Assessment of α_1 -adrenoceptor antagonists in benign prostatic hyperplasia based on the receptor occupancy theory

Kaori Ito^{1,2}, Hisakazu Ohtani^{1,3} & Yasufumi Sawada^{1,3}

¹Medico-Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, Kyusyu University, Fukuoka, Japan, ²Pfizer Inc., Groton, CT, USA and ³Laboratory of Drug Informatics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

Correspondence

Kaori Ito, Pfizer Global R & D,
Eastern Point Road, Groton,
CT 06340, USA.
Tel.: +1 860 686 2884
Fax: +1 860 715 1864
E-mail: kaori.ito@pfizer.com

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Aims

To assess the mechanistic relationship between doxazosin (α_1 -receptor antagonist) and receptor occupancy and a measure of pharmacological effect ($Q_{\max}$, the maximum urinary flow rate) and to compare the mean receptor occupancy ratio at clinical doses of doxazosin, tamsulosin, terazosin and prazosin in benign prostatic hyperplasia (BPH).

Methods

A ternary complex model, which described the mechanism of α_1 -receptor antagonists, was fitted to the pharmacological effects and receptor occupancy ratio data for doxazosin (standard tablet). In addition, mean receptor occupancy was calculated for other α_1 -receptor antagonists and the optimal receptor occupancy was evaluated. The clinical pharmacological effects of the controlled release formulation of doxazosin (doxazosin GITS) were estimated based on the receptor occupancy.

Results

The mechanistic based model was able to describe the pharmacological effects of doxazosin. Regardless of the plasma concentrations or clinical dose of each drug, the results suggest that receptor occupancy is useful to assess quantitatively and compare the pharmacological effects of drugs with similar mechanisms of action. The clinical dosage for doxazosin GITS was estimated to be at least 8 mg and the stable pharmacological effect is expected based on the estimated receptor occupancy.

Conclusions

A model for $Q_{\max}$ improvement in BPH based on the receptor occupancy theory was able to describe the clinical effects of the α_1 -receptor antagonists. Receptor occupancy is a useful index for predicting the clinical effects of α_1 -receptor antagonists.

Introduction

Benign prostatic hyperplasia (BPH) is a common condition occurring as a natural consequence of ageing in men. It is characterized by both obstructive and irritative components caused by the enlarged prostate [1]. The

first symptoms of BPH are usually slow urinary flow, frequent urination and the need to return to the bathroom shortly after voiding.

Today, α_1 -adrenoceptor antagonists are first-line therapy for treatment of BPH [2, 3]. Antagonism of

Figure 1

Pharmacodynamic ternary complex model based on the receptor occupancy theory. [A], [B], [R], and [T] represent agonist, antagonist, receptor, and transducer concentration, respectively. [AR] and [BR] respectively represent agonist and antagonist concentration bound to receptor, and [ART] is agonist-receptor-transducer complex concentration. K_A , K_B , and K_{AR} represent the dissociation constants for the AR, BR, and ART respectively. $[R_0]$, $[T_0]$, and $[ART_0]$ represent the total receptor concentration, the total transducer concentration, and the concentration of ART without antagonist, respectively

α_1 -adrenoceptors distributed in the bladder neck and prostate smooth muscle relieve urinary symptoms through mediation of muscle tone. Generally, significant improvements are obtained within a few weeks to a few months [4]. More recently, agents have been developed which have more α_1 subtype selectivity to improve the specific effects on BPH symptoms, but with fewer of the side-effects such as asthenia and dizziness of earlier agents.

The α_1 -adrenoceptor antagonists interact with the α_1 -receptors and competitively inhibit physiological agonists, such as norepinephrine, at the target site. The mechanism of pharmacological action of the α_1 -adrenoceptor is mediated through activation of GTP binding protein, which is similar to the β -receptor. The agonist-receptor-GTP binding protein complex, called the ternary complex model, activates adenylcyclase to produce cyclic AMP from ATP, and exerts the pharmacological effect [5, 6] (Figure 1).

The receptor occupancy theory is the concept that the receptor occupancy ratio, describing the binding magnitude of the drug to the receptor site, is thought to be an appropriate index to evaluate the pharmacological effect, because an agonist or an antagonist interacts directly with the receptor to produce the physiological signal [7]. It has been reported that the pharmacological effect is quantitatively evaluated with several agonists and antagonists based on the receptor occupancy theory [5, 7, 8]. The results indicate that the receptor occupancy is able to estimate the pharmacological

effects among the drugs with the same mechanism of action, even if their receptor dissociation constants, clinical dosages, or pharmacokinetic properties are different.

α_1 -receptor selectivity, clinical dosage and half-life are the major differences discussed in the literature between α_1 -adrenoceptor antagonists. An attempt to quantify clinical response from the basic underlying physiological mechanism has not been attempted. Using α_1 -adrenoceptor antagonists, this paper evaluates the quantitative pharmacological effects of the α_1 -receptor antagonists on $Q_{\max}$, a measure of the maximum urinary flow rate used clinically.

In order to relate the clinical effect to the basic underlying receptor occupancy, a newly developed adaptation of the ternary complex model utilizing receptor occupancy was used. The ternary complex model describes the mechanism of action of α_1 -receptor antagonists. In this analysis, the ternary complex model was fitted to the receptor occupancy and the pharmacological effects of doxazosin. The plasma concentration and the pharmacological effects were also evaluated with a standard $E_{\max}$ model. The 24-h time course of receptor occupancy was simulated for the doxazosin controlled release formulation from its pharmacokinetic data, and the efficacious clinical dosage was estimated based on the receptor occupancy theory. Mean receptor occupancy with other drugs (prazosin, terazosin, tamsulosin) was calculated at clinically recommended doses that produce 15–30%

increase in $Q_{\max}$ from the baseline as a clinical criterion, and the optimal receptor occupancy of the α_1 -antagonists in treatment of BPH was assessed.

Methods

A literature search of the preclinical (*in vitro*) and clinical data for α_1 -antagonists used for the treatment of BPH was conducted. There was no clinical study other than of doxazosin (standard tablets) that evaluated both pharmacokinetics and pharmacodynamics ($Q_{\max}$) in the same patients and the individual data were available. Therefore, two analyses were performed: the model fitting described below was applied with only doxazosin data, and then the mean receptor occupancy was calculated and compared among α_1 -antagonist drugs.

Doxazosin

Pharmacokinetics and pharmacodynamics of standard doxazosin Based on data from a 12-week trial containing 248 BPH patients randomized to treatment with either standard doxazosin (2, 4, 8 or 12 mg once daily) or placebo, the plasma concentrations of doxazosin were measured at 2–6 h postdose (peak) and approximately 24 h postdose (trough) after 12 weeks of treatment. Changes in $Q_{\max}$ compared with baseline were measured at the same time points [9, 10].

The receptor occupancy ratio (Φ) was calculated by Equation 1:

$$\Phi = \frac{[BR]}{[R_0]} = \frac{(C_f \times 1000 \div MW)}{K_I + (C_f \times 1000 \div MW)} \quad (1)$$

$$C_f = C_p \times f_u \quad (1.1)$$

where $[BR]$, $[R_0]$, C_f , C_p , f_u , MW and K_I represent antagonist concentration bound to receptor, total receptor concentration, plasma free drug concentration, plasma drug concentration, unbound fraction, molecular weight, and the pharmacodynamic parameter receptor disassociation constant, respectively. For doxazosin, f_u , MW and K_I are 0.02 [11], 451.45, and 0.23 [12], respectively.

Relationship between receptor occupancy and pharmacological effect The pharmacological effect of the α_1 -adrenoceptor antagonist (E_B) can be expressed with the ternary complex model by the following equation:

$$E_B = E_{BSL} + E_{B\max}$$

$$\times \left(1 - \frac{\alpha - [R_0] \times \frac{[BR]}{[R_0]} - \sqrt{\left(\alpha - [R_0] \times \frac{[BR]}{[R_0]} \right)^2 - \beta \left(1 - \frac{[BR]}{[R_0]} \right)}}{\alpha - \sqrt{\alpha^2 - \beta}} \right) \quad (2)$$

α and β represent:

$$\alpha = [R_0] + [T_0] + K_{AR} + K_A \times \frac{K_{AR}}{[A]} \quad (2.1)$$

$$\beta = 4[R_0] \times [T_0] \quad (2.2)$$

where E_{BSL} and $E_{B\max}$ represent baseline $Q_{\max}$ and maximal $Q_{\max}$ (change from baseline), $[T_0]$ and $[A]$ represent the total transducer concentration and agonist concentration, and K_{AR} and K_A represent the dissociation constants for the agonist–receptor–transducer complex (ART) and the agonist bound to receptor (AR), respectively. The transducer is a theoretical medium that transmits the signal from the receptor to produce the effect. The description for all parameters is found in Figure 1.

This analysis used the norepinephrine concentration (1.76 nM [13]) in healthy volunteers as a baseline agonist concentration $[A]$, and the norepinephrine disassociation constant (36 nM [14]).

For the purpose of comparison of the model, a linear slope model used in the literature [8] to describe the relationship between receptor occupancy and pharmacodynamic effect was also tested in this analysis.

Pharmacokinetic data of doxazosin GITS (gastrointestinal therapeutic system) Doxazosin has a long half-life and once-a-day treatment is recommended; however, its modified release formulation (GITS) is being developed to reduce side-effects mainly caused by high peak plasma concentrations ($C_{\max}$) of doxazosin standard tablets and to maintain effectiveness for 24 h [15].

Pharmacokinetic data used in this analysis were obtained from a Phase I study [12]. This study was two-way crossover study to evaluate the safety and pharmacokinetics of doxazosin GITS formulation compared with doxazosin standard formulation. Twelve healthy male Japanese subjects were randomized to the study

and 4 mg of doxazosin GITS and 4 mg of doxazosin standard formulation were administered once daily for 7 days (the wash-out periods were 10 days).

The GITS tablet employs a membrane-controlled, osmotically powered push–pull process to release doxazosin at an approximately steady rate as the tablet passes through the gastrointestinal tract [15]. To explore the best model to describe the plasma concentration of doxazosin after administration of doxazosin GITS, different models were evaluated: (i) a linear one-compartment model with zero order absorption to describe the formulation feature of doxazosin GITS, or (ii) a linear one-compartment model with first-order absorption was fit to the plasma concentrations of doxazosin GITS.

The one-compartment zero order, with lag time, first-order elimination is described by:

$$C_p = \frac{F \cdot D}{V \cdot k_{el} \cdot \tau} \cdot (e^{k_{el} \cdot b} - e^{k_{el} \cdot a}) \cdot e^{-k_{el} \cdot t} \quad (3)$$

where a and b are

$$a = \begin{cases} t & t < T_{lag} \\ T_{lag} & t \geq T_{lag} \end{cases} \quad (3.1)$$

$$b = \begin{cases} t & t < T_{au} \\ T_{au} & t \geq T_{au} \end{cases} \quad (3.2)$$

T_{lag} and T_{au} represent the lag time for starting drug release and the duration for drug release (time for passing through the gastrointestinal tract), respectively.

By using the obtained parameters with the pharmacokinetic model described above, the mean 24-h plasma steady-state concentration profiles were simulated. The mean receptor occupancy within 24 h of doxazosin GITS and standard tablet was also estimated.

The NONMEM software system, version V level 1.1 (GloboMax LLC, Hanover, MD, USA), the NM-TRAN subroutines version III level 1.1 and the PREDPP model library, version IV level 1.1 [16], was used in this analysis.

Other α_1 -antagonists

A literature search for pharmacokinetic data and clinical daily doses for other α_1 -antagonists revealed tamsulosin [17, 18], terazosin [19–21] and prazosin [22–24] to be the major treatments for BPH. The mean plasma concentrations and receptor occupancy for tamsulosin, terazosin and prazosin were estimated from the literature.

The mean plasma steady-state concentration was calculated as follows using the pharmacokinetic data in healthy volunteers [17–25]:

$$C_{ss,average} = \frac{AUC_{ss,\tau}}{\tau} = \frac{AUC_{0-\infty}}{\tau} \quad (4)$$

where $C_{ss,average}$, $AUC_{ss,t}$ and $AUC_{0-\infty}$ represent the average drug concentration in steady state, area under the time–concentration curve at the dosage interval (t), and area under the time–concentration curve from time zero to infinity, respectively.

The mean receptor occupancy for each drug was calculated by Equation 1. The value of the pharmacodynamic parameter receptor dissociation constant (K_I) of each drug was obtained from reported results of *in vitro* binding inhibition experiments using radioactive ligands in human prostatic membranes [26].

Results

Model fitting to the pharmacological effect of doxazosin

Figure 2 demonstrates the dose–response for Q_{max} for doxazosin observed in the Phase II efficacy study [9]. Figure 3 depicts the dose-dependent increase in doxazosin plasma concentration in PBH patients [9].

The ternary complex model and linear slope model were fitted to the pharmacological effect and receptor occupancy data of doxazosin. The parameter estimates and SE of the estimates from the models are summarized in Table 1 and Table 2. With the ternary complex model,

Figure 2

The change in Q_{max} from baseline after 12-week treatment of doxazosin [9]. Black box: Q_{max} change at peak (2 to 6 hours post-dose); White box: Q_{max} change at trough (around 24 hours post-dose). * $p < 0.05$, ** $p < 0.01$ compared to placebo

Figure 3

The peak (●) and trough (○) plasma concentration of doxazosin. [9]

Table 1

Summary of parameter estimate (ternary complex model)

Parameters	Estimate	Standard error
E_{BSL} (ml s ⁻¹)	0.963	0.375
E_{Bmax} (ml s ⁻¹)	8.86	5.93
R_0 (nM)	4260	3340
T_0 (nM)	0.01	—
K_{AR} (h ⁻¹)	5.17	10.4

Table 2

Summary of parameter estimate (linear slope model)

Parameters	Estimate	Standard error
E_{BSL} (ml s ⁻¹)	0.0953	0.467
Slope (ml s ⁻¹ %)	0.0297	0.00639

the concentration of transducer (T_0), which is a theoretical medium that transmits the signal from the receptor to produce the effect, was fixed due to the model instabilities.

The fitting curve in Figure 4 was obtained from the ternary complex model and the fitting line was obtained from the linear slope model. Open circles are individual observed data. Figure 5 shows the fitting results (the same with Figure 4) with the mean of receptor occupancy and the mean of Q_{max} for each dose (0, 2, 4, 8, 12 mg).

Figure 4

The relationship between receptor occupancy and pharmacological effect of Doxazosin in treatment with BPH

Figure 5

The relationship between receptor occupancy and pharmacological effect of Doxazosin. The plots are the mean of receptor occupancy and the mean of Q_{max} at each dose (0, 2, 4, 8, 12 mg). closed circle (●): peak, open circle (○): trough

Pharmacokinetic data of doxazosin GITS

The mean plasma concentration after multiple administration of doxazosin GITS 4 mg or doxazosin standard formulation is shown in Figure 6 [12]. After multiple administration of doxazosin GITS formulation, C_{max} on day 1 and day 7 was 10.0 and 15.3 ng ml⁻¹, C_{min} was 6.0 and 10.8 ng ml⁻¹ and AUC_{0-24} were 155 and 295 ng h⁻¹ ml⁻¹, respectively. The accumulation ratio (day 7/day 1) of C_{max} was 1.64, of C_{min} 1.91 and of AUC_{0-24} 2.02. The C_{max} of doxazosin standard formulation on day 7 was 39.7 ng ml⁻¹, which was much higher than that of the doxazosin GITS formulation (15.3 ng ml⁻¹). The T_{max} of doxazosin GITS formulation and doxazosin standard formulation was 12.2 and 3.1 h,

Figure 6

Mean plasma concentration of doxazosin GITS 4 mg (●) or doxazosin standard 4 mg (○) after 7 days repeated administration to healthy Japanese male volunteers. (Mean $\pm$ SD, $n = 12$) [12]

and $t_{1/2}$ was 18.1 and 21.4 h, respectively. The C_{min} of doxazosin GITS formulation and doxazosin standard formulation were similar (10.8 and 9.7 ng mL⁻¹). The plasma concentrations reached the steady state within 7 days' once-daily administration for both the doxazosin GITS and the doxazosin standard formulation. The peak–trough ratios of the plasma concentration (C_{max}/C_{min}) were 1.4 for the doxazosin GITS formulation and 4.2 for the doxazosin standard formulation, indicating that the doxazosin GITS formulation demonstrates well the feature of controlled release [12].

Model evaluation for doxazosin GITS

For the doxazosin standard formulation, a linear two-compartment model with first-order absorption was fitted to the plasma concentration based on the visual inspection of the profile. For the doxazosin GITS formulation, there was little or no difference in goodness-of-fit plots among a one-compartment model with zero order absorption model and first-order absorption model, or a two-compartment model (Figure 7). Therefore, a one-compartment model with zero order absorption that theoretically describes the feature of doxazosin GITS formulation was selected for further analysis.

The 24-h plasma concentration profiles at steady state with different dose strengths were simulated from the pharmacokinetic parameters obtained from the models, and the receptor occupancy (Φ) vs. time curve for doxazosin standard tablets and GITS tablets was generated to explore the potency of doxazosin GITS tablets (Figure 8). The average receptor occupancies within 24 h of different doses for doxazosin GITS and standard tablets are summarized in Table 3. The estimated

maximum/minimum receptor occupancy ratio with the doxazosin GITS tablet is close to 1, indicating that the pharmacological effect is expected to be relatively stable compared with the standard doxazosin tablet. The clinical dose of the doxazosin GITS tablet is predicted to be at least 8 mg from the receptor occupancy ratio.

Mean receptor occupancy among α_1 -antagonists at clinical dose

The mean plasma concentrations and the mean receptor occupancy were calculated when the clinically recommended doses of tamsulosin, terazosin or prazosin were administered. Although clinical dosage or K_i values were different among these α_1 -antagonists, the estimated mean receptor occupancy range was narrow (81.4–89.7%). The results support that optimal pharmacological effects will be obtained with 80–90% receptor occupancy (Table 4). These results indicate that the receptor occupancy theory will be useful to evaluate quantitatively the pharmacological effect of drugs having the same mechanism.

Discussion

Pharmacokinetic and pharmacodynamic modelling during drug development is widely recognized as a useful method to estimate efficacy and safety. However, the receptor binding of drugs, even if they have been well evaluated in an *in vitro* study, has not been integrated routinely into pharmacokinetic and pharmacodynamic modelling. The relationship between clinical effects of different α_1 -receptor antagonists and the receptor occupancy model was evaluated in this report. The result suggests that by calculating the receptor–binding ratio from the receptor affinity data and pharmacokinetic data (plasma concentration and protein binding ratio), the clinical effect of a new agent can be predicted from the clinical data of other drugs, if the drug exerts its pharmacological activity through the same receptor.

The ternary complex model is a theoretical model that describes the mechanism of action. It assumes that the pharmacological effect is closely related to the potency of receptor binding. We tried to fit this theoretical model to the doxazosin pharmacological data; however, the model was not stable (minimization was not successful) when T_0 (the concentration of transducer) was fixed to obtain the final parameter estimates (Table 1). This has several possible explanations: this model has too many parameters and some parameters may be correlated, such as T_0 and R_0 (the concentration of receptor), the parameters could not be precisely estimated with the available data, and the data themselves (Q_{max}) probably have large variability (discussed

One-compartment, zero-order absorption model **One-compartment, first order absorption model** **Figure 7**

Goodness-of-fit Plots for 1-compartment model with zero-order absorption (upper panel) and first order absorption model (lower panel) for doxazosin GITS formulation

below). The linear slope model is considered a preferred parsimonious model in terms of model stability and parameter estimates in this case. However, Figure 5 indicates that the ternary complex model fit better to the mean pharmacological data than the linear slope model, so we believe that the ternary complex model is still useful to describe the pharmacological effect of this type of drug. The parameter estimates could be improved with more data, or the model would be stable if the some of the parameters could be fixed based on the parameter estimates obtained from different drugs with the same mechanism of action. In addition, the receptor occupancy ratios from different drugs are similar at the clinical recommended dose (Table 4), which implies that the ternary complex model has the potential to be able to estimate the pharmacological effects with only preclinical (*in vitro*) and pharmacokinetic data with the same class of drug.

Although $Q_{\max}$ is recognized as a primary end-point for BPH clinical trials, the $Q_{\max}$ response is known to be

highly variable, depending on conditions. Another issue for the doxazosin study was that the data were not available for urine flow from the same individual on the same day. Individuals who voided at the time of the trough concentration could not also void at times of peak concentration (there was not enough time to develop enough urine to make the results meaningful). It is reported that, for purposes of $Q_{\max}$ evaluation in male subjects, the minimum acceptable volume voided should be 150 ml. Too many voiding tests will be invalid because of insufficient volume [27].

A temporal delay between drug concentrations in plasma and the onset of the drug effect is expected with α_1 -receptor antagonists in order for the drug to reach the site of action, the bladder. For this analysis, $Q_{\max}$ measures represent an average of subjects at steady state, who voided at peak or trough or were experiencing some kind of delay between drug administration and onset of the effect. Due to this, hysteresis was not observed in the concentration–effect relationship.

Figure 8

The α_1 adrenoceptor occupancy profile at prostate of doxazosin GITS (GITS) or doxazosin standard (STD) formulation (simulation). The shaded intervals (80–90%) indicate the optimal receptor occupancy ratio. GITS 12 mg (.....); GITS 8 mg (—); GITS 4 mg (---); STD 4 mg (—); STD 2 mg (.....)

Table 3

Twenty-four hour average receptor occupancy (%) estimates with different doses for doxazosin gastrointestinal therapeutic system (GITS) and standard tablets

Doxazosin dose (mg)	Mean (%)	(Max, Min)	Max/Min ratio
Std 2 mg	63.4	(77.9, 48.3)	1.61
Std 4 mg	77.2	(87.6, 65.2)	1.34
Std 8 mg	86.9	(93.4, 78.9)	1.18
GITS 2 mg	53.3	(57.1, 46.7)	1.22
GITS 4 mg	69.5	(72.7, 63.7)	1.14
GITS 8 mg	82.0	(84.2, 77.8)	1.08
GITS 12 mg	87.2	(88.9, 84.0)	1.06

Doxazosin GITS is a newly developed formulation designed to minimize the peak–trough ratio of the plasma concentration ($C_{\max}/C_{\min}$) compared with those of the doxazosin standard formulation to maintain effectiveness for 24 h. It is also suggested that 24-h stable pharmacological effects could be maintained with GITS from the receptor occupancy ratio vs. time curve. The clinical doses for the doxazosin GITS tablet were estimated to be 8 mg based on the optimal relative receptor

occupancy ratio (80–90%) obtained from this analysis. The clinically recommended dose of doxazosin GITS is 4–8 mg, slightly below the estimated clinical dose from the receptor occupancy model. It is assumed that the $Q_{\max}$ response is very variable and also affected by baseline $Q_{\max}$. As one example, the $Q_{\max}$ improvement ratio after 3-months' administration of 4 mg and 8 mg of doxazosin GITS tablets was small, and a significant improvement was observed only with the dose of 8 mg when their baseline $Q_{\max}$ was 15–16 ml s⁻¹ [28]. In another example, however, in the study whose baseline $Q_{\max}$ was around 10 ml s⁻¹, the significant $Q_{\max}$ improvement after 3 months' administration of 4 mg or 8 mg of doxazosin GITS tablets was observed [29]. Therefore, it would be important to control the baseline conditions of clinical trials to evaluate quantitatively the pharmacological effects, especially when the disease conditions are very variable, such as BPH symptoms.

α_1 -receptor antagonists tested in this analysis are highly protein bound. It is difficult to predict the effects of protein binding and its change on the pharmacological effects, because the changes of the unbound drug concentration are not simply reflected by changes in protein binding. For example, the plasma protein binding of tamsulosin is >98% and tamsulosin is also known to bind α_1 -acid glycoprotein. It has been reported, however, that unbound tamsulosin concentrations remained unchanged although total tamsulosin concentrations increased as plasma protein binding increased in patients with renal impairment [30]. If the unbound drug concentration is unchanged, then the receptor occupancy is also unchanged. Hence, the changes with receptor occupancy of tamsulosin are considered small as plasma protein binding increases. For the above reasons, further analysis was not conducted in the situation where the protein-binding ratio was changed.

In placebo-controlled clinical studies with BPH patients, a 15–30% increase in $Q_{\max}$ from baseline is considered to be a clinically significant improvement [31]. The baseline $Q_{\max}$ used in this analysis was around 10 ml s⁻¹, hence, >1.5 ml s⁻¹ change in $Q_{\max}$ is considered to be effective. From Figure 5, it can be assumed that the receptor occupancy ratio of 80–90% is preferable to exert clinically significant effects with an α_1 -antagonist. This is also supported by the fact that the mean receptor occupancy ratio estimated from different α_1 -antagonists at clinical recommended doses showed consistent values (81.4–89.7%, Table 4).

The receptor occupancy ratios in this study were calculated from several sources, such as the *in vitro* study results (K_i value using human prostate) and human pharmacokinetics data, and not from the drug concentration

Table 4

Clinically recommended dosage in treatment with benign prostatic hyperplasia and estimated receptor occupancy of α_1 -antagonists

Drug	Dosage (mg)	AUC (ng h ⁻¹ ml ⁻¹)	C _{ss} (ng ml ⁻¹)	MW	f _u	C _{ss1} (nM)	K _i (nM)	Φ (%)
Doxazosin	4 mg qd [12]	547 [25]	22.8	451.45	0.02 [11]	1.01	0.23 [13]	81.4
Tamsulosin	0.4 mg qd [17]	152 [18]	6.33	444.98	0.024 [18]	0.34	0.04 [26]	89.5
Terazosin	5 mg qd [19]	1049 [20]	43.7	387.44	0.08 [21]	9.03	1.04 [26]	89.7
Prazosin	2 mg bid [22]	119 [23]	9.94	383.27	0.05 [24]	1.30	0.26 [26]	83.3

qd, Once a day; bid, twice a day.

in the tissue of the target site. Considering these uncertainties, the optimal receptor occupancy ratio (80–90%) obtained in this analysis is regarded as a relative receptor occupancy ratio that could be used for comparisons between drugs. The direct measurement of receptor occupancy in tissues using positron emission tomography or single photon emission computed tomography [32] is expected to determine the real receptor occupancy ratio and to improve the accuracy of the estimates. However, the primary finding of this analysis is that a consistent value for receptor occupancy ratio is obtained from different α_1 -receptor antagonists, suggesting that the receptor occupancy theory is useful to compare clinically relevant doses among drugs with the same mechanism of action and estimate the response before starting clinical studies.

In conclusion, we have evaluated successfully the quantitative pharmacological effects of the α_1 -receptor antagonists on $Q_{\max}$ improvement in BPH based on the receptor occupancy theory. The results suggest that receptor occupancy theory is useful to compare the clinically relevant dose among drugs with the same mechanism of action.

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