Actions of A-131701, a Novel, Selective Antagonist for \textit{Alpha}-1A Compared with \textit{Alpha}-1B Adrenergic Receptors on Intraurethral and Blood Pressure Responses in Conscious Dogs and a Pharmacodynamic Assessment of \textit{in Vivo} Prostatic Selectivity

ARTHUR A. HANCOCK, MICHAEL E. BRUNE, DAVID G. WITTE, KENNAN C. MARSH, SWETA KATWALA, IVAN MILICIC, LYNN M. IRELAND, DEANNE CROWELL, MICHAEL D. MEYER and JAMES F. KERWIN, JR.

Abbott Laboratories, Pharmaceutical Products Division, Neurology and Urology Diseases Research Division, Abbott Park, Illinois

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Abstract

A-131701 (3-[2-[(3aR,9bR)-cis-6-methoxy-2,3,6a,4,5,9b, hexahydro-[1H]-benz[e]isoindol-2-yl]ethyl]pyrido [3’4’:5,6]pyrimidine-2,4(1H,3H)-dione) is a novel compound previously shown to be selective for \textit{alpha}-1A sites compared with \textit{alpha}-1B adrenoceptors in radioligand binding studies and isolated tissue bioassays and to block canine urethral pressure (IUP) responses to exogenous \textit{alpha}-1 adrenergic agonists to a greater extent than blood pressure responses. In conscious dogs in which IUP and mean arterial blood pressure (MABP) responses were measured periodically up to 24 hr, A-131701 blocked phenylephrine (PHE)-induced increases in IUP to a greater extent than MABP responses, and the blockade of the IUP effects of PHE was significantly different from control for up to 12 hr after doses greater than 0.3 mg/kg p.o., whereas blood pressure pressure effects were of a lesser extent and duration. In addition to the weak antagonism of PHE-induced blood pressure responses, A-131701 also exhibited minimal effects on basal blood pressure in the dog, unlike terazosin, doxazosin or tamsulosin. Pharmacokinetic analysis of plasma samples from dogs indicated that A-131701 had a half-life of 0.4 to 0.8 hr and a bioavailability of 30 to 50% in dogs. Somewhat longer half-lives were observed in rat and monkey, with bioavailability values in the 25 to 30% range. Evidence of nonlinearity of pharmacokinetics was obtained in dogs and monkeys. Pharmacodynamic analysis revealed differences between A-131701 and nonselective \textit{alpha}-1 adrenoceptor antagonists in selectivity for prostatic \textit{versus} vascular \textit{alpha}-1 adrenoceptors based on either extent or duration of blockade, which were either similar to or superior to compounds such as tamsulosin or REC 15/2739. These data demonstrate that A-131701 selectively blocks canine prostatic \textit{alpha}-1 adrenoceptors for prolonged periods compared with MABP responses \textit{in vivo}. Therefore, A-131701 should have clinical utility in the pharmacotherapy of benign prostatic hyperplasia.

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ABBREVIATIONS: A-131701, (3-[2-[(3aR,9bR)-cis-6-methoxy-2,3,6a,4,5,9b, hexahydro-[1H]-benz[e]isoindol-2-yl]ethyl]pyrido [3’4’:5,6]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-6-carboxamide); PHE, phenylephrine; IUP, intraurethral pressure; MABP, mean arterial blood pressure; AUC, area under the curve; BPH, benign prostatic hyperplasia; $t_{1/2}$, plasma elimination half-life; $V_p$, volume of distribution; $C_{max}$, maximal plasma concentration; $T_{max}$, time to reach maximal plasma concentration; $F$, oral bioavailability; CNS, central nervous system.
these reasons, we developed a conscious dog model to determine the effects of alpha-1 adrenoceptor antagonists on both prostatic and cardiovascular smooth muscle responses to exogenously administered alpha-1 adrenoceptor agonists for up to 24 hr (Brune et al., 1996).

In this conscious dog model, IUP and MABP (both basal and in response to exogenous agonist) were quantified periodically to determine the extent of antagonism of prostatic or vascular alpha-1 adrenoceptors. In contrast, previous models used to determine effects of alpha-1 antagonists on either IUP alone (Brune et al., 1995) or IUP and MABP (Kenny et al., 1994; Testa et al., 1994) quantified antagonist potencies at only one time after administration of the blocker. Shortcomings of this approach are: 1) relative potencies of agents are determined only at one point in time, not many; 2) important pharmacokinetic aspects of drug distribution to and elimination from the effect compartments are ignored; 3) generally, only intravenous administration of test agent has been possible because of the potential effects of anesthesia on compound absorption from the gastrointestinal tract, although an exception to the latter condition has been reported in which selectivity of alpha-1 adrenoceptor antagonists was estimated after intraduodenal administration in anesthetized dogs (Testa et al., 1994). In contrast, the conscious dog model avoids these limitations, has advantages of the use of oral dosing of a compound and is thus more akin to the conditions used in determining the oral pharmacokinetic properties of a new compound. For these reasons, A-131701 was tested in a conscious dog model where antagonism of alpha-1 adrenoceptors responsible for control of IUP and MABP to exogenous agonist could be determined. In addition, pharmacodynamic aspects of IUP or MABP responses were determined by a method analogous to that of Lemmens (1995) to compare A-131701 with several alpha-1 adrenoceptor antagonists that are used as both clinical and investigational agents.

As previously described (Meyer et al., 1997), A-131701 is an alpha-1 adrenoceptor antagonist selective for the alpha-1A subtype compared with the alpha-1B adrenoceptor in radioligand binding assays, in functional bioassays of alpha-1A adrenoceptors compared with alpha-1B subtypes in isolated smooth muscle and in IUP measurements in the anesthetized dog compared with MABP effects either in the dog or in spontaneously hypertensive rat models. Also, observing generally accepted conventions, the nomenclature recommendations of Bylund et al. (1994) are used to differentiate among the subtypes of alpha-1 adrenoceptors where upper case subscripts denote tissue-derived receptors and lower case subscripts denote cloned receptors.

Methods

Simultaneous Measurement of IUP and MABP in Conscious Dogs

The effects of compounds on MABP and IUP in conscious dogs were evaluated by methods described previously (Brune et al., 1996). Male beagle dogs were instrumented for the chronic, continuous measurement of arterial blood pressure by implanting a telemetry transducer/transmitter (TA11PA-C40, Data Sciences International, St. Paul, MN) into a carotid artery at least 1 week before compound testing. On test day, dogs fasted since the previous afternoon were placed in sling restraints, and an Abbocath-T™ i.v. catheter (18-G, 1998 Conscious Dog Studies of A-131701 629

Abbott Laboratories, North Chicago, IL) was inserted into a cephalic vein for blood sampling and for the administration of agonist. A telemetry receiver (RA1310, Data Sciences), placed near the head of each dog, was connected to an analog output adapter (R11CPA, Data Sciences) which then was interfaced to a computerized data acquisition system (Modular Instruments, Inc., Malvern, PA) which allowed continuous, calibrated recording of the arterial pressure waveform. Mean arterial pressure was obtained by electronically filtering this signal. Measurement of changes in IUP was performed essentially as described previously (Brune et al., 1996) and validated in anesthetized dogs (Brune et al., 1995). Dose responses of the intra-urethral and arterial pressor effects of 8, 16 and 32 μg/kg i.v. PHE were obtained before and at various times up to 24 hr after a single p.o. dose of each antagonist. PHE was dissolved in 0.9% saline and administered at a volume of 0.1 ml/kg whereas the antagonists were dissolved in water and given by gavage at a volume of 1 ml/kg. The increase in IUP and MABP caused by any agonist dose was allowed to return to base line before the next dose was administered. Dogs remained in slings with the urinary catheter in place from –1 to 7 hr after dosing, then again from 11.5 to 13 hr and 23.5 to 25 hr. At other times, the urinary catheters were removed and the dogs returned to their home cages with free access to food and water. Data were expressed as percent blockade of the base-line pressor responses obtained in the absence of antagonist. Area under the IUP and MABP blockade vs time curves (AUC) were calculated by trapezoidal rule integration. Hypotensive effects were expressed as net change from predose base-line MABP and were determined just before administration of PHE.

Statistical Analysis

One-way analysis of variance (Snedecor and Cochrane, 1967) was used to compare the extent of blockade of PHE-induced IUP or MABP effects at each time point during the course of the experiment. In addition, one-way analysis of variance was used to compare the AUC values for each agent in antagonizing PHE responses for both IUP and MABP. RS/1 procedures (BBN Software Products Corp., Cambridge, MA), with statistical significance indicated by a P value < .05, were used for these analyses. Comparisons between groups used Bonferonni’s multiple comparisons test or Duncan’s multiple range test.

Pharmacokinetic Analysis of Plasma Levels of A-131701

The pharmacokinetic behavior of A-131701 was evaluated in rat, dog and monkey. In a series of parallel studies, groups of Sprague-Dawley derived rats (male, n = 3–4/group), beagle dogs (male and female, n = 3/group) and cynomolgus monkey (female, n = 3/group) received either a single i.v. or oral dose of A-131701. Initial studies used a 2.5-mg base/ml solution of the parent compound prepared in an ethanol/proplylene glycol/5% dextrose in water (20:30:50, by volume) vehicle. Groups of dogs and monkeys received either a 2.5 mg/kg i.v. dose (1 ml/kg) or a 5 mg/kg oral dose (2 ml/kg); groups of rats received a 5 mg/kg i.v. or p.o. dose (2 ml/kg). A second series of studies evaluated the linearity of the pharmacokinetics after oral administration of the solution in rats, dogs and monkeys. The i.v. doses were administered as a slow bolus for ~1 min. The oral doses were administered by gavage in both rats and dogs or via nasogastric intubation in monkeys. Heparinized blood samples (~0.4–0.5 ml sample) were obtained from a tail vein of each rat 0.1 (i.v. only), 0.25, 0.5, 1, 1.5, 2, 4, 6, 9 and 12 hr after dosing. Heparinized blood samples (2.5–3 ml) were obtained from the jugular vein (dog) or femoral artery/vein (monkey) of each animal before dosing and at time points similar to those listed for the rats above. Plasma was separated from the red cells by centrifugation (4°C) and stored frozen (~20°C) until analysis. Parent drug was selectively removed from plasma contaminants by liquid-liquid extraction with a mixture of ethyl acetate and hexane under alkaline conditions. The components of interest were assayed by reverse-phase high-performance liquid
chromatography with either low-wavelength UV or MS/MS quantitation (in which the different quadrupoles of the instrument are arrayed for divergent functions of ionization, separation and detection of the analyte). Initial estimates of the pharmacokinetic parameters for NONLIN, VAX version 3.0 (SEI Software, Lexington, KY) were obtained with the program CSTRIP (Sedman and Wagner, 1976). AUC values were calculated by the trapezoidal rule during the time course of the study. The terminal-phase rate constant (β) was used in the extrapolation of the AUC from 0 hr to infinity. A comparison of the AUC after oral administration with that obtained after an i.v. dose provided an estimate of the bioavailability (F).

Pharmacodynamics of A-131701 and Other Alpha-1 Antagonists in the Conscious Dog Model

Comparison of AUC values of IUP and MABP blockade. AUC values for blockade of PHE-induced IUP responses were normalized to the maximal AUC value obtained with REC 15/2739 vs. 32 μg/kg i.v. PHE, a value of −621%-hr. Selection of this value allowed for normalization by interpolation of dose versus AUC plots of the other antagonist compounds (data not shown) and thus did not require extrapolation of data. Regression analysis of the IUP AUC values at each dose of antagonist generated the predicted dose and 95% confidence limits of dose of compound that would provide IUP AUC values equal to −621%-hr. This dose as well as the 95% confidence limits of dose were then used in regression analysis of the dose of antagonist vs. the MABP AUC values for that compound to generate the predicted values of the MABP AUC values for each compound.

Comparison of duration of action for IUP and MABP blockade. Plots of the percent blockade of PHE-induced IUP or MABP effects over time for each dog at each dose of each compound were generated for antagonism of both the 16 and 32 μg/kg i.v. PHE challenges. These plots then were analyzed for the duration of antagonism of either the IUP or MABP effects which were ≥50% blockade. Mean duration values for each dose of each compound were then calculated to determine the relative duration of antagonism and the selectivity of that antagonism for IUP or MABP effects.

Materials

A-131701 (as the dihydrochloride salt), prazosin, terazosin, doxazosin, tamsulosin (YM-617, R(-)-(d-(o-ethoxyphenoxy) ethyl)amino)propyl]-2-methoxybenzenesulfonamide hydrochloride) and REC-15/2739 were synthesized at Abbott Laboratories. PHE was purchased from Sigma Chemical (St. Louis, MO).

Results

Simultaneous Measurement of IUP and MABP in Conscious Dogs

The administration of 8, 16 or 32 μg/kg PHE i.v. to conscious dogs caused an increase in both IUP and MABP at each observation period (−1 to +24 hr after test drug or vehicle administration) that was proportional to the dosage of PHE administered (Brune et al., 1996). However, at early time points during the experiment, when PHE was administered more frequently, PHE-induced elevation of IUP or MABP was generally somewhat less (for a given dose) than during the control period or than later in the experiment, although responses tended to be more stable for IUP than for MABP. Part of the inconsistency of the PHE effect may be attributed to receptor desensitization after frequent PHE administration during early stages of the experiment or may have resulted from variations in the response levels of the dogs because of environmental or other factors (Brune et al., 1996; Witte et al., 1997). However, the variability of response was not large, generally amounting to less than 5 to 10 mm Hg for MABP, even less for IUP, even at the highest dose of PHE administered (data not shown). Therefore, quantification of antagonist ability to block PHE-induced IUP or MABP responses was based on the percentage blockade compared with the control response to a given dose of PHE.

Oral administration of A-131701 to conscious dogs resulted in marked inhibition of PHE-induced elevation of IUP (fig. 1, A and B). At a dose of 0.1 mg/kg p.o., A-131701 blocked PHE effects on IUP for 6 to 8 hr. Higher oral doses (0.3, 0.5 or 1.0 mg/kg) of compound tended to inhibit both 16 and 32 μg/kg i.v. PHE effects on IUP for longer periods (fig. 1, A and B). In addition, doses of A-131701 greater than 0.1 mg/kg, p.o. tended to produce nearly complete blockade of PHE-induced IUP effects during early time points. In contrast, A-131701 administration caused lesser effects on PHE-induced elevation of MABP (fig. 1, C and D). At early time points, A-131701 at doses of 0.5 mg/kg p.o. or greater tended to reduce the hypertensive effect of PHE injections, although the magnitude of the inhibitory response was only 50 to 60% of the maximal blockade (fig. 1, C and D), and was statistically significant, from vehicle controls only at 60 min at the 1.0 mg/kg p.o. dose of A-131701 when PHE was administered at 32 μg/kg i.v. (fig. 1D). A-131701 (0.5 and 1.0 mg/kg p.o.) was able to antagonize pressor effects of 16 μg/kg i.v. of PHE, although the antagonistic effects waned after several hours, and by 6 hr after administration, PHE responses were similar to those of vehicle-treated dogs (fig. 1, C and D). In contrast to the profile of A-131701, the quinazoline alpha-1 antagonists terazosin and doxazosin previously have been reported to have more substantial effects on PHE-induced MABP responses than IUP responses (Brune et al., 1996). Also, tamsulosin exhibited nearly equivalent effects on MABP and IUP responses to exogenous PHE (Brune et al., 1996), whereas REC 15/2739 was more efficacious on IUP than MABP responses to PHE (Brune et al., 1996). Compared with these compounds, A-131701 was more selective for antagonism of IUP effects of PHE than MABP responses to the antagonist at most doses and time points evaluated.

In addition to the minimal effects of A-131701 on PHE-induced elevation of MABP, A-131701 also had minimal effects on basal MABP in the absence of agonist (fig. 2E). In contrast, other alpha-1 adrenoceptor antagonists, e.g., terazosin, doxazosin, tamsulosin and REC 15/3729, showed more pronounced effects on MABP (fig. 2, A, B, C and D, respectively), particularly the nonselective compounds terazosin and doxazosin, whereas tamsulosin had an intermediate effect. REC 15/2739 was more similar to, although perhaps slightly more active than, A-131701 in decreasing basal MABP (compare fig. 2, D and E), although the latter two compounds were clearly the least hypotensive at the doses administered.

Previous experiments in our laboratories (Brune et al., 1996; Witte et al., 1997) demonstrated that nonselective alpha-1 adrenoceptor antagonists such as terazosin or doxazosin have much more profound and long-lasting effects on MABP responses to PHE than the IUP responses to the agonist. One means of quantifying the different potencies for IUP vs. MABP blockade of PHE-induced pressure effects is to compare the relative AUC for blockade of each response (Brune et al., 1996). For A-131701, the effects of both 16 and 32 μg/kg i.v. PHE on IUP were antagonized to approximately the same extent at every dose of A-131701 administered (fig.
3A) and increased with augmented doses of compound. In contrast, effects of PHE on MABP responses were antagonized to a lesser extent by A-131701, with no difference in PHE responses after doses of 0.01, 0.1 or 0.3 mg/kg p.o. for either 16 or 32 μg/kg i.v. of PHE (fig. 3B). Only at a dose of 0.5 mg/kg p.o. of A-131701 did there appear to be a significant blunting of the effect of 16 μg/kg i.v. PHE, although this was not apparent with the 32 μg/kg i.v. dose (fig. 3B). In addition, the blunting of the effects of PHE on MABP did not appear to be enhanced at the dose of 1 mg/kg p.o. of A-131701 (fig. 3B).

In contrast, nonselective alpha-1 adrenoceptor antagonists, e.g., terazosin or doxazosin, blocked the MABP pressor effects of PHE to a greater extent than A-131701 (fig. 4, C and D), and in addition, antagonized PHE effects on MABP to a greater extent for a given dose than these compounds did for PHE-induced increases in IUP (fig. 4, A and B). Tamsulosin also antagonized MABP-induced pressor responses to PHE, especially at a dose of 0.1 mg/kg p.o. (fig. 5C). The compound also suppressed IUP effects of PHE in a dose-dependent manner (fig. 5A), such that the intermediate dose of 0.01 mg/kg p.o. of tamsulosin appeared to have a significantly greater impact on IUP effects of PHE than was observed for MABP effects (compare fig. 5, A and C). REC 15/2739 showed minimal effects on the MABP effects of either 16 or 32 μg/kg i.v. PHE in conscious dogs (fig. 5D), consistent with its somewhat weaker effects on basal MABP (see above). The effect of REC 15/2739 on PHE-induced elevation of IUP was not as robust as observed with the other alpha-1 antagonists tested (compare fig. 5B with figs. 3A, 4A, 4B and 5A) and was not particularly dependent upon the dosage of REC 15/2739 administered (fig. 5B).

**Pharmacokinetic Analysis of A-131701 in Plasma**

Preliminary pharmacokinetic studies of A-131701 in animals were characterized by substantial interspecies variability. The pharmacokinetic studies revealed very low volumes...
of distribution in monkeys ($V_B = 0.18 \text{ l/kg}$) with slightly higher values noted in rats and dogs (see table 1). The compound was eliminated rapidly after i.v. dosing in dogs with a terminal elimination half-life of 0.65 hr. A slightly longer half-life was noted in the monkey (1.6 hr); a plasma elimination half-life of $\sim 3.6 \text{ hr}$ was noted after i.v. administration in rats.

The compound was absorbed rapidly from a solution formulation after a 5 mg/kg oral dose in all three species ($T_{\text{max}} < 1 \text{ hr}$, see table 1). Peak plasma concentrations averaged 5.89, 4.12 and 15.8 $\mu$g/ml in rat, dog and monkey, respectively, with apparent bioavailability values of 38.1, 52.6 and 37.8%, respectively. The plasma elimination half-lives after oral dosing paralleled those recorded after i.v. administration with values of 4.8, 0.8 and 1.3 hr for rat, dog and monkey, respectively.

The pharmacokinetic behavior of A-131701 appeared to be modulated by nonlinear behavior attributable to two different mechanisms. In the dog, in both oral and i.v. studies in the 0.5 to 5 mg/kg dose range, the compound was characterized by nonlinear pharmacokinetics that may be attributable to metabolic saturation. At the lowest dose evaluated in the dog (0.5 mg/kg), peak plasma concentrations averaged 0.21 $\mu$g/ml, with a plasma elimination half-life of 0.41 hr and 29.3% bioavailability. Increasing the dose 10-fold resulted in a 20-fold increase in peak plasma concentration with a doubling of the plasma elimination half-life. A similar trend was noted after increasing oral doses in the monkey. The pharmacokinetic behavior after a 0.5 or 1.0 mg/kg oral solution dosing in monkeys was linear with increases in peak plasma concent-

Fig. 2. Effects of alpha-1 adrenoceptor antagonists on basal MABP in conscious dogs. Aged dogs, instrumented as described for figure 1, were administered test agents, and basal blood pressure responses were measured before the administration of pressor doses of PHE periodically up to 24 hr after administration of compound. Terazosin (A), doxazosin (B) and tamsulosin (C) elicited dose-dependent decreases in basal MABP extending over several hours. REC 15/2739 (D) had minimal effects on MABP at the doses tested. Similarly, A-131701 had almost no effect on basal blood pressure at any dose tested (E).
Pharmacodynamics of A-131701 and Other Alpha-1 Antagonists in the Conscious Dog Model

Comparison of AUC values of IUP and MABP blockade. For the purpose of additional comparisons of the relative antagonistic activities of the tested alpha-1 blockers in the conscious dog model, AUC values for blockade of PHE-induced IUP responses were normalized to −621%-hr, a value that corresponded to the AUC for the highest dose of REC 15/2739 vs. 32 μg/kg i.v. PHE. Selection of this value allowed for normalization by interpolation of dose versus AUC plots of each antagonist (data not shown) and thus did not require extrapolation of data. Figure 6 shows IUP AUC values normalized to −621%-hr for all compounds. The corresponding MABP AUC values were determined from the dose vs. AUC plots (not shown) of each compound and represented the MABP AUC values from that dose of compound derived from the IUP/AUC plots that generated an AUC value of −621%-hr. Terazosin and doxazosin gave MABP AUC values greater than −621%-hr, namely −1329 and −1026%-hr, respectively, consistent with their characterization as MABP-selective compounds, whereas A-131701, REC 15/2739 and tamsulosin gave MABP AUC values of −108, −141 and −170%-hr, respectively, considerably less than −621%-hr, and consistent with the characterization of these agents as IUP-selective compounds.

Comparison of duration of action for IUP and MABP blockade. In addition to the AUC values for extent of PHE blockade, the duration of action of receptor antagonism can be viewed as a measure of efficacy of a test compound in a pharmacodynamic sense. In the current analysis, the duration of action was defined as the time (hours) during which blockade of PHE-induced responses (either IUP or MABP) remained equal to or greater than 50%. Duration of action values were estimated by inspection of blockade versus time plots [e.g., fig. 1, A–D, for A-131701, or Brune et al. (1996) for the other antagonists], except that individual plots for each dog at each dose were examined, rather than the mean plots. Figure 7, A and B, shows the duration of action for A-131701 for blockade of IUP and MABP responses, respectively. For blockade of IUP responses after PHE challenge at 16 μg/kg i.v., the duration of action showed a dose-dependent increase that ranged from 0 hr for the lowest dose (0.01 mg/kg) to 10.9 hr for the highest dose (1.0 mg/kg) of A-131701. Blockade of IUP responses by A-131701 after PHE challenge at 32 μg/kg i.v., resulted in a dose-dependent increase in duration that ranged from 0 hr for the lowest dose (0.01 mg/kg) to 9.0 hr for the highest oral dose (1.0 mg/kg) of A-131701. As would be expected, the ability to antagonize the PHE-induced IUP effect depended on the dose of PHE administered, such that both extent of blockade (as shown by AUC values in figs. 3–5) and duration of blockade generally were more robust versus the lower concentration of PHE. In contrast to its effects on IUP, the duration of action of A-131701 for blockade of PHE-induced MABP responses was negligible for all but the highest two doses (0.5 and 1.0 mg/kg p.o.) after 16 μg/kg i.v. PHE challenges and all but the highest dose (1.0 mg/kg p.o.) after 32 μg/kg i.v. PHE challenges. Moreover, the durations of action observed were relatively short for MABP antagonism and ranged from 0 to <4 hr, which indicates that A-131701 is selective on the basis of duration of action for the blockade of IUP responses compared with blockade of MABP responses.
Figure 8, A and B, shows the duration of action for blockade of PHE-induced IUP responses by terazosin and doxazosin, respectively. Figure 8, C and D, shows the duration of action for blockade of PHE-induced MABP responses by these quinazolines. The duration of action for blockade of PHE-induced IUP responses by terazosin (Fig. 8A) was dose dependent and ranged from 0 hr for the lowest dose (0.1 mg/kg) to 17 or 14 hr for the highest dose (1.0 mg/kg p.o.) after PHE challenges at 16 or 32 μg/kg i.v., respectively. In contrast, the duration of action for blockade of MABP responses was greater than that for blockade of IUP responses with values ranging from 16 to 8 hr for the lowest dose (0.1 mg/kg) to 24 hr or greater for the higher doses (0.3, 0.5 and 1.0 mg/kg p.o.) after PHE challenges at 16 or 32 μg/kg i.v., respectively.
respectively. MABP blockade was considerably greater than the 50% criterion at the end of the experiment (24 hr), particularly with the higher doses of terazosin (and doxazosin, see below). Thus, duration of action values are limited artificially to the 24-hr time point, providing an artificial maximum to these values, which limits the quantification of duration of the higher dose effects on MABP. Nevertheless, the results measuring duration of blockade of terazosin are consistent with results based on AUC values of extent of blockade over time which showed that terazosin is selective for blockade of PHE-induced MABP responses compared with blockade of PHE-induced IUP responses.

For doxazosin (fig. 8B), the duration of action for blockade of PHE-induced IUP responses ranged from 0 hr for the lowest dose (0.1 mg/kg), 3.6 hr for the intermediate dose (0.3 mg/kg) and 16.4 hr for the highest dose (1.0 mg/kg p.o.) after administration.
Pharmacokinetic evaluation of A-131701 after single i.v. or p.o. dosing in rat, dog or monkey

Rats, dogs and monkeys were administered A-131701 at various doses either i.v. or p.o. route as described under “Methods.” At periodic sampling intervals thereafter, blood samples were drawn, plasma isolated and the concentration of A-131701 determined by high-performance liquid chromatography, as described under “Methods.” Data are expressed as means (standard deviation). * Harmonic mean; nf, unable to calculate plasma elimination half-life; nc, unable to calculate.

Pharmacodynamic comparison of relative AUC values for blockade of IUP and MABP responses. Maximal AUC values for IUP blockade by REC 15/2739 were determined as described under “Methods.” This average was used to normalize the AUC values of the other antagonists tested for IUP and the mean AUC values determined by regression against the dose of antagonist required to provide equivalent IUP blockade to REC 15/2739 (namely, -621% hr). These doses of antagonist (and their 95% confidence limits) were then used in regression analysis of the AUC values of MABP responses to each dose of administered blocker to determine the mean AUC (±S.E.M.) for MABP blockade by those compounds. By this analysis, for comparable blockade of IUP responses (based on equivalent AUC values), terazosin and doxazosin had more profound effects on MABP responses (fig. 9C) also was dose-dependent, ranging from no antagonism of greater than 50% of MABP at the lowest dose to 9.8 to 23 hr for the higher doses (0.1–1.0 mg/kg p.o.) of doxazosin. These results show that doxazosin also is selective for blockade of PHE-induced MABP responses compared with blockade of PHE-induced IUP responses in the conscious dog model. As with terazosin, the MABP antagonistic effects of doxazosin were profound at the two higher doses, extending beyond 24 hr in many of the tested dogs.

Figure 9, A and B, shows the duration of action for blockade of PHE-induced IUP responses by tamsulosin and REC 15/2739, respectively, whereas figure 9, C and D, shows the duration of action for blockade of PHE-induced MABP responses by these agents. The duration of action for blockade of PHE-induced IUP responses by tamsulosin (fig. 9A) was dose-dependent and ranged from 0.2 to 1.8 hr at the lowest dose (0.001 mg/kg) to 15.5 hr for the highest oral dose (0.1 mg/kg) after PHE challenges at either 16 or 32 hr, 6.0 hr for the highest oral dose of REC 15/2739 (1.0 mg/kg) after PHE challenges at either 16 or 32 µg/kg i.v. The duration of action for blockade of PHE-induced MABP responses (fig. 9C) also was dose-dependent, ranging from no antagonism of greater than 50% of MABP at the lowest dose for most dogs (average <0.6 hr at 0.001 mg/kg) to 12.3 to 13.4 hr duration at the highest oral dose (0.1 mg/kg) after PHE challenges at either 16 or 32 µg/kg i.v. These results show that, in contrast to terazosin and doxazosin, tamsulosin is somewhat selective for blockade of PHE-induced IUP responses compared with blockade of PHE-induced MABP responses based on the relative duration of action of the compound for these effects.

The duration of action for blockade of PHE-induced IUP responses by REC 15/2739 (fig. 9B) was dose-dependent with durations ranging from 2.7 hr for the lowest dose to 6.0 hr for the highest oral dose of REC 15/2739 (1.0 mg/kg) after PHE challenges at 16 µg/kg i.v. With 32 µg/kg i.v. PHE challenges, the duration of action also was dose-dependent and ranged from 2.1 hr for the lowest dose (0.1 mg/kg) to 4.5 hr for the highest oral dose (1.0 mg/kg) of REC 15/2739. In contrast, the duration of action for blockade of PHE-induced MABP responses (fig. 9D) showed negligible duration for the lower doses (0–1.1 hr) and administration, the duration of action for blockade was also dose-dependent and ranged from 6 hr for the lowest dose (0.1 mg/kg) to 9.8 to 23 hr for the higher doses (0.3–1.0 mg/kg p.o.) of doxazosin. These results show that doxazosin also is selective for blockade of PHE-induced MABP responses compared with blockade of PHE-induced IUP responses in the conscious dog model. As with terazosin, the MABP antagonistic effects of doxazosin were profound at the two higher doses, extending beyond 24 hr in many of the tested dogs.

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moderate duration at the highest dose (1.0 mg/kg p.o.) of REC 15/2739 with values of 2.0 and 0.5 hr after PHE challenges at 16 and 32 μg/kg i.v., respectively. These results show that, in contrast to terazosin and doxazosin, REC 15/2739 is somewhat selective for blockade of PHE-induced IUP responses compared with blockade of PHE-induced MABP responses based on relative duration of action of the compounds for these effects.

Discussion

A-131701, as shown previously (Meyer et al., 1997), is a novel antagonist of alpha-1 adrenoceptors, with a preferentially greater potency for alpha-1A than for alpha-1B sites. Our previous observations also demonstrated a selective antagonism of prostatic function compared with cardiovascular function, as measured with anesthetized dogs in comparison.

Fig. 7. Pharmacodynamic comparison of the relative duration of blockade of PHE responses by A-131701. Duration of antagonism by ≥50% of either 16 or 32 μg/kg i.v. doses of PHE on either IUP (A) or MABP (B) responses were determined for each dog treated at each dose of A-131701, based on individualized time-response plots. Dose-dependent increases in the duration of IUP blockade by A-131701 were evident with both doses of PHE. For MABP responses, the duration of effective antagonism of PHE responses was considerably less than blockade of the IUP responses at any dose of A-131701 administered and was markedly less for the 32 μg/kg dose of PHE, which suggests surmountable antagonism.
with either spontaneously hypertensive rat blood pressure effects or antagonism of agonist-induced pressor effects in the dog (Meyer et al., 1997), but were limited to demonstrating the selectivity of blockade based on i.v. administration of compound and as determined at a single time point. The conscious dog model developed by Brune et al. (1996) extends the previous results with A-131701 in several ways. First, A-131701 exhibits dose-dependent antagonism of prostatic responses to PHE, as previously shown in anesthetized dogs (Meyer et al., 1997). Second, the results in the conscious dog demonstrate that this antagonism of prostatic responses extends over prolonged periods of time. Third, simultaneous analysis of cardiovascular responses to PHE showed that A-131701 was significantly less potent in blocking vascular

Fig. 8. Pharmacodynamic comparison of the relative duration of blockade of PHE responses by terazosin and doxazosin. Duration of antagonism by \( \geq 50\% \) of either 16 or 32 \( \mu \)g/kg i.v. doses of PHE on either IUP or MABP responses were determined for terazosin and doxazosin as described in the legend to figure 7. Dose-dependent increases in the duration of IUP blockade by terazosin (A) and doxazosin (B) were evident with both doses of PHE, but appeared more robust for terazosin, which suggests more complete antagonism of prostatic alpha-1 adrenoceptors by the former agent. For MABP responses (C, terazosin; D, doxazosin), the duration of effective antagonism of PHE responses was generally greater than blockade of the IUP responses at any dose of quinazoline administered and was often of greater duration than the \( 24\)-hr limit of the experiment, although for purposes of analysis those values were set to 24 hr.
alpha-1 adrenoceptors at each dose of compound and at each time point evaluated. Notably, effects on IUP responses were pronounced up to 12 hr after drug administration, whereas MABP effects not only had lower magnitude, but also lesser duration of effect. At the most rudimentary level, these results indicate that A-131701 is absorbed sufficiently via the oral route in the dog to block prostatic alpha-1 adrenoceptors; these results were not available in previous experiments. In addition, the results of the conscious dog model indicate a prolonged duration of effect on IUP with A-131701, extending many hours after administration, which suggests that A-131701 reaches concentrations in the canine prostate that are of sufficient magnitude to significantly block alpha-1 adrenoceptors in this tissue for many hours. These results, in particular, are of clinical relevance because clinically efficacious alpha-1 adrenoceptor antagonists used for human BPH...
also exhibit prolonged IUP effects in this model (Brune et al., 1996).

A-131701 had no significant effect in reducing basal blood pressure in the conscious dog model, a finding of potential clinical importance. Terazosin, doxazosin and tamsulosin lowered mean arterial pressure in the conscious dog in a dose-dependent manner. These latter drugs, particularly the non-subtype-selective quinazolines, can cause adverse cardiovascular effects in some patients, probably resulting from blockade of vascular alpha-1 adrenoceptors, although most patients exhibit few cardiovascular side effects with terazosin therapy and no significant decreases in either systolic or diastolic blood pressures have been observed in the largest clinical trials to date of any alpha-1 adrenoceptor antagonist (Roehrborn et al., 1996). This would indicate that the conscious dog model offers an additional advantage over the anesthetized dog models in detecting subtle effects on basal blood pressure that could be clinically relevant. For example, A-131701 has equal alpha-1 antagonistic potency in the anesthetized dog models to terazosin, doxazosin or alfuzosin (Hancock et al., submitted for publication), and yet is considerably less hypotensive in the conscious dog and less potent and/or less efficacious in antagonizing the MABP effects of i.v. PHE. The fact that A-131701 is equipotent to terazosin and other drugs in its ability to antagonize pressor effects of i.v. PHE, but is less hypotensive, must result from more than the differences in the affinities of these antagonists for the various subtypes of alpha-1 adrenoceptors, and may result from differences in the anatomical localization of these subtypes within the vasculature. For example, vascular alpha-1 adrenoceptors may be both synaptically and extrasynaptically on the smooth muscle cells, and both receptors could contribute to pressor effects elicited by administration of exogenous agonists. If synaptic alpha-1 adrenoceptors were of the alpha-1B subtype, nonselective agents like the quinazolines could block PHE-induced pressor effects primarily via antagonism of the alpha-1B sites. In contrast, if extrasynaptic alpha-1 adrenoceptors were either alpha-1A or alpha-1D subtypes, then a compound like A-131701 might block PHE-induced pressor effects primarily via antagonism of these extrasynaptic alpha-1A or alpha-1D sites. Thus compounds differing in their subtype selectivity might appear equally potent in their abilities to antagonize PHE- or epinephrine-induced pressor responses, but might differ in their abilities to lower endogenous blood pressure, which would be mediated more by the actions of neuronally released norepinephrine on synaptic alpha-1B adrenoceptors. For this reason, the ability to determine basal blood pressure responses in the conscious dog model is an important feature of this paradigm and of the pharmacology of compounds like A-131701 and highlights this parameter as being a key element to understanding the pharmacological effects of alpha-1A subtype selective agents. These findings also suggest that the selectivity indices obtained using the anesthetized dog model (e.g., Kenny et al., 1994) might be confounded by potential differential anatomical localization of alpha-1 adrenoceptor subtypes within the vasculature.

One important aspect of the use of both the conscious and anesthetized dog models of IUP and MABP, however, is the value obtained by comparing the relative potency relationships and selectivity ratios obtained across models. Because no in vivo dog model is a perfect representation of clinical BPH, the vagaries and inaccuracies inherent in any animal model could lead to over-interpretation or misinterpretation of data. In our studies of alpha-1 adrenoceptor antagonists in the anesthetized and conscious dog, the relative IUP and MAP order of potencies of both nonselective and selective antagonists are consistent, and compounds that appear selective in one model maintain that selectivity in the other. This is useful in that the pseudo-pA2 values obtained in the anesthetized model serve to quantify the relative potencies of antagonist effects on both IUP and MABP in a way that is more difficult in the conscious dog model, whereas the latter model offers the benefit of p.o. administration of drugs, the absence of confounding effects of anesthesia on the physiology of the dog or on drug absorption and distribution parameters and allows for prolonged observation of effects of compounds on IUP and MABP.

Analysis of the concentration of A-131701 in the plasma of several species after either i.v. or p.o. administration revealed important aspects regarding the pharmacokinetics of the compound. In rat, dog and monkey, the compound was absorbed rapidly via the oral route, with \( T_{\text{max}} \) values of less than 0.5 hr after dosing in the rat and dog. The compound was also reasonably bioavailable in all three species, ranging from 25% to more than 50%, depending on the dose. For our conscious dog studies of IUP and MABP, the pharmacokinetic analyses verify that rapid and adequate absorption of the compound via the oral route led to plasma concentrations that would account for the rapid antagonism of PHE-induced effects on both IUP and MABP. The observation that the plasma half-life of A-131701 was less than 1 hr in the dog, irrespective of route of administration, may contribute to the transient nature of the effects of A-131701 on either basal MABP or the blockade of PHE-induced vascular pressor responses. What is not known from the pharmacokinetic analysis is the concentration of A-131701 in the prostate gland of the dog, although the prolonged effect of A-131701 to antagonize PHE-induced IUP responses suggests that the compound occupies urethral and/or prostatic alpha-1A adrenoceptors for prolonged periods after oral administration or that the dissociation rate from prostatic or vascular alpha-1 adrenoceptors may differ for A-131701 and other compounds.

Pharmacokinetic studies in the rat revealed that A-131701 had a long half-life, such that our prior studies (Meyer et al., 1997) of the hypotensive effects of A-131701 in spontaneously hypertensive rats (in which MABP was quantified for 60 min post drug administration) probably were not influenced during this time frame by the pharmacokinetic properties of the compound. The pharmacokinetic studies in the monkey demonstrated that A-131701 exhibited similar pharmacokinetic properties in the primate as in the dog, such that our efficacy studies in the dog should have relevance to the effects of the compound in primates, including humans. The minor degree of nonlinearity observed in some of the pharmacokinetic studies probably is not sufficient to markedly influence the effects of the compound in any of our animal models. In our analysis of dose-response relationships in these models, A-131701 produced dose-dependent effects across the dosage range tested, which suggests that the levels of the drug in the effect compartment were increased with increasing dose administered.

The evaluation of A-131701 in the conscious dog model also allowed a pharmacodynamic comparative analysis of several
alpha-1 adrenoceptor antagonists. For example, determination of those doses of compound that gave equivalent blockade of the IUP effects of PHE showed that a clear distinction could be drawn between nonselective alpha-1 antagonists such as terazosin and doxazosin compared with more subtype-selective agents like tamsulosin, REC 15/2739 and A-131701. This analysis demonstrated that terazosin and doxazosin had greater effects on vascular alpha-1 adrenoceptors (based on blockade of PHE effects on MABP) than on prostatic alpha-1 sites, whereas tamsulosin, REC 15/2739 and A-131701 had substantially weaker effects on MABP effects than on IUP responses.

Additional pharmacodynamic considerations of duration of apparent antagonism of either prostatic or vascular alpha-1 adrenoceptors are of considerable interest, because clinically used agents such as terazosin and doxazosin have prolonged durations of effect based on long pharmacokinetic half-lives (Lepor, 1995; Samara et al., 1996), and tamsulosin, recently approved for treatment of BPH in the United States in a modified release capsule, has been formulated to optimize pharmacodynamic properties (Wilde and McTavish, 1996). We considered that blockade of IUP or MABP effects by ≥50% by the various alpha-1 antagonists would represent a robust pharmacological response with statistical relevance. From this perspective, A-131701 demonstrated a dose-dependent increase in the duration of IUP blockade, with little or no duration of MABP blockade. In contrast, both terazosin and doxazosin were characterized by more prolonged effects on MABP (often extending past the 24 hr of the experiment) than on IUP. Tamsulosin, although showing greater duration of effects on IUP than MABP at an intermediate dose, was essentially nonselective in terms of duration of effect on IUP vs. MABP at the highest dose tested. These results are somewhat analogous to recent findings which show that tamsulosin has less pronounced effects than terazosin on hemodynamic effects of PHE in human volunteers (Michel et al., 1997). REC 15/2739, although having a longer duration of antagonistic effect on IUP than MABP at each dose tested, did not demonstrate either a robust effect on IUP duration at any dose tested, nor did it demonstrate an increased duration in proportion to dose. This may be a reflection of the extensive metabolism of this compound to shorten its biological half-life because the compound is poorly absorbed (approximately 20% as well as terazosin) and disappears more rapidly from the blood after passing through the liver (extraction 40-fold more extensive than terazosin; Buckner and Morse, unpublished observations).

Currently available alpha-1 antagonists have shown certain common side effects in clinical use other than those directly attributable to cardiovascular phenomena. These include dizziness, somnolence and asthenia which have been observed with not only the quinazoline-type compounds (Wilde et al., 1993; Lepor et al., 1997), but also with tamsulosin (Wilde and McTavish, 1996). It is likely that some of these side effects may result from blockade of alpha-1 adrenoceptors within the CNS, although specific sites have not been identified. The fact, however, that the clinical use of the somewhat alpha-1A selective antagonist, tamsulosin, also elicits these effects (Kaplan and Kaplan, 1996; Kirby, 1997) suggests that subtype selectivity alone may prove insufficient to minimize the incidence of some side effects. Unfortunately, no experimental models currently exist that predict these CNS-mediated adverse events at the preclinical level. Therefore, one means of minimizing these adverse events would be to reduce penetration of the compound into the CNS. Studies with radiolabeled terazosin and A-131701 have shown that the brain-to-plasma ratios for A-131701 are a small fraction of the ratios of terazosin, after administration of equivalent doses, at several time points after administration (J. Ferrero, unpublished observations). These data suggest that considerably lower CNS penetration of A-131701 might be anticipated with the potential for decreased incidence of CNS-mediated adverse events in human clinical usage.

In conclusion, the studies detailed in this report demonstrate that A-131701 has a prolonged duration of action in the conscious dog model in measures of prostatic urethral smooth muscle function, with far weaker and more transient effects on cardiovascular alpha-1 adrenoceptor function. These efficacy results are consistent with parallel studies that delineate the pharmacokinetic properties of the compound. Pharmacodynamic analysis of the effects of A-131701 also show prolonged blockade of prostatic compared with vascular alpha-1 adrenoceptors. Taken as a whole, A-131701 is quite different from other alpha-1 adrenoceptor antagonists. It is selective for alpha-1A adrenoceptors compared with alpha-1B sites, unlike the quinazoline compounds, in receptor binding, functional bioassays and in vivo tests of prostastic versus cardiovascular alpha-1 adrenoceptors. A-131701 differs from the somewhat alpha-1A subtype selective agent tamsulosin, which does not demonstrate robust selectivity in functional models in vitro (Meyer et al., 1997) and also lowers basal blood pressure in conscious dogs and hypertensive rats (Hancock et al., submitted for publication), and humans (Andersson et al., 1997). A-131701 is more selective for prostatic urethral alpha-1 adrenoceptors than REC 15/2739, based on studies in both anesthetized (Hancock et al., submitted for publication) and conscious dog models (this report), and has a greater duration of effect. Overall, the results of our studies with A-131701 across several models in different species and diverse experimental paradigms present a consistent profile of a compound with preferential affinity for alpha-1A adrenoceptors in the prostatic urethra, in particular, with lesser effects on other alpha-1 sites. Such a compound should have utility in the amelioration of the symptoms of BPH (Kenny et al., 1997) and represent a useful pharmacological probe in the greater understanding of the pharmacology of alpha-1 adrenoceptors and their subtypes.

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