

Comparison of Vascular α_1 -Adrenoceptor Antagonism of Tamsulosin in Oral Controlled Absorption System (OCAS) and Modified Release (MR) Formulations

Martin C. Michel^{a,*}, Cees Korstanje^b, Walter Krauwinkel^b, Michael Shear^b, Jonathan Davies^c, Adrian Quartel^c

^aDepartment of Pharmacology and Pharmacotherapy, University of Amsterdam, AMC, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands

^bYamanouchi Europe, Leiderdorp, The Netherlands

^cYamanouchi Europe, Egham, UK

Abstract

Objective: The cardiovascular α_1 -adrenoceptor (AR) antagonism of the new oral controlled absorption system (OCAS) 0.4 mg tablet formulation of tamsulosin was compared with that of the modified release (MR) 0.4 mg capsule formulation in healthy male volunteers after a single dose in the fasted state.

Methods: Eighteen healthy volunteers were to be randomised in a 3-way, cross-over study consisting of three one day study periods. On each study day one of the following treatments was tested: placebo, tamsulosin OCAS 0.4 mg tablet or tamsulosin MR 0.4 mg capsule. The cardiovascular α_1 -AR antagonism was assessed by measuring the inhibition of phenylephrine (PE)-induced increases in diastolic blood pressure (DBP) and total peripheral resistance (TPR) 2 hours before and 2, 4, 6, 8 and 10 hours after dosing with the test drug. Additionally, the pharmacokinetics (PK) and adverse events (AEs) were assessed.

Results: Eighteen healthy volunteers (mean age 29.9 years) were enrolled. Two of the 18 subjects discontinued the study; one because of an AE and one was lost to follow up. Tamsulosin OCAS 0.4 mg tablets showed a lower maximum plasma concentration (mean C_{\max} : 6.4 vs. 18.6 ng/ml) but a similar time to C_{\max} (approximately 6 hours) relative to tamsulosin MR 0.4 mg capsules. This was accompanied by less inhibition of PE-induced increases in DBP and TPR for tamsulosin OCAS 0.4 mg tablets than for tamsulosin MR 0.4 mg capsules at all post-dose time points; these differences were statistically significant ($p \leq 0.05$) at all but the 2 hour post-dose time point for TPR. There were no apparent differences in AEs between the two formulations.

Conclusions: Tamsulosin OCAS 0.4 mg tablets show less cardiovascular α_1 -AR antagonism, i.e. less inhibition of vasoconstriction and total peripheral resistance, than tamsulosin MR 0.4 mg capsules following single dosing in fasting healthy volunteers. This is most likely related to reduced drug exposure by the OCAS formulation. The data indicate that on an empty stomach tamsulosin OCAS may provide a better cardiovascular safety profile than tamsulosin MR.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Tamsulosin; Controlled release formulation; Modified release capsule; Oral controlled absorption system; Receptors adrenergic α_1 ; Vasoconstriction

1. Introduction

α_1 -adrenoceptor (AR) antagonists are currently the first line treatment for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

(LUTS/BPH) [1]. α_1 -AR antagonists block α_1 -ARs in the prostate, bladder neck and urethra and as such relax smooth muscles in these tissues and reduce the dynamic component of obstruction. Due to the presence of α_1 -ARs in the blood vessels, α_1 -AR antagonists also relax vascular smooth muscle which induces vasodilatation and reduces blood pressure. This can induce typical adverse events (AEs) such as dizziness,

* Corresponding author. Tel. +31 20 5666762; Fax: +31 20 6965976.
E-mail address: m.c.michel@amc.uva.nl (M.C. Michel).

symptomatic orthostatic hypotension and even syncope. Many LUTS/BPH patients are elderly subjects with an impaired cardiovascular regulation. They are particularly at risk for cardiovascular AEs, which are not only unpleasant, but can also lead to serious morbidity such as falls and fractures potentially resulting in hospitalisation, nursing home placement and/or death [2,3]. The risk can be further increased when they suffer from concomitant cardiovascular disease(s) and/or take cardiovascular concomitant medication(s). Conditions such as exercising (e.g. gardening or playing sports), a heavy meal, heat stress (e.g. hot climates/bathing) [4], dehydration or diarrhoea can also further “stress” the impaired homeostatic reserves in the elderly and increase the risk of cardiovascular AEs [2]. To reduce this risk, α_1 -AR antagonists used in the treatment of LUTS/BPH should minimally affect the cardiovascular system. Of all α_1 -AR antagonists currently available (alfuzosin, doxazosin, terazosin and tamsulosin), tamsulosin modified release (MR) 0.4 mg has the lowest potential of interfering with blood pressure control and inducing cardiovascular AEs [5–8]. Tamsulosin MR 0.4 mg is recommended to be taken after the first meal of the day, as it has been demonstrated that tamsulosin has a 30–35% higher exposure in the fasted state than in the fed state [9]. Administration of tamsulosin on an empty stomach increases the incidence of orthostatic events following postural changes [10,11] which may subsequently increase the risk of syncope and recurrent falls in the elderly [2,12].

A new formulation of tamsulosin using the proprietary oral controlled absorption system (OCAS[®]) has recently been developed. Tamsulosin OCAS 0.4 mg tablets have a different pharmacokinetic (PK) profile with a lower maximum plasma concentration (C_{\max}) and a more prolonged release than tamsulosin MR 0.4 mg [13]. It has been shown that the PK profile of tamsulosin OCAS 0.4 mg is not influenced by food [13]. Because of the improved PK profile, it is expected that tamsulosin OCAS will display a higher cardiovascular safety compared to the MR formulation, in particular when administered on an empty stomach. This hypothesis was tested in the present study, in which the cardiovascular safety of tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg was evaluated by comparing their ability to inhibit the increases in diastolic blood pressure (DBP) and total peripheral resistance (TPR) following graded infusions of phenylephrine (PE) in healthy volunteers. This design was previously used by Schäfers et al. [7]. PE is an α_1 -AR agonist that mimics the endogenous agonist noradrenaline. Administration of PE regulates haemodynamics

following e.g. a postural change or when exercising by inducing peripheral vasoconstriction which increases DBP and TPR. By blockade of vascular α_1 -ARs, α_1 -AR antagonists have the potential to inhibit the PE-induced elevation in DBP and TPR, which may cause vulnerability to orthostasis when exercising or after e.g. a postural change. The degree of inhibition of the PE-induced increase in DBP and TPR is a measure of the cardiovascular α_1 -AR antagonism of a drug. The more the PE-induced increase in DBP and TPR is inhibited, i.e. the higher the dose of PE required to increase the DBP or TPR to a certain extent or the more the PE dose response curve is shifted to the right, the more the α_1 -AR antagonist blocks α_1 -ARs in the vascular system [14]. This method is a scientifically acceptable way to establish the potential of α_1 -AR antagonists to interfere with this haemodynamic adaptation mechanism. It is expected that tamsulosin OCAS 0.4 mg will have less cardiovascular effects, i.e. will inhibit the PE-induced increase in DBP and TPR to a lesser extent, than tamsulosin MR 0.4 mg because of the difference in PK.

2. Materials and methods

2.1. Ethics

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol was reviewed by an independent ethics committee. Subjects gave written informed consent.

2.2. Study population (inclusion/exclusion criteria)

A total of 18 healthy male volunteers (aged 18–45 years) with a body mass index of 18–30 kg/m² were to be randomised into the study. Their cardiovascular system had to be within normal limits based on medical history, physical examination and 12-lead electrocardiogram (ECG). The resting blood pressure at screening should lie between 110/60 mm Hg and 140/85 mm Hg. Subjects with a history or evidence of allergy to an α -AR antagonist and/or combined α/β -AR antagonist, first-dose hypotension following initiation of an α -AR antagonist or other antihypertensive or symptomatic vagotonia, with a resting heart rate below 45 beats per minute (bpm) or with a positive orthostatic test at screening were excluded as well as subjects with a cardiovascular disorder, malignancy, renal or hepatic insufficiency, bladder/ureter/kidney stone disease or a history of gastro-intestinal dysfunction. Subjects had to stop treatment with an α -AR antagonist, α -AR agonist, drugs with anticholinergic activity (including antihistamines), antispasmodics and parasympathomimetics and cholinomimetics at least 2 weeks prior to study start.

2.3. Study design

A 3-way, cross-over, single-dose study in healthy young volunteers was done to assess the effect of placebo, tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 mg capsules on the cardiovascular responses to graded PE infusions under fasting conditions. Eighteen subjects were each to be randomised to one of six

possible treatment sequences. The study was single-blind with respect to treatment with placebo or active medication to allow the investigator to select the appropriate PE starting dosage level. The study was double-blind, double dummy with respect to the active medication. The study was executed in a single centre (Aster-Céphac, Paris, France)

2.4. Endpoints

Based upon a previous study [7], the primary endpoint was the inhibition index (*I*) calculated at 2, 4, 6, 8, and 10 hours post-dose based on the changes from pre-infusion in DBP. A logical definition for *I* is:

$$I = \frac{\Delta\text{DBP}_{\text{placebo}} - \Delta\text{DBP}_{\text{active}}}{\Delta\text{DBP}_{\text{placebo}}} \times 100\%$$

where $\Delta\text{DBP}_{\text{placebo}}$ represents the change from pre-infusion DBP on placebo, and $\Delta\text{DBP}_{\text{active}}$ represents the change from pre-infusion DBP on the active treatment.

To allow for situations where the inhibition index would generate insensible results (for example, a DBP decrease on the active treatment rather than an increase following PE infusion would generate an index above 100%, while an increase in DBP after active medication that was greater than the corresponding increase on placebo would generate a negative index), the following sigmoid transformation was applied to constrain the inhibition index values between 0 and 100% [7]:

$$I = \frac{a}{a + \exp(c \cdot \Delta\text{DBP}_{\text{active}})} \times 100\%,$$

where $a = p/(1 - p)$, $c = 2 \times \log(a)/\Delta\text{DBP}_{\text{placebo}}$, $p = 0.9$.

Since the PE concentrations used for the active and placebo treatments were likely to be different, the inhibition index calculation was performed by using the DBP values collected at the highest PE dose common to all three treatments: I_{maxall} . Since for safety reasons the maximum increase in DBP to be achieved was set at 30 mmHg, the PE dose on placebo was expected to be the lowest dose used. It was anticipated that differences between the two active treatments would be larger at higher doses of PE, therefore *I* was calculated as well from the DBP values at the highest PE dose common to the active treatments (tamsulosin OCAS and tamsulosin MR) relative to the highest PE dose on placebo: I_{maxact} . As shown previously [7], I_{maxall} realistically reveals effects of the α_1 -AR antagonists relative to placebo but underestimates differences between the α_1 -AR antagonists, whereas I_{maxact} has greater power to reveal differences between α_1 -AR antagonists but underestimates their absolute effects.

As a secondary analysis, both I_{maxall} and I_{maxact} were calculated for the change from pre-infusion in TPR rather than DBP. The TPR estimates were derived from impedance cardiographic measurements [7].

2.5. Treatments

Tamsulosin MR 0.4 mg capsules, tamsulosin OCAS 0.4 mg tablets and matching placebo for both tamsulosin formulations were manufactured by Yamanouchi Europe. PE solutions of 0.2 mg/kg in 50 ml 0.9% saline were prepared for each individual subject at the pharmacy of the investigational site.

2.6. Study procedures

Subjects were screened at the investigational site one week before the study and if eligible randomised to one of six

possible treatment sequences. The study consisted of three treatment days each separated by a wash-out period of at least one week. Subjects were admitted to the unit the day before dosing and were given a light meal consisting of pasta with cheese and tomato sauce at 22:00 hours. Subjects were dosed in the morning on an empty stomach; the medication was taken with 200 ml of water. Nine hours post-dosing, a light meal was supplied consisting of pasta with cheese and tomato sauce. No fluid intake was allowed between 2 hours prior to dosing until 3 hours post-dosing when a glucose-containing sport drink (Powerade®) was provided. After that time decaffeinated fluids were allowed.

2.7. Phenylephrine challenge procedure

The cardiovascular response to stepwise increasing doses of intravenous PE infusion was assessed at 2 hours pre-dose and at 2, 4, 6, 8 and 10 hours following the administration of the treatment. The duration of each dose-response infusion was approximately 1 hour. There were seven possible dosage steps with infusion rates of 250, 500, 1000, 1500, 2000, 3000 and 4000 ng/kg/min possible and each infusion rate was given for 10 minutes. The choice of the five incremental dosage steps to use was at the discretion of the investigator who was aware whether a subject was given placebo or active medication but blinded regarding which active medication was administered. The following non-invasive assessments of cardiovascular function were done at each time point following each infusion step of PE: heart rate (HR) (measured once), systolic and diastolic blood pressure (SBP/DBP) (measured 5 times during the last 5 minutes of the infusion with a 1 minute interval between each measurement), and TPR (same measurement schedule as for DBP and SBP). The average of the five DBP and TPR measurements collected for each subject and treatment at each time point and PE concentration was used for the analysis. Systolic time intervals and impedance cardiographic estimates of stroke volume and cardiac output were also collected during each PE infusion. Blood pressure was measured by an automatic device (Nippon collin). The impedance cardiographic measurements were performed by a cardioscreen® 1000 by Medis device (Medizinische Messtechnik GmbH, Ilmenau, Germany) using niccom® software. Stroke volume, cardiac output and TPR were calculated as described in [7].

2.8. Pharmacokinetics

Blood sampling to measure plasma tamsulosin concentrations was done 2 hours pre-dose and at 2, 4, 6, 8 and 10 hours post-dosing. At pre-dose, the sample was taken immediately prior to the PE profile; at each post-dosing time point, blood samples were taken both immediately before and after the PE profiles.

Blood samples were collected into standard polyethylene tubes with lithium-heparin. They were kept on ice for up to 30 minutes following collection until centrifuging at 2500 g for 10 minutes at 4 °C. Plasma was harvested and stored at –70 °C until being measured. The bioanalytical method for the quantification of tamsulosin HCl in human plasma was based on high performance liquid chromatography-mass spectrometry (HPLC-MS). After addition of AB-289 (internal standard) to 200 µl of plasma, tamsulosin and the internal standard were extracted from plasma using liquid-liquid extraction (ethylacetate:cyclo-hexane (3:1 %v/v)) under alkaline conditions. The organic phase was removed and evaporated at 50 °C and the residue re-dissolved in 100 µl of 20 mM ammonium acetate:acetonitrile (9:1 %v/v). A volume of 25 µl was injected into an LC-MS/MS system to separate tamsulosin and the internal standard from matrix

constituents using Waters Symmetry[®] C18 material with a mean size of 3.5 μm in a stainless steel column of 100 mm \times 2.1 mm. Detection was performed using a triple stage quadrupole mass spectrometer (Thermo Finnigan Surveyor and Thermo Finnigan TSQ 7000). Tamsulosin parent/daughter ions were detected with an $M/z = 409.2/228.0$; the internal standard AB-289 parent/daughter ions at $M/z = 423.2/285.1$. This method is suitable for the quantification of tamsulosin (as tamsulosin HCl) in human plasma at concentrations ranging between 0.10 and 50 ng/ml. C_{max} and time to C_{max} (t_{max}) were calculated using WinNonlin software (version 4.1, Pharsight Corp., Mountain View, CA, USA) using non-compartmental analysis.

2.9. Assessments of safety/tolerability

A 12-lead ECG and laboratory evaluations (biochemistry, haematology and urinalysis) were done at screening and at the post study visit at 1–2 weeks after the last study medication day. Vital signs were measured at each visit both in the supine and standing position using an automated device.

All observed or spontaneously reported AEs were recorded and assessed for severity and causality. They were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system.

2.10. Statistical methods and sample size

The sample size of the present study was based on a previous study done by Schäfers et al. [7]. The expected inhibition index I_{maxall} for subjects treated with tamsulosin OCAS 0.4 mg was 68% and for subjects treated with tamsulosin MR 0.4 mg was 90%. Assuming a standard deviation (SD) of 16%, a sample size of 13 would have a power of 90% to detect a difference of 22% in the inhibition index between the two active treatments using a 2-group t -test with a 0.05 two-sided significance level. As a multiple of 6 subjects was necessary given the six possible treatment sequences, the sample size was increased to 18.

The difference in the inhibition index (I_{maxall} and I_{maxact}) between treatments, at each post-dose time point, was subjected to an Analysis of Covariance (ANCOVA), including treatment and period as fixed factors, subject as a random factor, and the baseline inhibition index as a covariate.

3. Results

3.1. Number of subjects

Eighteen healthy male volunteers (15 Caucasian, 2 Black and one West Indian) who met the inclusion and exclusion criteria were randomised. They had the following demographic characteristics: mean age 29.9 years (range 24–44 years), mean weight 73.0 kg (range 64–87 kg), mean height 1.77 m (range 1.65–1.90 m), and mean body mass index 23.4 kg/m² (range 20.2–26.6 kg/m²). Two subjects discontinued the study: one due to an AE (atrial fibrillation while receiving placebo) and the other was lost to follow-up (after having had tamsulosin OCAS 0.4 mg). Consequently data were available for 17 subjects on placebo, 18 on tamsulosin OCAS 0.4 mg and 16 on tamsulosin MR 0.4 mg.

3.2. Phenylephrine challenge results

The PE infusion rates used for subjects treated with placebo were between 250 and 3000 ng/kg/min. The infusion of increasing dose rates of PE during placebo treatment caused dose-dependent increases in DBP compared to pre-infusion with a mean increase in DBP between 19.4 and 23.7 mmHg at 2000 ng/kg/min. The data for the mean increase in DBP after the highest PE dose at the 2 hours before dosing time point were similar for each of the three treatments (placebo, tamsulosin OCAS and tamsulosin MR). The PE infusion rates after dosing with active treatment of either tamsulosin OCAS or tamsulosin MR were between 500 and 4000 ng/kg/min. As an example of the type of data generated, Fig. 1 shows the mean effect of the different PE doses on the DBP at 4 and 6 hours post-dosing, which represent the time points around the t_{max} for tamsulosin OCAS and MR. In general, higher PE doses induced larger increases in DBP following placebo than after treatment with either formulation of tamsulosin 0.4 mg. Both tamsulosin OCAS and tamsulosin MR induced a shift in the curve for the increase in DBP to higher PE doses indicating that higher PE doses were needed to achieve a similar increase in DBP to that of placebo. The shift for tamsulosin MR was larger than that for the OCAS formulation. Comparable findings were seen at 2, 8 and 10 hours post-dosing (data not shown).

Using the DBP data collected at each time point, the inhibition indices I_{maxall} and I_{maxact} were calculated and the mean change from baseline for these indices is presented in Fig. 2(A) (I_{maxall}) and 2(B) (I_{maxact}). The least square (LS) mean change from baseline for I_{maxall} was between 19% and 26% lower for the OCAS formulation compared with the MR formulation at all time points after dosing and each difference was statistically significant ($p \leq 0.0268$). Similar results were observed for I_{maxact} .

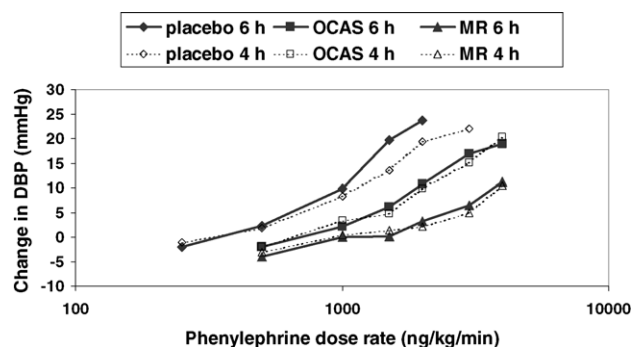


Fig. 1. Change from pre-infusion in DBP following infusion of PE at 4 and 6 hours after the dosing of test drug. For each subject, the DBP was calculated as the average of all measurements during that infusion.

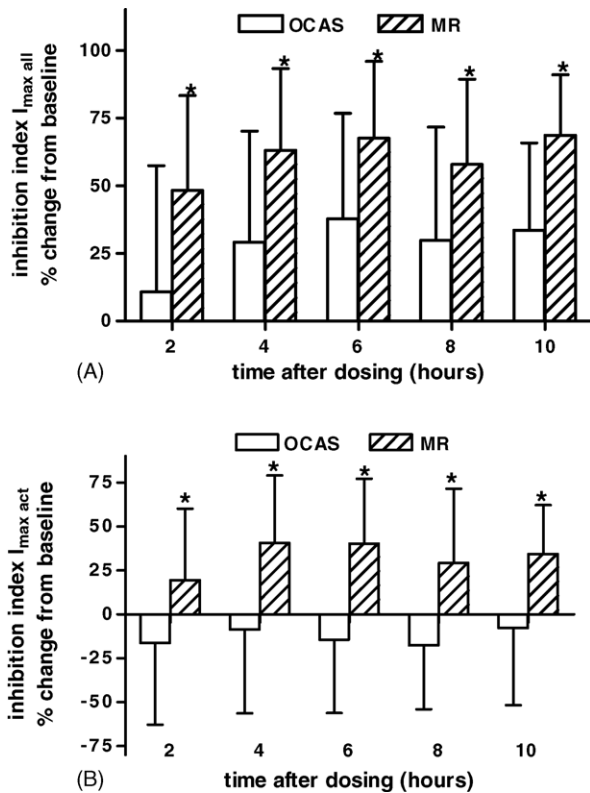


Fig. 2. Percentage change from baseline of the inhibition indices $I_{\max all}$ (A) and $I_{\max act}$ (B) based on the change from pre-infusion in DBP. Data are means \pm SD. * $p \leq 0.05$ vs. tamsulosin OCAS 0.4 mg tablets in mean change from baseline using Analysis of Covariance.

The infusion of increasing doses of PE caused a mean increase in the TPR relative to pre-infusion up to almost $1500 \text{ dyn}\cdot\text{s}/\text{cm}^{-5}$ at the highest infused dose during the placebo treatment period. At the 2 hours before dosing assessments, the mean TPR increases following each PE dose were similar between the three treatments. Fig. 3 provides an example of the TPR data collected at 4 and 6 hours post-dosing on all three treatments. The curves for tamsulosin OCAS and tamsulosin MR were again shifted to the right indicating that higher doses of PE are required to achieve a

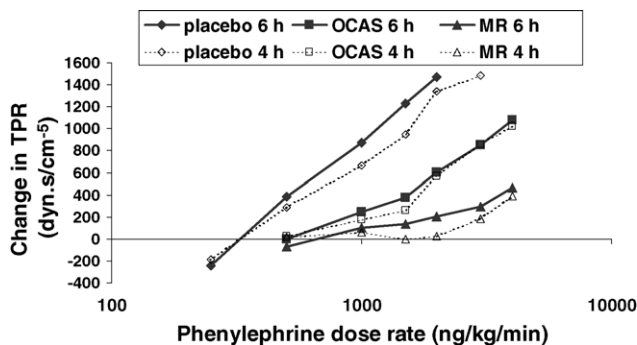


Fig. 3. Change from pre-infusion in TPR following infusion of PE at 4 and 6 hours after the dosing of test drug ($N = 15$ –17). For each subject, the TPR was calculated as the average of all measurements during that infusion.

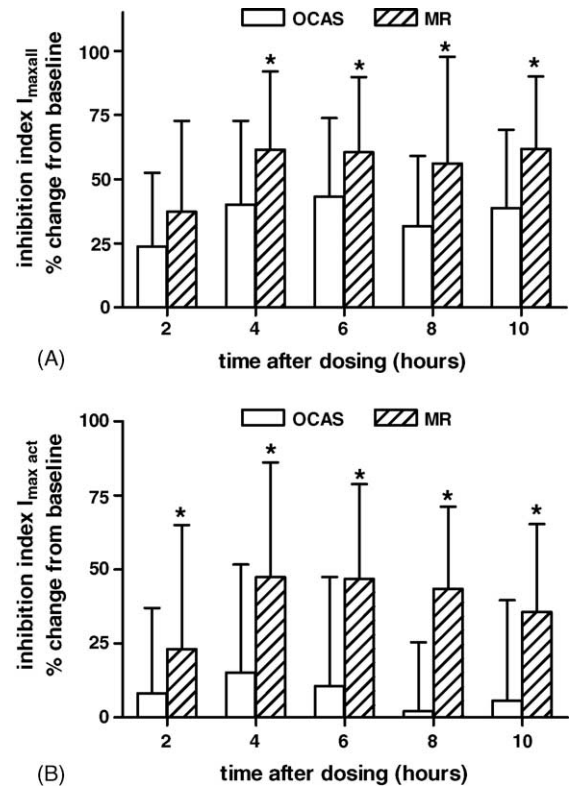


Fig. 4. Percentage change from baseline of the inhibition indices $I_{\max all}$ (A) and $I_{\max act}$ (B) based on the change from pre-infusion in TPR ($N = 14$ –15). Data are means \pm SD. * $p \leq 0.05$ vs. tamsulosin OCAS 0.4 mg tablets in mean change from baseline using Analysis of Covariance.

similar increase in TPR to that of placebo. The curve for the MR formulation was shifted further to the right than the curve for the OCAS formulation.

For the TPR data, inhibition indices $I_{\max all}$ and $I_{\max act}$ are presented in Figs. 4(A) and 4(B). The change from baseline for both indices at all time points was smaller for tamsulosin OCAS than for tamsulosin MR representing a greater inhibition of response on tamsulosin MR than on tamsulosin OCAS. These differences were all statistically significant ($p \leq 0.0280$), with the exception of $I_{\max all}$ at 2 hours post dosing ($p = 0.1167$).

3.3. PK results

The PK profiles following single dosing with tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 mg capsules are presented in Table 1 and Fig. 5. After administration of tamsulosin MR 0.4 mg, tamsulosin was gradually absorbed. C_{\max} was reached at a median value of 4.95 hours, after which the plasma concentration started to decline immediately. With tamsulosin OCAS, C_{\max} was reached at a similar time than with the MR formulation, though the plasma concentration did not immediately decline after C_{\max} had been attained. Instead, in the majority of subjects

Table 1

PK parameters of tamsulosin following single dosing with either tamsulosin MR 0.4 mg or tamsulosin OCAS 0.4 mg

Treatment	Statistic	t_{\max} (h)	C_{\max} (ng/ml)
Tamsulosin MR 0.4 mg	Mean	5.53	18.60
	SD	1.15	5.04
	Min	2.9	9.1
	Max	7.0	29.4
	Median	4.95	18.35
	<i>N</i>	16	16
Tamsulosin OCAS 0.4 mg	Mean	6.02	6.44
	SD	1.69	3.12
	Min	2.9	2.4
	Max	11.0	15.0
	Median	5.82	5.95
	<i>N</i>	17	17

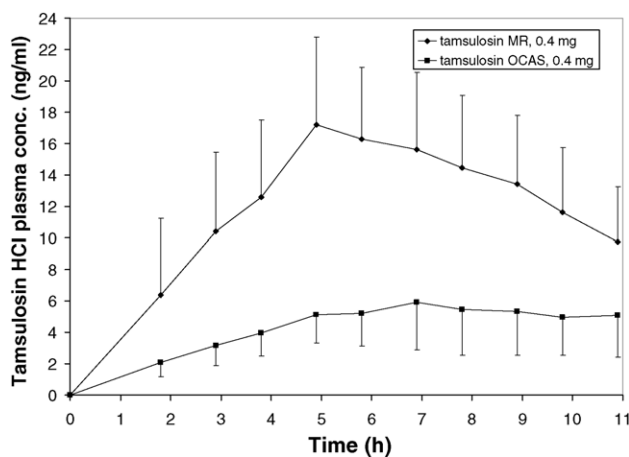


Fig. 5. Plasma concentration time curve following single doses of tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg under fasting conditions. Data are means \pm SD.

the plasma concentration remained nearly constant up to the last sampling point at 11 hours post-dose in accordance with the improved prolonged release characteristics of tamsulosin OCAS. Mean C_{\max} observed with tamsulosin MR 0.4 mg was 18.6 ng/ml, while a lower value of 6.4 ng/ml was obtained with tamsulosin OCAS 0.4 mg.

3.4. Safety/tolerability results

Six out of 18 randomised subjects reported in total 8 treatment-emergent AEs which are presented in Table 2. There were no apparent differences between the treatments, especially because several of the AEs appeared to be procedural rather than drug-related.

4. Discussion

The present single dose data confirm that tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 mg capsules exhibit different PK profiles [11,13]. Thus, compared to tamsulosin MR 0.4 mg capsules, tamsulosin OCAS 0.4 mg tablets exhibit a similar t_{\max} but a slower rise in plasma concentrations and reduced C_{\max} , $C_{\max}/C_{\text{trough}}$ ratio and area under the curve (AUC). Thus, a given dose of tamsulosin in the OCAS formulation causes less systemic drug exposure and, perhaps even more importantly, smaller maximum plasma concentrations than the same dose administered in the MR formulation.

Tamsulosin OCAS 0.4 mg tablets produced less inhibition of PE-induced, α_1 -AR-mediated vasoconstriction than tamsulosin MR 0.4 mg capsules as evidenced by both inhibition indices ($I_{\max\text{all}}$ and $I_{\max\text{act}}$), i.e. showed significantly less cardiovascular α_1 -AR

Table 2

Number of patients with at least 1 treatment emergent AE (TEAE; MedDRA coded terms; safety population)

	Placebo (<i>N</i> = 17)	Tamsulosin MR 0.4 mg (<i>N</i> = 16)	Tamsulosin OCAS 0.4 mg (<i>N</i> = 18)
At least 1 TEAE	3	1	2
Cardiac disorders	1	0	0
• Atrial fibrillation	1	0	0
General disorders and administration site conditions	0	0	1
• Injection site inflammation	0	0	1
Injury, poisoning and procedural complications	0	0	1
• Clavicle fracture	0	0	1
Nervous system disorders	1	1	1
• Headache	1	1	1
Respiratory, thoracic and mediastinal disorders	1	0	0
• Bronchitis NOS	1	0	0
Vascular disorders	1	0	0
• Orthostatic hypotension	1	0	0

antagonism. The reduction in vascular α_1 -AR antagonism by tamsulosin OCAS 0.4 mg relative to tamsulosin MR 0.4 mg in the present study is comparable to that previously reported for tamsulosin MR 0.4 mg relative to terazosin 5 mg [7]. The lower exposure to tamsulosin following tamsulosin OCAS than tamsulosin MR, i.e. the smaller plasma concentrations of tamsulosin upon ingestion of the same dose, is the most likely explanation of the reduced vascular α_1 -AR antagonism by tamsulosin OCAS. This finding is in line with a separate study in which the effect of tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg on the incidence of positive orthostatic tests following a single dose in the fasted state was investigated [11]. In this study, the incidence of positive orthostatic stress tests was lower with tamsulosin OCAS 0.4 mg than with tamsulosin MR 0.4 mg [11]. Importantly, the reduced drug exposure is not associated with a decreased therapeutic efficacy since both tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 capsules produced similar improvement in LUTS/BPH symptoms in a direct comparative study [15]. Taken together these data demonstrate that the OCAS formulation maintains the therapeutic efficacy of tamsulosin in LUTS/BPH patients while further reducing cardiovascular effects.

The present and a concomitant study on orthostatic stress testing [11] compared tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 mg capsules under fasting conditions. Administration of tamsulosin MR 0.4 mg capsules under fasting conditions enhances drug exposure [9] and is associated with an increased tendency for cardiovascular effects [10,11]. Therefore, it is generally recommended to take tamsulosin MR 0.4 mg capsules after the first meal of the day. In contrast, the PK of tamsulosin OCAS 0.4 mg tablets are not affected by the absence or presence of concomitant food intake [13]. Therefore, it could be proposed that the present study design was in favour of tamsulosin OCAS 0.4 mg tablets. However, the recommended mode of dosing is not always adhered to by patients in real life, particularly in the frail elderly, a group of patients which is particularly vulnerable to orthostatic hypotension to begin with [2,12]. Therefore, it is to be expected that the reduced vascular

α_1 -AR antagonism with tamsulosin OCAS 0.4 mg demonstrated in the present study and the reduced tendency for orthostasis shown in a separate study [11] will be representative for some clinical situations and should translate into a further improvement of the overall cardiovascular safety of tamsulosin. Indeed a direct comparison between tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 mg capsules in a large clinical study hinted at an improved cardiovascular safety of tamsulosin OCAS 0.4 mg tablets [15]. An improved cardiovascular safety with tamsulosin OCAS 0.4 mg tablets can particularly be expected in real life in risk groups such as the (very) elderly and/or patients with cardiovascular co-morbidity and/or co-medication who are more vulnerable for orthostatic hypotension, in particular during situations which further stress the cardiovascular system such as taking a hot bath, playing sports, etc. [2,16]. Even in the absence of such risk factors, the new OCAS 0.4 mg formulation provides the practical benefit of offering dosing flexibility with respect to intake of the medication with or without food.

5. Conclusions

PE infusions performed up to 10 hours after a single dose of tamsulosin OCAS 0.4 mg tablets on an empty stomach demonstrate increases in DBP and TPR that are more similar to those of placebo with correspondingly smaller increases in the inhibition index for these variables than after dosing with tamsulosin MR 0.4 mg capsules. This implies that tamsulosin OCAS 0.4 mg tablets show significantly less antagonism at cardiovascular α_1 -ARs, i.e. less inhibition of vasoconstriction, than tamsulosin MR 0.4 mg capsules. This finding is in line with the PK profile of the OCAS formulation showing improved controlled release characteristics with a lower exposure but prolonged release of tamsulosin.

Acknowledgements

This study was sponsored by Yamanouchi Europe, Egham, United Kingdom.

References

- [1] AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia. Chapter 1: diagnosis and treatment recommendations. *J Urol* 2003;170:530–47.
- [2] Coffey D. Controversies in the management of lower urinary tract symptoms: an overview. *Br J Urol* 1998;81(Suppl 1):1–5.
- [3] Souverein PC, van Staa TP, Egberts ACG, de la Rosette JJMCH, Cooper C, Leufkens HGM. Use of α -blockers and the risk of hip/femur fractures. *J Int Med* 2003;254:548–54.
- [4] Crandall CG, Cui J, Wilson TE. Effects of heat stress on baroreflex function in humans. *Acta Physiol Scand* 2003;177:321–8.

- [5] De Mey C, Terpstra I. Orthostatic effects of alfuzosin twice daily vs. tamsulosin once daily in the morning. *J Urol* 2000;163(4 Suppl): 220.
- [6] De Mey C, Michel MC, McEwen J, Moreland T. A double-blind comparison of terazosin and tamsulosin on their differential effects on ambulatory blood pressure and nocturnal orthostatic stress testing. *Eur Urol* 1998;33:481–8.
- [7] Schäfers RF, Fokuhl B, Wasmuth A, Schumacher H, Taguchi K, De Mey C, et al. Differential vascular α_1 -adrenoceptor antagonism by tamsulosin and terazosin. *Br J Clin Pharmacol* 1999;47:67–74.
- [8] Djavan B. α_1 -adrenoceptor antagonists for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): state of the art. *Eur Urol Suppl* 2004;3(4): 23–30.
- [9] Lyseng-Williamson KA, Jarvis B, Wagstaff AJ. Tamsulosin. An update of its role in the management of lower urinary tract symptoms. *Drugs* 2002;62:135–67.
- [10] Michel MC, Korstanje C, Krauwinkel. Cardiovascular safety of tamsulosin modified release in the fasted and fed state in elderly healthy subjects. *Eur Urol Suppl* 2005;4(2):9–14.
- [11] Michel MC, Korstanje C, Krauwinkel W, Shear M, Davies J, Quartel A. Cardiovascular safety of the oral controlled absorption system (OCAS) formulation of tamsulosin compared to the modified release (MR) formulation. *Eur Urol Suppl* 2005;4(2):53–60.
- [12] Verhaeverbeke I, Mets T. Drug-induced orthostatic hypotension in the elderly. Avoiding its onset. *Drug Safety* 1997;2:105–18.
- [13] Michel MC, Korstanje C, Krauwinkel W, Kuipers M. The pharmacokinetic profile of tamsulosin oral controlled absorption system (OCAS[®]). *Eur Urol Suppl* 2005;4(2):15–24.
- [14] Sumner DJ, Elliott HL, Reid JL. Analysis of the pressor dose response. *Clin Pharmacol Ther* 1982;32:450–8.
- [15] Chapple CR, Al-Shukri SH, Gattegno B, Holmes S, Martínez-Sagarra JM, Scarpa RM, et al. Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): efficacy and tolerability in a placebo and active comparator controlled phase 3a study. *Eur Urol Suppl* 2005;4(2):33–44.
- [16] De Mey C. Cardiovascular effects of alpha-blockers for the treatment of symptomatic BPH: Impact on safety and well-being. *Eur Urol* 1998;34(Suppl 2):18–28.