Differential vascular α_1-adrenoceptor antagonism by tamsulosin and terazosin

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Aims In patients with lower urinary tract symptoms suggestive of benign prostatic obstruction the α_1–adrenoceptor antagonist terazosin lowers blood pressure whereas only very small if any alterations were reported with the α_1-adrenoceptor antagonist tamsulosin. Therefore, we have compared the vascular α_1-adrenoceptor antagonism of tamsulosin and terazosin directly.

Methods Ten healthy subjects were investigated in a randomized, single-blind, three-way cross-over design and received a single dose of 0.4 mg tamsulosin, 5 mg terazosin or placebo on 3 study days at least 1 week apart. Before and 1, 3, 5, 7, 10 and 23.5 h after drug intake, alterations of diastolic blood pressure and other haemodynamic parameters in response to a graded infusion of the α_1-adrenoceptor agonist phenylephrine were determined non-invasively.

Results At most time points tamsulosin inhibited phenylephrine-induced diastolic blood pressure elevations significantly less than terazosin (5 h time point: median difference in inhibition 35%, 95% CI: 18.7–50.3%). On the other hand, phenylephrine-induced changes of cardiac output, heart rate and stroke volume were similar during both active treatments.

Conclusions In doses equi-effective for treatment of lower urinary tract symptoms tamsulosin causes less inhibition of vasoconstriction than terazosin.

Keywords: tamsulosin, terazosin, α_1–adrenoceptor, vasoconstriction

Introduction

The sympathetic nervous system plays an important role in the maintenance of vascular tone and thus peripheral vascular resistance. The vasoconstricting effects of the sympathetic nervous system are mainly mediated by α-adrenoceptors. While both α_1- and α_2-adrenoceptors can mediate vasoconstriction, only α_1-adrenoceptor antagonists are used for blood pressure lowering in clinical practice [1]. We have recently demonstrated that the vasoconstriction following systemic infusion of noradrenaline in man is mediated mostly by α_1-adrenoceptors with an only small, if any, contribution of α_2-adrenoceptors [2].

In recent years α_1-adrenoceptor antagonists originally developed as anti-hypertensives (e.g. doxazosin and terazosin) are increasingly used for symptomatic treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO) [3, 4]. As expected they lower blood pressure and sometimes produce symptoms of orthostatic hypotension in patients with LUTS [5–7]. Tamsulosin, a new α_1-adrenoceptor antagonist developed primarily for LUTS treatment, lacked clinically relevant hypotensive effects in phase III placebo-controlled studies [8–10]. Even in patients with concomitant antihypertensive treatment (diuretics, β-adrenoceptor antagonists, Ca^{2+} entry blockers, angiotensin converting enzyme inhibitors) only marginal blood pressure alterations were seen [11]. It has been postulated that the lack of hypotensive effects may explain why tamsulosin, in contrast to doxazosin and terazosin, did not exhibit significantly more side effects attributable to the cardiovascular system than placebo in clinical trials although all three drugs were similarly effective in symptom relief of patients with LUTS suggestive of BPO [4]. However, no comparative haemodynamic studies of tamsulosin *vs* standard α_1-adrenoceptor antagonists have been reported in man.

In trying to understand the differential effects of tamsulosin *vs* doxazosin and terazosin, pharmacokinetic and pharmacodynamic reasons can be envisioned. Doxazosin and terazosin typically reach peak plasma concentrations within 1–2 h following oral ingestion [12–14], while tamsulosin in its commercially available modified release formulation reaches peak plasma concentrations after 5–6 h [15, 16]. Tamsulosin also differs from the others on a pharmacodynamic basis. Thus, at least three subtypes of α_1-adrenoceptors exist which have been designated α_{1A}, α_{1B} and α_{1D} [17]. Most studies have reported that tamsulosin has somewhat, i.e. 12–15 fold, greater affinity for α_{1A}- than for α_{1B}-adrenoceptors with intermediate values at α_{1D}-adrenoceptors, while doxazosin and terazosin have similar affinity for all α_1-adrenoceptor subtypes [18]. *In vitro* data with animal blood vessels have suggested that all three subtypes of α_1-adrenoceptors may participate in mediating vasoconstriction depending on the vascular bed and species under investigation [19]. Whether pharmacokinetic or pharmacodynamic factors underly the differential blood pressure effects of tamsulosin and conventional α_1-adrenoceptor antagonists in man, is unknown.

Due to the marked pharmacokinetic differences between the α_1-adrenoceptor antagonists, a reasonable analysis of their differential haemodynamic profile has to include multiple time points including the peak and trough levels of the respective drugs. Therefore, we have performed graded infusions of the α_1-adrenoceptor agonist phenylephrine in healthy volunteers before and at six time points after oral ingestion of single doses of 0.4 mg tamsulosin or 5 mg terazosin in a single-blind, three-way cross-over, placebo-controlled study.

Methods

Subjects and study protocol

The following study protocol was approved by the ethics committee of the University of Essen Medical School. Study conduct and data verification procedures complied with the principles of Good Clinical Research Practise as specified by the European Guidelines and Boehringer Ingelheim standard operating procedures. Twelve male subjects (median age: 27 years, range: 22–36 years) judged to be healthy on the basis of medical history, physical examination, electrocardiogram and routine laboratory screening, participated after having given written informed consent. Exclusion criteria included a resting heart rate <45 beats min^{-1}, and the following haemodynamic changes during a standard orthostatic test: an increase of heart rate >20 beats min^{-1}, a decrease of systolic blood pressure >20 mm Hg or a standing diastolic blood pressure <60 mm Hg. None of the subjects was on any regular medication.

The study was a partially single-blind, randomized cross-over in 12 subjects. Double blinding was not performed for safety reasons, i.e. to allow adjustment of infused agonist doses against treatment (see below). The subjects completed 3 study days during which they each received one tablet of terazosin 5 mg (purchased as Flotrin® from a German pharmacy), one capsule of tamsulosin 0.4 mg (provided by Yamanouchi Europe B.V., Leiderdorp, Netherlands), or one capsule of placebo matching tamsulosin. Study days were at least 7 days apart. According to the original protocol the first two subjects received 10 mg terazosin and 0.8 mg tamsulosin. The inhibition of phenylephrine-induced vasoconstriction by these antagonist doses was too pronounced, particularly with terazosin, to allow further analysis. Therefore, the dosing was lowered to 0.4 mg tamsulosin and 5 mg terazosin for the remaining 10 subjects. Only these 10 subjects are included in the analysis.

On each study day subjects reported to the laboratory at 07.00 h after an overnight fast. Two indwelling catheters were placed into forearm veins which were used for phenylephrine infusions (obtained as Neo Synephrine® from Sanofi Winthrop, New York, NY, USA) and blood withdrawals. The subjects remained in the supine position until after the last phenylephrine infusion on the next morning. Following a resting period to allow stabilization of baseline values, the first graded intravenous phenylephrine infusion was performed. Two hours after start of this infusion the subjects received their medication. Additional phenylephrine infusions were performed 1, 3, 5, 7, 10 and 23.5 h after drug intake; immediately prior to each infusion blood samples were taken for the determination of plasma drug concentrations and radioreceptor assays [16]. A light snack (single serving of cereal with 200 ml of skimmed milk) was given after the 7 h infusion, and a pizza or pasta dish of the subject's choice after the 10 h infusion. While drinking of water was allowed *ad libitum*, no other food intake was permitted during study days to avoid interference with the haemodynamic measurements.

Haemodynamic measurements

The duration of each phenylephrine infusion was approximately 60 min. During that time up to 5 consecutive dosages were chosen out of 7 possible incremental steps (0.25, 0.5, 1, 1.5, 2, 3 and 4 $\mu g\ kg^{-1}\ min^{-1}$) each lasting 10 min. The incremental steps started at 0.25 $\mu g\ kg^{-1}\ min^{-1}$ if the subject had taken placebo, but were allowed to start at 0.5 or 1 $\mu g\ kg^{-1}\ min^{-1}$ if the subjects had taken active medication.

Increase in diastolic blood pressure (DBP) was chosen as the primary parameter of vasoconstriction. During the phenylephrine dose-response profiles, cardiovascular

function (heart rate, blood pressure, and impedance cardiographic estimates of stroke volume) was measured. Heart rate and blood pressure were measured 5 times at 1 min intervals within the 5 min preceding the start of the infusion and every min during the last 5 min of each phenylephrine dosage step. The other cardiovascular variables were measured just before starting the infusion and at the end of each dosage step immediately following the last blood pressure measurement. We aimed for an elevation of DBP of ≈ 20 mm Hg. When that was obtained or when the 4 μg kg^{-1} min^{-1} dose limit was reached, no further dosage steps were investigated. For safety reasons, the infusions were stopped if DBP increased from baseline by more than 30 mm Hg or heart rate decreased to values < 36 beats min^{-1}.

Blood pressure (mmHg) was measured with a standard mercury sphygmomanometer with DBP taken as the disappearance of Korotkoff's sound. Total peripheral resistance (dyn s cm^{-5}) was calculated as mean arterial pressure divided by cardiac output multiplied by 80, where mean blood pressure was defined as DBP plus one third of the pulse pressure. Cardiac output was measured non-invasively by impedance cardiography using the standard approach with circular tape electrodes and graphical signal analysis [20]. Estimates of stroke volume (ml) were calculated from the maximum change in transthoracic impedance and the duration of left ventricular ejection time (measured from the carotid pulse tracing) by use of Kubicek's equation [20]. Cardiac output (1 min^{-1}) was then calculated as the product of heart rate and stroke volume divided by 1000. Heart rate was calculated from the RR-Interval of the ECG.

Data analysis

We have quantified the degree of inhibition by the antagonists in three ways: Firstly we determined 'responder rates' for each assessment time. A responder was defined as a subject in which phenylephrine infusion increased DBP by more than twice the standard deviation of basal (pre-phenylephrine) values, i.e. 7.6 mm Hg. Secondly and thirdly we determined two inhibition indices designated 'I$_{all}$' and 'I$_{act}$'. They were defined as the percentage inhibition of DBP elevation during antagonist treatment relative to the change in DBP seen in the same subject at the same time point on placebo. The calculation used the highest phenylephrine dose achieved in a given subject common to all three experimental days (I$_{all}$, almost always 1 μg kg^{-1} min^{-1}) or the highest phenylephrine dose achieved common to active treatment days as compared to the highest phenylephrine dose on placebo (I$_{act}$).

To allow for points when phenylephrine decreased rather than increased DBP (presumably due to

β-adrenoceptor agonism) all inhibition indices were transformed with the sigmoidal function

$$\% \text{ inhibition} = \frac{a}{a + \exp(c \cdot \Delta_{test})}$$

with $a = p/(100-p)$, $c = 2 \times \log(a)/\Delta_{placebo}$ and $p = 90$. This transformation guarantees that all inhibition indices lie between 0% and 100%. The parameter p was chosen such that $\Delta_{test} = 0$ (complete inhibition) corresponds to a calculated value of 90%, and $\Delta_{test} = \Delta_{placebo}$ (no inhibition) corresponds to a value of 10%. In the range between 20% and 80% inhibition transformed and untransformed indices are nearly identical.

Since DBP is a composite measure of peripheral vasoconstriction, vascular compliance and cardiac output, we have compared the haemodynamic effects of tamsulosin and terazosin in more detail using the 5 h time point as an example. At this time point phenylephrine-induced alterations of DBP, mean arterial pressure, total peripheral resistance, cardiac output, heart rate and stroke volume were compared during both active treatments using the phenylephrine dose which was also used in the I$_{act}$ calculations. The 5 h time point was chosen because it represents the t_{max} for tamsulosin but is already 4 h after the t_{max} for terazosin [16]; thus, this time point should be particularly powerful in elucidating differences between the two treatments.

All quantitative data are shown as median with upper and lower quartiles in parentheses. Comparisons between tamsulosin and terazosin treatments were done by Wilcoxon's signed rank test separately for each time point. If this indicated a statistically significant difference between treatments, the precision of comparison is presented as median difference with 95% confidence intervals. For the additional analyses at the 5 h time point, the same test was applied to compare phenylephrine effects in the presence of tamsulosin *vs* those in the presence of terazosin. A $P < 0.05$ was considered as significant. No adjustments for multiple comparisons were made. Thus, all resulting P values are to be interpreted in a descriptive manner.

Results

Infusion of phenylephrine in the absence of antagonist dose-dependently increased DBP. The median increase caused by 1 μg kg^{-1} min^{-1} phenylephrine 2 h before administration of test medication was 16.8 mm Hg; data from a representative subject 5 h after administration of test medication are shown in Figure 1. There were no major differences in phenylephrine responses at the -2 h time point between the three study days, and the elevations of DBP reached by the highest phenylephrine
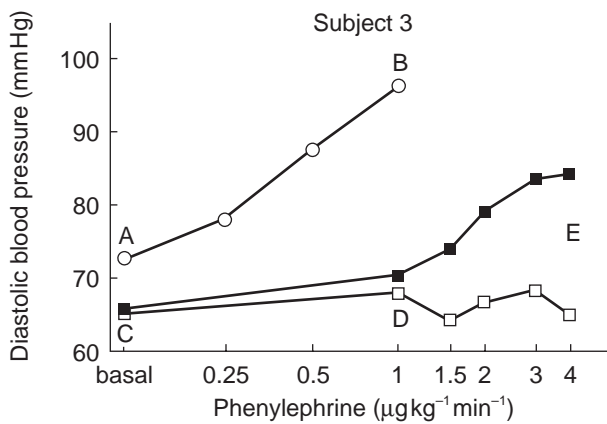
Figure 1 Diastolic blood pressure elevations induced by infusion of phenylephrine. The figure shows original data from a representative subject obtained 5 h after intake of placebo (open circles), 0.4 mg tamsulosin (filled squares) or 5 mg terazosin (open squares). The inhibition index I_{all} (Figure 3) was calculated as $[1—(D-C)/(B-A)] \times 100$, while the inhibition index I_{act} (Figure 4) was calculated as $[1—(E-C)/(B-A)] \times 100$.

dose allowed in the protocol did not undergo major diurnal changes on the placebo day (data not shown).

On the placebo day the number of responders with regard to DBP was 10 out of 10 subjects at all time points (Figure 2). On terazosin there were no responders for DBP from 1 to 3 h after administration, while on tamsulosin at least 8 subjects were responders at all time points (Figure 2). The inhibition index I_{all} for DBP peaked at 90% 1 h after terazosin intake and remained above 66% even after 23.5 h (Figure 3). In contrast the I_{all} for DBP following tamsulosin intake peaked at 82% after 5 h and declined to median values of less than 20%
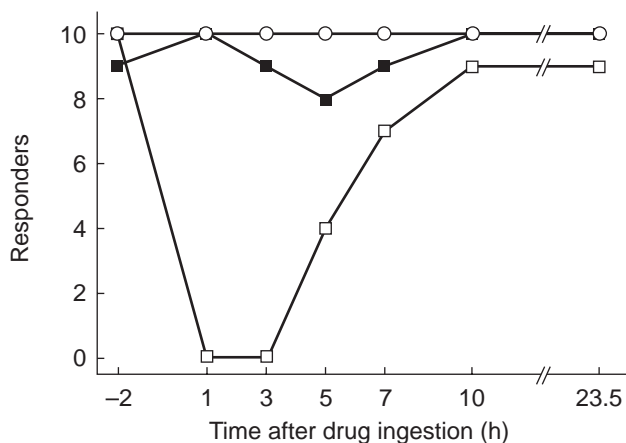

Figure 2 Number of responders with regard to diastolic blood pressure upon infusion of phenylephrine. Responders were defined as subjects with an increase of >7.6 mm Hg in diastolic pressure upon the highest agonist dose allowed in the protocol. Shown are the number of responders out of 10 subjects studied at the indicated times following intake of placebo (open circles), 0.4 mg tamsulosin (filled squares) or 5 mg terazosin (open squares).
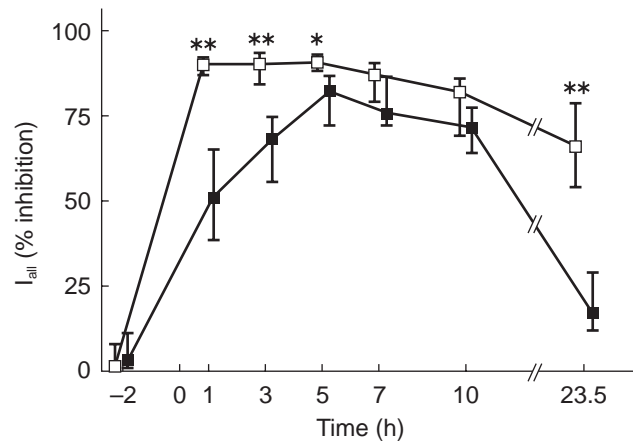

Figure 3 Inhibition of phenylephrine infusion-induced elevations of diastolic blood pressure by 0.4 mg tamsulosin (filled squares) or 5 mg terazosin (open squares). Inhibition was calculated at each time point relative to the highest phenylephrine dose which was reached on all study days including the placebo day ('I_{all}', $1 \ \mu g \ kg^{-1} \ min^{-1}$ in almost every case, for calculation see Figure 1) and is shown as medians with upper and lower quartiles. ★ and ★★: $P<0.05$ and <0.01, respectively, *vs* tamsulosin in a Wilcoxon signed rank test.

after 23.5 h (Figure 3). Thus, I_{all} was significantly different between treatments at the 1, 3, 5 and 23.5 h time points; the median difference at the 5 h time point was 6.9% (95% CI: 4.3–15.9%). The inhibition index I_{act}, which discriminates treatments more effectively (Figure 1), peaked at 93% after 1 h in terazosin-treated subjects and was 59% even after 23.5 h (Figure 4). In tamsulosin-treated subjects I_{act} peaked at 39% after 5 h and declined
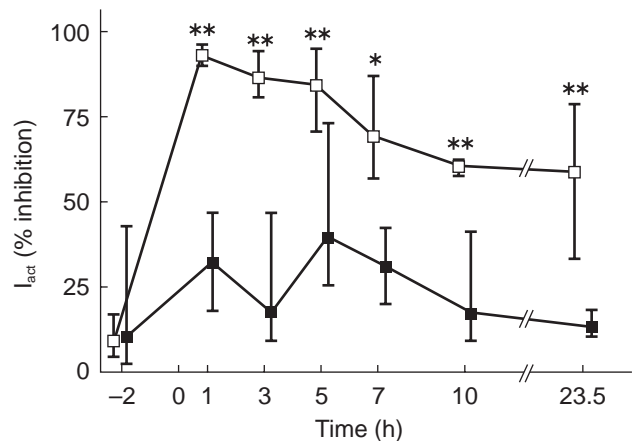

Figure 4 Inhibition of phenylephrine infusion-induced elevations of diastolic blood pressure by 0.4 mg tamsulosin (filled squares) or 5 mg terazosin (open squares). Inhibition was calculated at each time point relative to the highest phenylephrine dose which was reached on both study days during active treatment and compared with the highest phenylephrine dose on the placebo day ('I_{act}', for calculation see Figure 1) and is shown as medians with upper and lower quartiles. ★ and ★★: $P<0.05$ and <0.01, respectively, *vs* tamsulosin in a Wilcoxon signed rank test.

to 13% after 23.5 h (Figure 4). The difference between tamsulosin and terazosin with regard to I_{act} was statistically significant at all time points; the median difference at the 5 h time point was 35.0% (95% CI: 18.7–50.3%).

A more detailed haemodynamic analysis at the 5 h time point demonstrated that phenylephrine caused significantly smaller elevations of DBP, mean arterial pressure and total peripheral resistance in terazosin- than in tamsulosin treated subsjects (Figure 5); the median differences were 13.0 (95% CI: 9.2–16.0) mm Hg, 12.5 (95% CI: 7.1–14.8) mm Hg, and 295 (95% CI: 103–359) dyn s cm^{-5}, respectively. However, phenylephrine increased cardiac output and stroke volume and reduced heart rate to a similar extent in tamsulosin- and terazosin-treated subjects (Figure 6).

Discussion

Methodological considerations

The aim of the present study was to compare the haemodynamic effects of two $α_1$-adrenoceptor antagonists, tamsulosin and terazosin, which have previously been shown to differentially affect blood pressure in the treatment of patients with LUTS suggestive of BPO [6–9]. A head-to-head comparison of both antagonists faces two obstacles. Firstly, both drugs have distinct pharmacokinetic properties. To address the role of this factor, we have investigated six different time points in the first 24 h following drug intake. Secondly, vascular $α_1$-adrenoceptor antagonism is dose-dependent. Therefore, the comparison of two drugs requires that both are studied at doses which are clinically equi-effective. Our choice of antagonist doses was based on the following considerations: In dose-finding studies in patients with LUTS suggestive of BPO 0.4 mg once daily was found to be the maximum effective dose of tamsulosin [8, 10]. In similar studies with terazosin maximum effective doses of terazosin were 10 mg once daily, while 5 mg once daily had only submaximal effects [21]. Placebo-controlled studies in patients with LUTS suggestive of BPO have reported a similar overall efficacy of tamsulosin (fixed dose of 0.4 mg [8, 9]) and terazosin (fixed dose of 10 mg [22] or dose-escalation studies with 1–10 mg terazosin, in which the median final dose was 10 mg [6, 7]). Finally, a direct comparative study in patients with LUTS suggestive of BPO has reported similar efficacy for 0.2 mg day^{-1} tamsulosin and 5 mg day^{-1} terazosin [23]. Therefore, we have chosen to compare 0.4 mg tamsulosin with 5 mg terazosin in the present study. If anything this dosage choice would be expected to cause a bias to detect less vascular inhibition by terazosin relative to tamsulosin. The bias was introduced on purpose to enhance the power of our
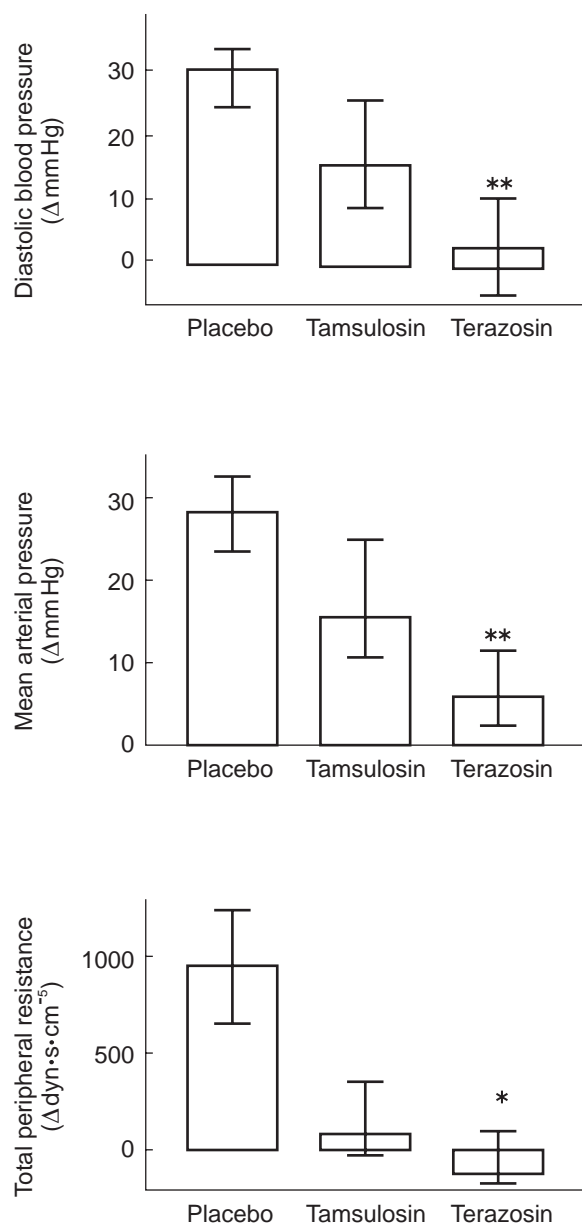

Figure 5 Effects of 0.4 mg tamsulosin and 5 mg terazosin on phenylephrine-induced alterations of diastolic blood pressure (upper panel), mean arterial pressure (middle panel) and total peripheral resistance (lower panel) as determined 5 h following medication. Data are based on the highest phenylephrine dose achieved during both active treatments ('I_{act}', for calculation see Figure 1) and are shown as medians with upper and lower quartiles. ★ and ★★: $P < 0.05$ and < 0.01 *vs* tamsulosin in a Wilcoxon signed rank test. Phenylephrine effects during placebo treatment are shown for comparison; they were not compared statistically to the data obtained during active treatment since they were determined at a different phenylephrine dose.

study in light of the previous reports on lack of blood pressure lowering with tamsulosin [9, 23, 24].

The classical method for analysis of receptor antagonism *in vivo* is the administration of increasing doses of agonist with measurement of shifts in the dose-response curve in
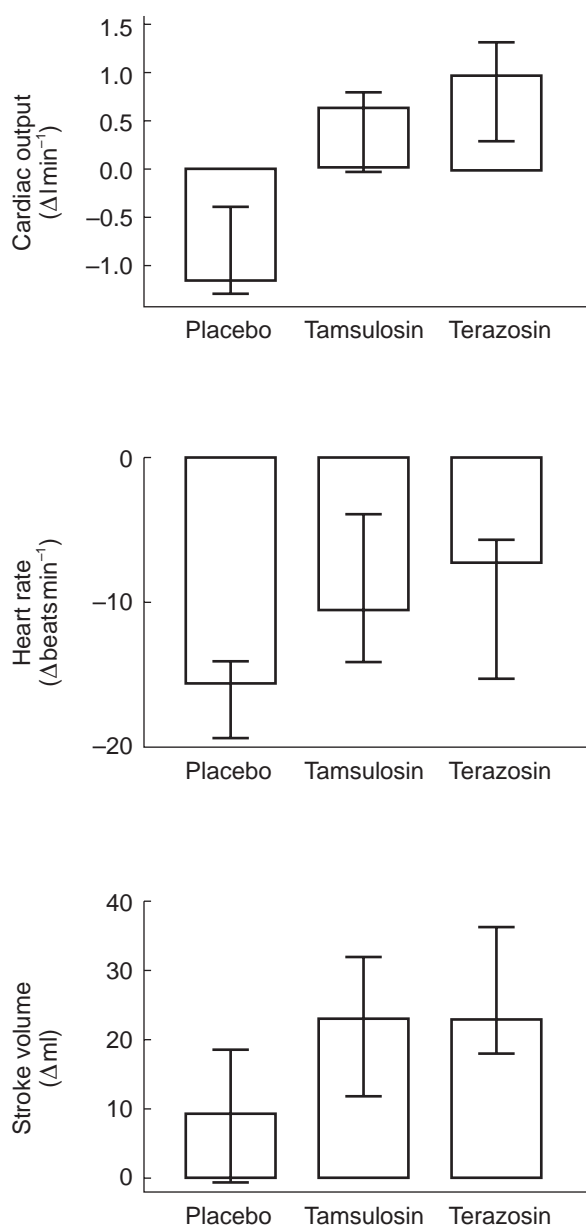
Figure 6 Effects of 0.4 mg tamsulosin and 5 mg terazosin on phenylephrine-induced alterations of cardiac output (upper panel), heart rate (middle panel) and stroke volume (lower panel) as determined 5 h following medication. Data are based on the highest phenylephrine dose achieved during both active treatments ('I_{act}', for calculation see Figure 1) and are shown as medians with upper and lower quartiles. Effects of tamsulosin and terazosin were not significantly different in a Wilcoxon signed rank test. Phenylephrine effects during placebo treatment are shown for comparison; they were not compared statistically to the data obtained during active treatment since they were determined at a different phenylephrine dose.

the presence of antagonist. For studies of α_1-adrenoceptor antagonists this usually involves the agonist phenylephrine with measurements of DBP elevations as an indicator of arterial vasoconstriction [25–28]. When standard therapeutic doses of tamsulosin (0.4 mg) and terazosin (5 mg)

were given to fasting, healthy subjects, the extent of inhibition of DBP responses at several time points was so pronounced, especially for terazosin, that shifts of the phenylephrine dose-response curve could not formally be calculated. Higher phenylephrine doses might theoretically have overcome the inhibition, but were not tested due to cardiac stimulation by those doses of phenylephrine, presumably via β-adrenoceptor-stimulating properties of the agonist. Therefore, we have assessed the extent of antagonism by tamsulosin and terazosin by three other means. Firstly, we have determined responder rates, which are robust but only semiquantitative parameters. Second, we have calculated an inhibition index designated I_{all}; while this accurately reflects the degree of inhibition by both antagonists, it may underestimate a possible difference between them (Figure 1). Third, we have calculated an inhibition index designated I_{act}; while this may underestimate the degree of inhibition it is more sensitive in the detection of differences between the antagonists. While this approach may be less powerful than classical dose-response curve shifts, we feel that the combination of all three forms of quantification of antagonism yields a reliable means to compare the haemodynamic properties of tamsulosin and terazosin.

Haemodynamic analysis

In the present study tamsulosin caused significantly less inhibition of vasoconstriction than terazosin at most time points, regardless of how inhibition was assessed. The extent of differentiation between the two antagonists was largest for responder rates and smallest for I_{all}; while these differences reflect the specific advantages and disadvantages of the three inhibition indices, it cannot be decided from the present data which reflects the clinical situation with endogenous agonist more closely. Despite the quantitative differences between the inhibition indices, all three consistently differentiated between tamsulosin and terazosin. This is remarkable since we have compared a dose of terazosin which is submaximally effective in patients with LUTS against a dose of tamsulosin which is maximally effective in such patients, i.e. our study was biased to detect less inhibition by terazosin (see above). Moreover, this differential inhibition was evident even at the 5 h time point, i.e. when tamsulosin blood concentrations peaked while terazosin blood concentrations had already declined for 4 h [13–16]. A more detailed haemodynamic analysis at the 5 h time point demonstrated that three parameters of vasoconstriction, i.e. phenylephrine-induced elevations of DBP, mean arterial pressure and total peripheral resistance, were significantly smaller in terazosin- than in tamsulosin-treated subjects. On the other hand, phenylephrine-induced changes of parameters of cardiac function, i.e. cardiac output, heart rate and

stroke volume, were similar during both treatments. Thus, the differential effects of tamsulosin and terazosin on DBP are due to quantitatively different antagonism at the vascular level. These observations are consistent with the results from placebo-controlled clinical studies with tamsulosin in patients with LUTS suggestive of BPO, in which no clinically relevant blood pressure reductions were observed [8, 9]. Moreover, in a direct comparison 0.2 mg day^{-1} tamsulosin did not alter blood pressure while 5 mg day^{-1} terazosin significantly lowered it, despite the fact that both drugs caused similar improvements of LUTS [23].

A differentiation was also found for inhibition of finger tip arterial and dorsal hand vein vasoconstriction in a comparison of tamsulosin with another non-subtype-selective α₁-adrenoceptor antagonist, doxazosin, although only a single time point was investigated in that study [29]. Another study by the same group of investigators has also reported a differential inhibition of finger tip vasoconstriction by the non-selective prazosin *vs* the sligthly α₁ₐ-selective urapidil over a full time course [30]. Thus, our data demonstrate unequivocally that in LUTS-equivalent doses tamsulosin causes less inhibition of vasoconstriction than terazosin. The comparison with published data on doxazosin, prazosin and urapidil indicated that this might relate to its relative selectivity for the α₁ₐ-adrenoceptor subtype. To test this hypothesis directly, we have determined *ex vivo* occupancy of human α₁ₐ-, α₁ᵦ-and α₁ᵈ-adrenoceptors using a radioreceptor assay at all time points [16]. However, we were unable to define the α₁-adrenoceptor subtype predominantly mediating phenylephrine-induced DBP elevations with this approach (data not shown). Therefore, identification of the α₁-adrenoceptor subtype mediating vasoconstriction in man will require future studies with alternative approaches, e.g. the use of antagonists with greater subtype selectivity.

In vitro studies on a human conductance vessel, the isolated iliac artery, have implicated α₁ᵦ-adrenoceptors in vasoconstriction [31], but results with human resistance arteries have not been communicated to our knowledge. Most studies on rat mesenteric or renal resistance vessels have found a predominant involvement of α₁ₐ-adrenoceptors [32–35]. Studies in other blood vessels of experimental animals demonstrate that all three α₁-adrenoceptor subtypes can mediate vasoconstriction depending on the vascular bed and species under investigation [19]. Thus, human vasoconstriction may also involve a mixture of α₁-adrenoceptor subtypes.

In conclusion, we have shown that the α₁-adrenoceptor antagonists, tamsulosin and terazosin, when given in similarly effective doses with regard to the treatment of LUTS suggestive of BPO, differ markedly in their haemodynamic effects. Thus, tamsulosin caused some

inhibition of vasoconstriction under our experimental conditions which involved young healthy volunteers, fasting drug intake, and administration of exogenous agonist. However, tamsulosin produced considerably less inhibition of α₁-adrenoceptor-mediated vasoconstriction than terazosin at most time points irrespective of the distinct pharmacokinetic profile of both drugs. Whether this differential haemodynamic profile is due to the modest selectivity of tamsulosin for α₁ₐ-adrenoceptors, remains to be studied.

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