1B-receptor show diminished blood pressure responses to phenylephrine injection compared with homozygous controls (Cavalli et al., 1997). These observations suggest that α1B-receptors are more important for blood pressure regulation, and that compounds having reduced activity at α1B-sites compared with other α1-receptors would be expected to cause fewer cardiovascular side effects than classical α1-antagonists (Take et al., 1998), supporting the concept that an α1A-selective compound would be useful in BPH (Hancock et al., 1998a). Tamsulosin causes fewer hypotensive side effects in clinical practice (de Mey, 1998) and in animal studies (Hancock et al., 1998a,b), despite only moderate differences (≥20 fold) in affinity at α1A compared with either α1H or α1D-receptors (Hancock, 1996). However, several highly selective α1A-antagonists intended to be uroselective, including REC 15/2739 (Leonardi et al., 1997) and Ro-70-0044 (Williams et al., 1999), failed to improve both voiding and irritative symptoms in the clinic, such that the hypothesis of α1A-selectivity correlating to uroselectivity remains unproven. Recent observations suggest that blockade of α1A-receptors may promote relief of voiding symptoms but not the irritative and filling symptoms in BPH (Michel et al., 2000). In contrast, α1D-receptors may have a key role for irritative and filling symptoms consistent with detrusor instability (Broten et al., 1998; Michel et al., 2000; Schwinn and Michelotti, 2000), a frequent and major component of BPH symptomatology (Rosier et al., 1995). In a rat model of bladder obstruction, reversal of the ratio of detrusor α1A- to α1D-receptors (73:25) was seen after 6 weeks of urethral obstruction (22:75) (Hampel et al., 2000). Spinal or supraspinal α1D-receptors (Smith et al., 1999; Michel et al., 2000) may also be important to control bladder function. Thus, a selective α1A/α1D-antagonist, relative to α1H-receptors, may have the potential to treat both voiding and filling symptoms of BPH without the hemodynamic liabilities of currently used agents.

A confounding issue arises from studies of α1H-receptors, which demonstrate low affinity for antagonists such as prazosin in some studies (Ford et al., 1993; Muramatsu et al., 1994; Leonardi et al., 1997; Testa et al., 1997). Because signal transduction (Chang et al., 1998) and radioligand binding (Ford et al., 1997; Chang et al., 1998; Mason et al., 1998) assays show low affinity of some compounds at α1H-receptors, the α1H-site may represent an altered affinity state of the α1A-subtype (Ford et al., 1997) or an artifact (Narayan and Towari, 1998).

In this article, the initial in vitro and in vivo pharmacology of fiduxosin (ABT-980; Fig. 1), a novel α1-antagonist with preferential affinity for those sites that may be important for BPH pharmacotherapy, namely, α1A-, α1D-, and putative α1L-receptors, with low potency at α1B-receptors, is described. The goal of these studies was to determine whether this compound might represent a “uroselective” antagonist.

### Experimental Procedures

#### Radioligand Binding Assays

Radioligand binding assays were performed as described (Hancock et al., 1998b), by using recombinant human α1-receptors expressed in mouse fibroblast cells (LTK). Membranes were prepared from confluent cells of stable single cell clones as previously described (Hancock et al., 1998b).

Radioligand binding was determined in tubes containing 0.05 ml and filling symptoms of BPH without the hemodynamic liabilities of currently used agents.

A confounding issue arises from studies of α1H-receptors, which demonstrate low affinity for antagonists such as prazosin in some studies (Ford et al., 1993; Muramatsu et al., 1994; Leonardi et al., 1997; Testa et al., 1997). Because signal transduction (Chang et al., 1998) and radioligand binding (Ford et al., 1997; Chang et al., 1998; Mason et al., 1998) assays show low affinity of some compounds at α1H-receptors, the α1H-site may represent an altered affinity state of the α1A-subtype (Ford et al., 1997) or an artifact (Narayan and Towari, 1998).

In this article, the initial in vitro and in vivo pharmacology of fiduxosin (ABT-980; Fig. 1), a novel α1-antagonist with preferential affinity for those sites that may be important for BPH pharmacotherapy, namely, α1A-, α1D-, and putative α1L-receptors, with low potency at α1B-receptors, is described. The goal of these studies was to determine whether this compound might represent a “uroselective” antagonist.

#### Experimental Procedures

Radioligand Binding Assays. Radioligand binding assays were performed as described (Hancock et al., 1998b), by using recombinant human α1-receptors expressed in mouse fibroblast cells (LTK), Membranes were prepared from confluent cells of stable single cell clones as previously described (Hancock et al., 1998b).

Radioligand binding was determined in tubes containing 0.05 ml

---

1 In this article, nomenclature used to differentiate among the subtypes of α1-receptors uses uppercase subscripted letters to describe tissue-sourced receptors and lowercase subscripts to define cloned receptors (Bylund et al., 1994).
of water (total binding); 10 μM final concentration of phentolamine (nonspecific binding) or compound of interest; 0.45 ml [3H]prazosin, approximately 200 pM; and 0.5 ml of receptor preparation (generally 0.83-mg wet weight or approximately 0.1 mg of protein/assay tube) in 50 mM Tris-HCl, pH 7.4; and samples were incubated 60 min at 25°C. Under these conditions, less than 10% of added radioligand was bound to the receptors. Fiduxosin was dissolved in 10% DMSO and all serial dilutions were performed manually because of the tendency of this compound to adhere to automated pipetting devices. Assays were terminated by filtration under vacuum through Whatman GF/B filters and data analyzed as previously described (Hancock et al., 1998b).

**Isolated Tissue Bioassays for Functional Activity in Vitro.** Rat vas deferens, spleen, or aorta or canine prostate glands (male beagles aged >3 years) were studied as previously described (Hancock et al., 1998b). For isolated rabbit urethra, female New Zealand White rabbits (1.75–3.5 kg) were sacrificed by means of a 0.5-ml/kg i.p. injection of pentobarbital solution (Somlethal; J. A. Webster Inc., Sterling, MA). The urethra was removed with the urinary bladder and immediately placed into Krebs-Henseleit buffer of the following composition: 119 mM NaCl, 4.7 mM KCl, 1.2 mM KH2PO4, 2.5 mM CaCl2, 0.01 mM K2EDTA, 20 mM NaHCO3, 1.5 mM MgSO4, 11 mM dextrose, and 0.004 mM propranolol. The urethra was separated from the bladder, cut into four tissue rings approximately 3 to 4 mm in width, and subsequently fixed between a stationary glass rod and a force-displacement transducer as previously described for other isolated tissues (Hancock et al., 1998b). After equilibration with intermittent rinsing for 45 to 60 min, tissues were primed with 80 mM KCl, rinsed to baseline tension and stimulated with 10 μM phenylephrine (PE). After 60 min equilibration, a control (PE) cumulative concentration response was determined for each tissue. After a 15-min washout, agonist concentration-response curves were generated in the presence and absence of test compounds and the data analyzed as described previously (Hancock et al., 1998b). Fiduxosin was dissolved in 100% DMSO with subsequent dilution in DMSO. Because test drugs were diluted 1000-fold in the organ bath, DMSO had no effect on tissue responses. For studies with fiduxosin, tissues were rinsed after the initial agonist concentration-response curve, and fiduxosin was added to the tissue bath and allowed to equilibrate for 4 h. After each hour, fresh buffer was applied and fiduxosin replaced in the tissue bath.

**Measurement of IUP in Anesthetized Dogs.** Experimental procedures described below were reviewed and approved by the Institutional Animal Care and Use Committee of Abbott Laboratories. Intraurethral pressure (IUP) responses to i.v. epinephrine (EPI) were recorded by inserting a balloon catheter into the prostatic urethra through the penis of isoflurane-anesthetized dogs as previously described (Hancock et al., 1998a). Briefly, a lubricated 7F Swan-Ganz balloon catheter was inserted into the urethral orifice and advanced until the balloon tip was placed within the bladder. The balloon was inflated with 1 ml of room air and the catheter slowly withdrawn just past the first resistance felt at the bladder neck, placing the balloon within the prostatic urethra. The balloon port of the catheter was connected to an Abbott Transpac pressure transducer (42556-01; Abbott Laboratories, North Chicago, IL) interfaced to a data acquisition system for measurement of IUP. EPI and test compounds were administered through a cannula in the cephalic vein. In male dogs greater than 2 years of age, EPI causes robust, dose-dependent increases in IUP between 10 and 50 mm Hg for doses of 10 to 100 nmol/kg i.v., respectively (Hancock et al., 1998a).

**Blood Pressure Measurements in Conscious SHR.** MAP (mm Hg) was measured in rats as previously described (Hancock et al., 1998b). In brief, rats (15–20 weeks in age) were anesthetized with methohexital (Abbott Laboratories) while the left femoral artery and vein were catheterized using polyethylene 50 tubing for measurement of MAP and compound administration, respectively. The catheters were filled with heparinized 0.9% saline (10 U/ml), passed subcutaneously to a point behind the neck, exteriorized, and the arterial catheter connected to a Gould Statham P23Dd pressure transducer interfaced to a Grass polygraph. MAP was determined on-line by using a BUXCO cardiovascular analyzer (BUXCO Electronics, Sharon, CT). After 2 to 3 h of recovery from surgery and a 30-min predose control period, each rat was given one dose of a test antagonist i.v. and MAP was monitored for an additional 2.5 h. The percentage of change from an average predose control value was calculated for each time point and the area under the hypotensive response curve from 0 to 60 min postdosing (T60 AUC) was determined using a trapezoidal rule integration of that data set. Periodically rats were exposed to 90° head-up tilt either before or after compound administration to determine the potential for interference with reflux control of blood pressure during postural events (Hancock et al., 1998b).

**Data Analysis and Statistical Procedures.** One-way analysis of variance (ANOVA; Snedecor and Cochran, 1967) of individual Kᵢ values was used to compare compound potencies in receptor binding assays by using RS/1 (BBN Software Products, Cambridge, MA) with statistical significance indicated by a P value < 0.05. For isolated tissue bioassays, individual pKᵢ values of each compound were determined and compared across tissue types by using ANOVA procedures in RS/1. For anesthetized dog experiments, the effects of antagonists on EPI-induced responses were determined as shifts in the agonist dose-response curves and data were analyzed according to previously described methods (Hancock et al., 1998a). The standard error and S.E.M. of the pA₂ values were determined using methods previously described (Hancock et al., 1998b).

To quantify the magnitude and duration of hypotensive responses in SHR, the area under the curve between 0 and 60 min for the hypotensive response of each dose of antagonist was determined. By analyzing AUC values for each animal at each dose of compound using ALLFIT (Hancock et al., 1998b), an estimate of the dose of compound required to reduce MAP of SHR to the midpoint toward normotensive levels was obtained. The negative logarithms of these doses were compared on a molar basis (pED₅₀ values) to determine the relative potencies of antagonists as antihypertensive agents by using either F tests in ALLFIT, or by using ANOVA after RS/1 procedures with statistical significance indicated by a P value < 0.05. For comparison of orthostatic hypotensive responses in SHR, paired t tests were used to determine significant responses to tilt at each time point, comparing the blood pressure effect of the compound alone with any additive effect of tilt.

**Materials.** Fiduxosin (ABT-980), A-131701, prazosin, terazosin, doxazosin, alfuzosin, tamsulosin, and REC 15/2739 were synthesized at Abbott Laboratories. [3H]Prazosin (75–80 Ci/mmol) was purchased from PerkinElmer Life Sciences (Boston, MA). L-Epinephrine and L-PE were purchased from Sigma Chemical (St. Louis, MO). Phentolamine was obtained from Novartis Pharmaceuticals (Summit, NJ).

**Results**

**Radioligand Binding Assays.** The potency of fiduxosin in radioligand binding assays is compared with the predominant clinically used α₁-agonists terazosin and tamsulosin at cloned human α₁-adrenoceptors (Table 1). The affinity of fiduxosin for α₁a-, α₁b-, and α₁d-adrenoceptors was 0.160 nM (0.096–0.267, 95% CL), 24.9 nM (1.92–32.3), and 0.920 nM (0.659–1.28), respectively (pKᵢ values of 9.80, 7.60, and 9.04, respectively; Table 1). Fiduxosin was approximately 155-fold more potent at α₁a- than at α₁b-adrenoceptors, but was only 6-fold more potent at α₁a- than at α₁d-adrenoceptors. In contrast, terazosin displayed minor potency differences at the three receptors [Kᵢ = 1.81 nM (1.45–2.26, 95% CL), 1.16 nM (0.79–1.70), and 0.667 nM (0.549–0.810) for
Comparative radioligand binding potencies of fiduxosin and standard α₁-adrenoceptor antagonists at subtypes of α₁-receptors

Membranes containing α₁-receptors were incubated with various concentrations of test agents in the presence of [³²P]prazosin as described under Experimental Procedures. Values are the negative log of geometric means of nanomolar affinity (pKᵢ) and the S.E.M. of n separate determinations.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Receptor</th>
<th>Human α₁a</th>
<th>Human α₁b</th>
<th>Human α₁d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiduxosin</td>
<td></td>
<td>9.80 (±0.096) [6]</td>
<td>7.60 (±0.049) [9]</td>
<td>9.04 (±0.063) [9]</td>
</tr>
<tr>
<td>Terazosin</td>
<td></td>
<td>8.74 (±0.046) [19]</td>
<td>8.94 (±0.076) [12]</td>
<td>9.18 (±0.038) [12]</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td></td>
<td>10.54 (±0.041) [5]</td>
<td>9.22 (±0.111) [7]</td>
<td>10.24 (±0.039) [4]</td>
</tr>
</tbody>
</table>

- Fiduxosin potency order was α₁a > α₁b > α₁d, with each difference of statistical significance (ANOVA, P < 0.05).
- Values shown: pKᵢ (±S.E.M.) [n].
- Terazosin potency order was α₁a > α₁b > α₁d, with only the potency difference between α₁a and α₁d of statistical significance (ANOVA, P < 0.05).
- Tamsulosin potency order was α₁a ≥ α₁b > α₁d, with only the lower potency at α₁b-sites of statistical significance (ANOVA, P < 0.05).

α₁a*, α₁b*, and α₁d-adrenoceptors, respectively (pKᵢ values of 8.74, 8.94, and 9.18; Table 1), with statistical significance achieved only in comparing the α₁a* and α₁d-potency values. Tamsulosin was ~20-fold α₁a*-selective compared with α₁b- and α₁d-adrenoceptors (Kᵢ = 0.029 nM (0.022–0.038 95% CL) and 0.602 nM (0.328–1.1) for α₁a and α₁b-d-adrenoceptors, respectively), but nonselective compared with α₁d-receptors [Kᵢ = 0.058 nM (0.044–0.077) for α₁d-adrenoceptors] as previously reported (Kenny et al., 1994; Hancock, 1996). (Corresponding pKᵢ values for tamsulosin were 10.54, 9.22, and 10.24, respectively; Table 1.) Fiduxosin displayed low affinity for other adrenoceptors, including cloned human α₉a* [92 nM (52–160, 95% CL)] and α₂-adrenoceptors [22 nM (12–42, 95% CL)] and rat neonatal lung α₂-adrenoceptors [21 nM (12–38, 95% CL)], as well as β-adrenoceptors (2–5 μM; data not shown). Fiduxosin also had low affinity for 5HT1A receptors in rat cortex [29 nM (18–47, 95% CL)] compared with its affinity at α₁a-adrenoceptors (0.160 nM). Thus, fiduxosin is approximately 180-fold selective for α₁a*- compared with 5HT1A receptors, unlike a number of compounds from the orthomethoxypiperazine class of compounds (e.g., BMY 7378, 5-methyl-urapidil), which have higher priority for 5HT1A compared with α₁a-adrenoceptors (Hancock, 1996).

Preclinical Pharmacology of Fiduxosin

Table 2

Table 2: Comparative functional antagonistic potencies of fiduxosin and standard α₁-adrenoceptor antagonists at α₁-adrenoceptors in isolated smooth muscle in vitro

Isolated smooth muscle strips or rings were incubated in tissue baths in the presence of various concentrations of fiduxosin and standard α₁-adrenoceptor antagonists, as described under Experimental Procedures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rat Vas Defeners α₁a</th>
<th>Canine Prostate α₁a</th>
<th>Rabbit Urthra α₁L</th>
<th>Rat Spleen α₁b</th>
<th>Rat Aorta α₁D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiduxosin*</td>
<td>6.62 (±0.44)</td>
<td>8.51 (±0.23)</td>
<td>7.58 (±0.19)</td>
<td>7.08 (±0.07)</td>
<td>8.92 (±0.86)</td>
</tr>
<tr>
<td>Slope (±S.E.M.)</td>
<td>0.83 (±0.07)</td>
<td>0.80 (±0.05)</td>
<td>0.92 (±0.13)</td>
<td>0.90 (±0.05)</td>
<td>0.78 (±0.08)</td>
</tr>
<tr>
<td>[n]</td>
<td>[18]</td>
<td>[20]</td>
<td>[15]</td>
<td>[14]</td>
<td>[20]</td>
</tr>
<tr>
<td>Terazosin*</td>
<td>8.04 (±0.45)</td>
<td>7.44 (±0.24)</td>
<td>6.77 (±0.30)</td>
<td>8.60 (±0.46)</td>
<td>8.65 (±0.29)</td>
</tr>
<tr>
<td>Slope (±S.E.M.)</td>
<td>0.83 (±0.17)</td>
<td>0.79 (±0.09)</td>
<td>0.99 (±0.07)</td>
<td>0.94 (±0.14)</td>
<td>0.99 (±0.13)</td>
</tr>
<tr>
<td>[n]</td>
<td>[12]</td>
<td>[33]</td>
<td>[13]</td>
<td>[12]</td>
<td>[9]</td>
</tr>
<tr>
<td>Tamsulosin*</td>
<td>9.47 (±0.21)</td>
<td>9.54 (±0.17)</td>
<td>8.86 (±0.22)</td>
<td>9.69 (±0.44)</td>
<td>10.6 (±0.43)</td>
</tr>
<tr>
<td>Slope (±S.E.M.)</td>
<td>1.06 (±0.14)</td>
<td>1.12 (±0.08)</td>
<td>1.41 (±0.26)</td>
<td>0.84 (±0.15)</td>
<td>0.94 (±0.11)</td>
</tr>
<tr>
<td>[n]</td>
<td>[22]</td>
<td>[8]</td>
<td>[16]</td>
<td>[10]</td>
<td></td>
</tr>
</tbody>
</table>

* One-way analysis of variance indicated the following potency order of statistically significant differences for fiduxosin: rat vas deferens > rat aorta = canine prostate > rabbit urthra > rat spleen α₁a-adrenoceptor antagonism.

One-way analysis of variance indicated the following potency order of statistically significant differences for terazosin: rat aorta = rat spleen > rat vas deferens > canine prostate > rabbit urthra α₁d-adrenoceptor blockade.

One-way analysis of variance indicated the following potency order of statistically significant differences for tamsulosin: rat aorta > canine prostate > rabbit urthra, but canine prostate = rat vas deferens = rat spleen and rat vas deferens = rat spleen = rabbit urthra α₁a-adrenoceptor antagonism.
PE-induced responses with a pA₂ value of 7.58, intermediate between the high potency of tamsulosin and the weaker affinity of terazosin (Table 2) and several other α₁-antagonists (Fig. 2). The low potency of prazosin and the other quinazolines to block PE-induced contractions in the urethra model is consistent with these receptors being of the α₁A-type (Leonardi et al., 1997; Testa et al., 1997; Van der Graaf et al., 1997). However, the potency order of structurally diverse antagonists in this model was highly correlated to the potency of these compounds at α₁A-adrenoceptors in radioligand binding studies, but not with either the α₁B- or α₁D-receptor (Fig. 2). As predicted from radioligand binding data, terazosin was essentially equipotent as an antagonist of α₁D- and α₁A-adrenoceptors (Table 2) in isolated tissues, although it was less potent in rabbit urethra. Tamsulosin, as previously reported (Hancock, 1996), inhibited maximal responses in the rat vas deferens consistent with a noncompetitive blockade of some α₁A-adrenoceptors, and was not selective for α₁A- compared with α₁D-adrenoceptors in functional tests in vitro (Hancock et al., 1998b).

**Measurement of IUP in Dogs.** Fiduxosin, administered at doses of 30, 100, and 300 μg/kg i.v. (0.051, 0.168, and 0.507 μmol/kg i.v.) antagonized IUP responses to i.v. EPI in anesthetized dogs (Fig. 3A), presumably via blockade of α₁A-adrenoceptor-mediated smooth muscle contraction within the prostatic stroma (Brune et al., 1995). Fiduxosin caused rightward shifts to the EPI dose-response curve, yielding an in vivo pseudo-pA₂ value of 8.12 ± 0.17 (Fig. 3B; Table 3). Comparable data for terazosin and tamsulosin are illustrated in Fig. 3, C to F, and summarized in Table 3. The rank order of potencies for blocking EPI-induced pressor responses in the dog for fiduxosin and several other α₁-antagonists was similar to the potency order of these compounds at isolated canine prostatic strips, rabbit urethral smooth muscle, or rat vas deferens (Table 2), less similar at α₁D-adrenoceptors in rat aorta, and distinct from the potency order at rat spleen α₁B-adrenoceptors (Table 2). The potency order for blockade of IUP responses was also highly correlated to compound affinities in receptor binding assays of cloned human α₁A₁-adrenoceptors for fiduxosin and several chemical classes of α₁-antagonists (Fig. 4A), but lesser correlations were observed for either α₁A₁- or α₁D-receptors (Fig. 4, B and C).

**Fig. 2.** Correlation analysis of antagonism of rabbit urethral α₁-adrenoceptors to compound affinities at cloned human α₁-adrenoceptor subtypes. Blockade of PE-induced contractions of rabbit urethra was quantified as pA₂ values (Table 2) and compared with radioligand binding affinities (Table 1; Hancock et al., 1998b) for cloned human α₁A- (A), α₁B- (B), and α₁D-adrenoceptors (C), respectively. The correlation coefficients were 0.93 for α₁A-adrenoceptors, with a slope of 1.02. For α₁B-adrenoceptors the correlation coefficient was 0.15, with a slope of −0.17, whereas for α₁D-adrenoceptors the correlation coefficient was 0.50, with a slope of 0.67.

**Fig. 3.** Effects of α₁-adrenoceptor antagonists on IUP in anesthetized dogs. Fiduxosin (A and B), terazosin (C and D), and tamsulosin (E and F) were administered as described under Experimental Procedures to anesthetized dogs in various doses, followed by intravenous administration of epinephrine over a range of doses. Intraurethral pressure was measured as described under Experimental Procedures. A, C, and E, shifts of the epinephrine dose-response curve caused by the different doses of the α₁-antagonists. Solid lines indicate control epinephrine dose responses in the absence of antagonist. Increasing doses of fiduxosin of 10, 30, and 100 μg/kg i.v.; terazosin of 100, 300, or 1000 μg/kg i.v.; or tamsulosin of 1, 3, and 10 μg/kg i.v. elicited dose-dependent rightward shifts of the epinephrine dose-response relationship. B, D, and F, Schild plots of the shifts of the dose-response curves to generate the pseudo-pA₂ values listed in Table 3. Dashed lines are the regression lines of the data sets, whereas the solid lines indicate the slope of the Schild line constrained to equal 1. For fiduxosin, the estimated pA₂ value was 8.12, but 8.16 when the slope was constrained to 1. Values for terazosin (6.67 and 6.90) and tamsulosin (8.57 and 9.36) were also obtained in the absence and presence, respectively, of the constraint. The difference was greatest for tamsulosin because the slope of the Schild plot was 1.76 (Table 3).
TABLE 3
Comparative antagonistic potencies of fiduxosin and standard α₁-adrenoceptor antagonists at α₁-adrenoceptors in canine prostatic urethra and SHR vascular smooth muscle in vivo

Dogs (n = 4 per compound) were anesthetized with methoxyflurane, and prostatic urethral responses to EPI were determined as described under Experimental Procedures. Potencies of α₁-antagonists were determined from Schild analysis and expressed as pK₅₀ values. SHR (n = 3 per compound) were administered test agents i.v., and potencies (pED₅₀ doses) to reduce blood pressure were determined as described under Experimental Procedures. The selectivity ratio was calculated as the antilog of the difference between the pK₅₀ value versus EPI in the isoflurane-anesthetized canine and the pED₅₀ in the SHR.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Isoflurane-Anesthetized Dog, IUP vs. i.v. EPI pK₅₀ ± S.E.M. (Slope ± S.E.M.)</th>
<th>SHR, MAP pED₅₀ ± S.E.M. (Slope ± S.E.M.)</th>
<th>Selectivity Ratio, Antilog of (pK₅₀-pED₅₀) (IUP-MAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiduxosin</td>
<td>8.12 ± 0.17 (1.1 ± 0.19)</td>
<td>5.23 ± 0.48 (0.83 ± 0.14)</td>
<td>770</td>
</tr>
<tr>
<td>Terazosin</td>
<td>6.67 ± 0.18 (1.44 ± 0.42)</td>
<td>6.64 ± 0.76 (0.85 ± 0.17)</td>
<td>1.1</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>8.87 ± 0.19 (1.76 ± 0.45)</td>
<td>7.35 ± 0.30 (0.37 ± 0.15)</td>
<td>35</td>
</tr>
</tbody>
</table>

Fig. 4. Correlation analysis of antagonism of canine IUP and SHR MAP responses to compound affinities at cloned human α₁-adrenoceptor subtypes. Blockade of EPI-induced elevations of IUP was quantified as pseudo-pK₅₀ values (Table 2) and compared with radioligand binding affinities (Table 1; Hancock et al., 1998b) for cloned human α₁ₐ- (A), α₁₁- (B), or α₁₂-adrenoceptors (C), respectively. The correlation coefficients were 0.96 for α₁ₐ-adrenoceptors, with a slope of 0.92. For α₁₁-adrenoceptors the correlation coefficient was 0.16, with a slope of −0.17, whereas for α₁₂-adrenoceptors the correlation coefficient was 0.62 with a slope of 0.72. Hypotensive responses in SHR were quantified as pED₅₀ values (Table 2) and were compared with radioligand binding affinities (Table 1; Hancock et al., 1998b) for cloned human α₁a- (D), α₁b- (E), or α₁c-adrenoceptors (F), respectively. The correlation coefficients were 0.016 for α₁a-adrenoceptors, with a slope of −0.019. For α₁b-adrenoceptors the correlation coefficient was 0.94, with a slope of 1.2, whereas for α₁c-adrenoceptors the correlation coefficient was 0.63 with a slope of 0.92.

Blood Pressure Measurements in Conscious Spontaneously Hypertensive Rats. Fiduxosin, administered to SHR at doses of 0.3, 1, 3, or 10 μmol/kg i.v. (178, 592, 1780, and 5920 μg/kg i.v.), elicited transient effects on blood pressure, particularly at doses of 0.3, 1, or 3 μmol/kg i.v. (Fig. 5), with no effect of the lowest dose on MAP compared with vehicle and transient hypotension with doses between 1 and 3 μmol/kg i.v. (Fig. 5). Only when the dose of fiduxosin was increased to 10 μmol/kg i.v. was the hypotensive effect sustained (Fig. 5), although the decrease in MAP even at the highest dose was considerably less than the hypotension observed with nonselective α₁-antagonists at equivalent or considerably lower doses (Hancock et al., 1998b). For example, prazosin, doxazosin, terazosin, and alfuzosin all decreased blood pressure by greater than 40% at doses of 1 to 3 μmol/kg i.v., generally for the entire observation period of 150 min (Hancock et al., 1998b). Note that the lowest dose of fiduxosin tested in SHR (178 μg/kg i.v.) exceeds the highest dose tested in the canine IUP model (100 μg/kg i.v.), demonstrating that doses of fiduxosin that robustly block IUP responses in the dog elicit no significant hypotensive effect in SHR.

Using a hypotensive index described under Experimental Procedures, the potency of fiduxosin (mol/kg i.v.) was converted to a pED₅₀ value of 5.23 (Table 3). We have previously determined (Hancock et al., 1998b) that if compounds are assessed using either a 30-min AUC or the peak hypotensive effect, the rank order of potencies is virtually identical, sug-
gesting that the 60-min AUC values provide a useful quantification of MAP effects. The pED\text{50} value observed for fiduxosin is considerably higher than that for typical \( \alpha_1 \)-adrenoceptor antagonists (Hancock et al., 1998b). For example, the pED\text{50} values for prazosin (7.45), doxazosin (6.50), terazosin (6.64), alfuzosin (6.58), and tamsulosin (7.33) were 10- to 100-fold lower (Hancock et al., 1998b), consistent with the greater hypotensive effect of these \( \alpha_1 \)-blockers. If the potency (pA\text{2}) of fiduxosin to block IUP effects in the canine is compared with its potency (pED\text{50}) to lower blood pressure, a relative index of selectivity of almost three orders of magnitude (770-fold) is obtained, making fiduxosin the most selective of the compounds for IUP compared with MAP effects (Hancock et al., 1998b). In addition, the relative hypotensive potency of fiduxosin and other \( \alpha_1 \)-adrenoceptor antagonists was highly correlated to their affinity at \( \alpha_{1B} \)-adrenoceptors in radioligand binding studies (Fig. 4E), but less well correlated with the potency of these compounds at either \( \alpha_{1A} \) or \( \alpha_{1D} \)-adrenoceptors (Fig. 4, D and F, respectively). It is noteworthy that fiduxosin is the least potent compound of those tested in measures of hypotensive efficacy (Fig. 4, D–F) and affinity for the \( \alpha_{1B} \)-adrenoceptor, consistent with the concept that hypotensive effects of \( \alpha_1 \)-adrenoceptor antagonists primarily result from their antagonism of \( \alpha_{1B} \)-adrenoceptors.

SHR were also studied for effects of postural changes on MAP after intermittent 90° head-up tilt. For fiduxosin, doses of 0.3 and 1 \( \mu \)mol/kg i.v. (178–592 \( \mu \)g/kg i.v.) failed to lower blood pressure markedly, and there was no further diminution upon head-up tilt (Fig. 6). Fiduxosin (3 \( \mu \)mol/kg or 1780 \( \mu \)g/kg i.v.) slightly reduced MAP, but head-up tilt caused further diminution of MAP at only the 15-min observation with minimal additional changes in MAP at times \( \geq \)30 min postdosing (Fig. 6). At the highest dose of fiduxosin (10 \( \mu \)mol/kg or 5920 \( \mu \)g/kg i.v.), a moderate additive effect to the postural hypotensive response was noted beyond 30 min after compound administration (Fig. 6). However, these hypotensive responses to tilt were considerably less marked than those observed with other \( \alpha_1 \)-antagonist compounds (Hancock et al., 1998b).

## Discussion

Pharmacotherapy has become the treatment of choice for new cases of BPH with more than 80% of patients of primary care physicians being prescribed an \( \alpha_1 \)-antagonist (Narayan and Tewari, 1998). Successful amelioration of symptoms has been observed with each of the long-acting \( \alpha_1 \)-blockers currently approved for BPH, terazosin, doxazosin, and tamsulosin (Narayan and Tewari, 1998). Nevertheless, adverse events often limit effective pharmacotherapy (de Mey, 2000). Postural hypotension or other cardiovascular side effects may be related to the relative lack of \( \alpha_1 \)-adrenoceptor subtype selectivity of agents such as terazosin and doxazosin as shown by the lower incidence of these events with tamsulosin (Take et al., 1998), a compound with high potency for \( \alpha_{1A} \)-adrenoceptors, albeit modest subtype selectivity (Hancock, 1996). A number of compounds highly selective for the \( \alpha_{1A} \)-adrenoceptor have been identified in recent years (Testa et al., 1994; Forray et al., 1995; Wetzel et al., 1995; Ford et al., 1996) in search of a uroselective agent for lower urinary tract symptoms associated with BPH, but to date, none have passed clinical development hurdles to validate the proposition that \( \alpha_{1A} \)-adrenoceptor selectivity can enhance the efficacy or reduce the side effect incidence more successfully than currently available agents. Fiduxosin represents a new class of \( \alpha_1 \)-antagonists that may offer the potential to treat BPH based on its selective blockade of prostatic or lower urinary tract \( \alpha_{1B} \)-adrenoceptors compared with its effects on cardiovascular responses.

Fiduxosin demonstrated high affinity for \( \alpha_{1A} \)-adrenoceptors in radioligand binding studies and \( \alpha_{1A} \)-adrenoceptors in functional bioassays, and a high degree of selectivity for these sites in comparison with \( \alpha_{1B} \) or \( \alpha_{1D} \)-adrenoceptors. In radioligand binding assays, the compound was 155-fold selective for \( \alpha_{1A} \)-adrenoceptors, whereas tamsulosin was only 21-fold \( \alpha_{1A} \)-versus \( \alpha_{1B} \)-selective. If the lower incidence of cardiovascular side effect liability encountered with tamsulosin results from this 21-fold selectivity then fiduxosin would be expected to have an even lower incidence of cardiovascular effects. This would contrast with the clinical profile of nonselective \( \alpha_1 \)-blockers such as, e.g., terazosin and doxazosin, which generally are slightly more potent antagonists of the \( \alpha_{1B} \)-adrenoceptor (Hancock, 1996). However, the clinical profile of tamsulosin may be a function of both receptor selectivity and optimization of formulation used in therapy of BPH, or perhaps higher prostatic concentrations of the drug, compared with plasma, at least in the dog (Sato et al., 2001). Thus, the clinical inadequacy of REC 15/2739 or Ro-70-0004 might have resulted from pharmacodynamic components and/or their lack of antagonistic action on \( \alpha_{1D} \)-adrenoceptors. In contrast, key pharmacological (selective blockade of both \( \alpha_{1A} \) and \( \alpha_{1B} \)-adrenoceptors) and pharmacokinetic properties of fiduxosin (long half-life and prolonged in vivo efficacy; Witte et al., 2002) may contribute to a more favorable clinical profile.

Fiduxosin has similar affinities at \( \alpha_{1A} \) and \( \alpha_{1D} \)-adrenoceptors in radioligand binding (differences of 6-fold or less), whereas tamsulosin was only 2-fold less potent at \( \alpha_{1D} \) compared with \( \alpha_{1A} \)-adrenoceptors. These selectivity profiles are
generally maintained in the isolated tissue studies where fiduxosin was 5-fold more potent at $\alpha_{1A}$-adrenoceptors in rat vas deferens compared with its potency at $\alpha_{1D}$-adrenoceptors in the rat aorta, whereas tamsulosin actually showed higher potency at rat aortic $\alpha_{1D}$-adrenoceptors than in any other tissue studied. Although the exact role of $\alpha_{1D}$-adrenoceptors remains enigmatic, these receptors may have a role in bladder function (Broten et al., 1998; Malloy et al., 1998), such that antagonism of these sites could reduce bladder-related dysfunctional components of lower urinary tract symptoms in BPH (Schwinn and Michelotti, 2000). In addition, antagonism of $\alpha_{1D}$-adrenoceptors in the central sympathetic innervation of the prostate and bladder by $\alpha_{1A}$/SAR, selective antagonists may ameliorate irritative symptoms (Smith et al., 1999; Michel et al., 2000).

Despite the selective antagonism of $\alpha_{1A}$-adrenoceptors demonstrated by a number of compounds and the predominance of these receptors in prostatic smooth muscle both from a functional and molecular biological perspective, the failure of several $\alpha_{1A}$-adrenoceptor-selective antagonists to demonstrate blockade of both obstructive and irritative symptoms has led to uncertainty regarding the role of $\alpha_{1A}$-adrenoceptors in BPH symptomatology. In addition, some studies have indicated pharmacological heterogeneity of prostatic $\alpha_1$-adrenoceptors (Muramatsu et al., 1994). Several investigators (Muramatsu et al., 1994; Leonardi et al., 1997; Martin et al., 1997; Testa et al., 1997) have proposed that other receptor interactions might be of functional importance in controlling prostatic tone and contribute to uroselectivity. Prostatic $\alpha_1$-adrenoceptors have been suggested to belong to the $\alpha_{1L}$-class of adrenoceptors because of their low affinity for prazosin (Muramatsu et al., 1994), and the pharmacological effects of REC 15/2739 have been linked to blockade of $\alpha_{1L}$-receptors (Leonardi et al., 1997; Testa et al., 1997). In vitro models of the $\alpha_{1L}$-adrenoceptor have been proposed (Muramatsu et al., 1995), including rabbit urethral tissue (Leonardi et al., 1997; Testa et al., 1997), and it has been suggested that blockade of these receptors would be important to the amelioration of BPH (Leonardi et al., 1997; Testa et al., 1997). Our studies with fiduxosin demonstrated antagonism of contractions mediated by urethral $\alpha_1$-adrenoceptors, although the potency of fiduxosin to block these sites was considerably weaker than the potency observed at $\alpha_{1A}$-adrenoceptors. However, the rank order of potencies of a number of selective and nonselective $\alpha_1$-antagonists correlated best with the potency order at $\alpha_{1A}$-adrenoceptors, less well with $\alpha_{1D}$-adrenoceptors, and very poorly with $\alpha_{1B}$-adrenoceptors. Thus, there appeared to be a frame shift in the observed potencies of compounds at urethral $\alpha_1$- compared with $\alpha_{1A}$-adrenoceptors. These results, and the observations that potency at $\alpha_{1A}$/SAR-adrenoceptors can be modulated by assay conditions (Ford et al., 1997), are consistent with the concept that urethral $\alpha_1$-adrenoceptors belong to the $\alpha_{1A}$-class. Irrespective of the nomenclature used, the present data clearly indicate that fiduxosin can antagonize urethral $\alpha_1$-adrenoceptors more potently than $\alpha_{1D}$-adrenoceptors, suggestive of uroselectivity. In contrast, terazosin and tamsulosin, both efficacious in BPH, are more potent at $\alpha_{1D}$-adrenoceptors in vitro than at rabbit urethral $\alpha_1$-adrenoceptors. In addition, fiduxosin is approximately 10-fold more potent at urethral $\alpha_1$-adrenoceptors than terazosin, suggesting that a compound exhibiting this enhanced potency would offer effective blockade of these sites in the amelioration of BPH symptoms.

The selectivity profile obtained with fiduxosin also suggests that the compound would have lower cardiovascular effects than other non- or weakly selective agents such as terazosin, doxazosin, or tamsulosin. This hypothesis was supported by results obtained in SHR, in which fiduxosin was less hypotensive than other agents on a mole per kilogram basis, and also elicited weaker, more transient effects in a postural hypotension challenge. Similar results have been reported with the $\alpha_{1A}$-selective compounds Ro-70-0004 (Williams et al., 1999), RWJ-38063, and RWJ-69736 (Pulito et al., 2000), supporting the importance of $\alpha_{1A}$-adrenoceptors for cardiovascular function as suggested by data with knock-out mice lacking the $\alpha_{1A}$-adrenoceptor gene (Cavalli et al., 1997). Recently, a novel compound has been described, B8805-033 (Eltze et al., 2001), with chemical and pharmacological similarities to 5-methyl-urapidil and fiduxosin. B8805-033 is of lower absolute affinity for $\alpha_{1A}$-adrenoceptors than fiduxosin but is apparently more selective compared with $\alpha_{1B}$- and $\alpha_{1D}$-adrenoceptors (150–1200-fold). Interestingly, although also less potent at putative $\alpha_{1L}$-sites compared with $\alpha_{1A}$-adrenoceptors by approximately 10-fold, B8805-033 maintains high selectivity for $\alpha_{1L}$-sites compared with either $\alpha_{1B}$- or $\alpha_{1D}$-adrenoceptors. However, B8805-033 has higher radioligand binding affinity at 5HT1A sites than at $\alpha_{1A}$-adrenoceptors, unlike fiduxosin, which is 180-fold less potent at rat cortical 5HT1A sites. Despite high-affinity agonist activity at 5HT1A receptors comparable in potency to fiduxosin and 5-methyl-urapidil, B8805-033 elicits minimal hypotensive effects in SHR (Eltze et al., 2001). B8805-033 shows properties of uroselectivity in the anesthetized dog, with a selectivity ratio of approximately 52. Although the uroselectivity indices differ between studies of B8805-033 and our protocol with fiduxosin, both data sets suggest that compounds with low affinity for $\alpha_{1B}$-adrenoceptors (such as B8805-033 or fiduxosin) compared with $\alpha_{1A}$-, $\alpha_{1L}$- or $\alpha_{1D}$-adrenoceptors may have uroselective properties. Whether the preclinical models available can also elucidate the relative contribution of $\alpha_{1D}$-adrenoceptor blockade to amelioration of clinical symptoms of BPH may require clinical evaluation. However, it is of interest to note that although fiduxosin has a high affinity for $\alpha_{1D}$-adrenoceptors, the compound elicits minor cardiovascular effects. This would suggest that the $\alpha_{1D}$-adrenoceptor does not play a substantial role in blood pressure control. This is underscored by the lower correlation between $\alpha_{1D}$-adrenoceptor potency and hypotension (correlation coefficient of 0.63; Fig. 4F) compared with $\alpha_{1B}$-adrenoceptor potency (correlation coefficient of 0.94; Fig. 4E). In contrast, a similar analysis with a battery of less subtype-selective compounds was unable to distinguish a substantial difference in the potential contributions of the $\alpha_{1B}$- and $\alpha_{1D}$-adrenoceptor subtypes. In that previous analysis (Table 9 of Hancock, 1996), the correlations between $\alpha_{1B}$- and $\alpha_{1D}$-adrenoceptor potency and hypotensive changes in SHR ranged from 0.77 to 0.91. However, the addition of more selective compounds such as fiduxosin to this analysis would suggest that $\alpha_{1D}$-adrenoceptors are less important for blood pressure control than $\alpha_{1B}$-adrenoceptors.

In contrast to weak cardiovascular effects with fiduxosin, the compound elicited highly potent antagonism of prostatic contractile responses to epinephrine in anesthetized dogs,
confirming the in vivo efficacy of fiduxosin. In addition, the ratio between IUP effects in dogs and hypotensive effects in SHR was consistent with the high selectivity for prostatic effects seen with other α1A-selective compounds (Hancock et al., 1998a,b) and indicative that fiduxosin would also selectively antagonize prostatic versus cardiovascular α1-adrenoceptors in vivo. The results of additional studies that highlight selective blockade of prostatic compared with cardiovascular α1-adrenoceptor-mediated effects in conscious dogs will be presented subsequently (Brune et al., 2002). In summary, preferential antagonism of fiduxosin for α1A, and α1D versus α1B-adrenoceptors in vitro, the blockade of putative α1L-sites, and selective effects on lower urinary tract function versus blood pressure in vivo suggest the potential utility of this compound for the treatment of BPH.

Acknowledgments

We thank James P. Sullivan for helpful insights, John C. Cain for technical assistance, and Earl Gubbins and Robert Smoller for molecular biological support. The contributions of David G. Witte are also gratefully acknowledged.

References


Address correspondence to: Dr. Arthur A. Hancock, Department 4MN, Pharmacological and Urological Research Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Rd., Abbott Park, IL 60064-6125. E-mail: a.a.hancock@abbot.com.