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Cardiovascular Safety of the Oral Controlled Absorption System (OCAS) Formulation of Tamsulosin Compared to the Modified Release (MR) Formulation

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Abstract

Objective: The potential to interfere with efferent adrenergic drive in the cardiovascular system was tested in elderly healthy subjects for the new oral controlled absorption system (OCAS) 0.4 mg tablet formulation of tamsulosin compared to the modified release (MR) 0.4 mg capsule formulation of tamsulosin after single dosing in the fasted state.

Methods: Forty healthy, elderly (≥60 years) male volunteers were to be enrolled in a double-blind, double-dummy, two-period crossover study. After a placebo run-in assessment period, the subjects were randomised to one of the two treatment sequences in which single doses of tamsulosin OCAS 0.4 mg tablets and tamsulosin MR 0.4 mg capsules were tested. Orthostatic stress tests were done at 30 minutes before dosing and at 4, 6 and 8 hours after dosing as the primary cardiovascular safety assessment. Additionally, the effect on pharmacokinetics (PK), vital signs and adverse events was measured.

Results: None of the 40 enrolled healthy male volunteers (mean age 67 years) discontinued from the study. Tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg both increased the incidence of positive orthostatic stress tests after single dosing from 2.5% at baseline to 17.5% of all post-dose assessments for tamsulosin OCAS and 31.7% for tamsulosin MR. At all time points, the incidence of a positive orthostatic test outcome following tamsulosin OCAS was lower than following tamsulosin MR (15% versus 35%, 22.5% versus 30%, and 15% versus 30% for tamsulosin OCAS relative to tamsulosin MR at 4, 6 and 8 hours post-dose, respectively). From the analysis of the discordant pairs (that is, those time points that showed a positive test outcome for only one of the two treatments) it emerged that the treatment differences measured overall and at 4 hours after dosing were statistically significant ($p = 0.006$ and $p = 0.0215$ respectively). The analysis of the vital signs at 2, 4, 6, 8 and 10 hours post-dose confirmed that the OCAS formulation caused smaller blood pressure reductions and increases in pulse rate compared to the MR formulation which were statistically significant at 2 and 4 hours post-dosing for the systolic blood pressure and pulse, and at 4 hours post-dosing for the diastolic blood pressure. PK analysis showed a lower maximum plasma concentration (mean C_{max}: 6.8 vs. 17.9 ng/ml) with the OCAS compared to the MR formulation; the time to C_{max} was similar between the treatments (median t_{max}: 6.2 vs. 6.1 hours).

Conclusions: Tamsulosin OCAS 0.4 mg demonstrates a lower incidence of positive orthostatic tests following single dosing in fasting healthy elderly subjects compared to tamsulosin MR 0.4 mg. This is probably related to the improved controlled release characteristics (lower C_{max}) of the OCAS formulation. It indicates that on an empty stomach tamsulosin OCAS provides a better cardiovascular safety profile than tamsulosin MR.

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

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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, 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 the patients suffer from concomitant cardiovascular disease(s) and/or take concomitant cardiovascular medication(s). Conditions such as exercising (e.g. gardening or playing sports), a heavy meal, hot climates/bathing, 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 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 capsules have the lowest potential of interfering with blood pressure control and inducing cardiovascular AEs [4–7]. 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 [8]. Administration of tamsulosin on an empty stomach increases the incidence of orthostatic events following postural changes [9] which may subsequently increase the risk of syncope and recurrent falls in the elderly [2,10].

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 [11]. It has been shown that the PK profile of tamsulosin OCAS 0.4 mg is not influenced by food [11]. Because of the improved pharmacokinetics, it is expected that tamsulosin OCAS 0.4 mg tablets will show less inhibition of adaptive responses in the cardiovascular system to change of posture compared to tamsulosin MR 0.4 mg capsules. In normal circumstances, the body adapts to postural changes and maintains homeostasis through activation of the autonomic nervous system [12]. Stimulation of α_1-ARs in the blood vessels and of β-ARs in the heart increases total peripheral resistance (TPR) and cardiac output, respectively, which accommodate for the change in blood pressure dynamics and are vital for optimal functioning of the cardiovascular system. Administration of an α_1-AR antagonist inhibits the adaptive responses of the body following postural changes and because stimulation of β-ARs (increased heart rate) is a poorly efficient compensatory mechanism, especially in the elderly, this may result in orthostatic hypotension [12]. The higher the incidence of positive orthostatic stress tests, the larger the cardiovascular α_1-AR antagonism of a drug. The present study was designed to look specifically into the cardiovascular safety of the new tamsulosin OCAS 0.4 mg formulation compared to the MR capsule 0.4 mg using orthostatic stress tests following single doses of both tamsulosin OCAS and MR capsules when administered on an empty stomach. As most LUTS/BPH patients are elderly subjects, who are in particular prone to orthostasis when using an α_1-AR antagonist [12], the study was performed in healthy elderly subjects.

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. An independent ethics committee reviewed and approved the protocol. All subjects gave their written consent after receiving oral and written explanation of the study.

2.2. Study design

The study was executed at a single centre (Pharma Bio-Research, Zuidlaren, The Netherlands). It was performed as a randomised, double-blind, double-dummy, single-dose, two-way, crossover study. A placebo run-in period of one day was followed by two study periods of one day each, separated by a wash-out period of at least seven days. PK and orthostatic stress testing were assessed after dosing of placebo, tamsulosin OCAS 0.4 mg or tamsulosin MR 0.4 mg under fasted conditions.

2.3. Objectives

The primary objective was to demonstrate superior cardiovascular safety of tamsulosin OCAS 0.4 mg compared with tamsulosin MR 0.4 mg during orthostatic stress testing. The secondary objective was to compare single dose PK of the two tamsulosin formulations in elderly male subjects.

2.4. Study population (inclusion/exclusion criteria)

Forty healthy elderly subjects (age $\geq$ 60 years) were to be enrolled in the study. The cardiovascular system had to be within normal limits according to medical history, physical examination and 12-lead ECG. The supine blood pressure had to be within the following range: systolic from 110 to (age + 100) mmHg and diastolic from 70 to 95 mmHg. Subjects with heart disease (e.g. angina pectoris, myocardial infarction, heart failure), severe nervous system disease, renal or hepatic insufficiency, bladder/ureter/kidney stone disease or malignancies as well as subjects with a medical history of falling, syncope, first dose hypotension following initiation of an α_1-AR antagonist or other antihypertensive or allergy to α-AR antagonists and/or combined α/β-AR antagonists at screening were excluded from the study. In addition, subjects with a symptomatic orthostatic stress test (for definition see Section 2.7) at screening and following the placebo run-in day were excluded. Subjects stopped any treatment with α-AR antagonists, α-AR agonists, drugs with anticholinergic activity (including antihistamines), antispasmodics and parasympathomimetics and cholinomimetics at least 2 weeks prior to study start.

2.5. Treatments

Tamsulosin OCAS tablets 0.4 mg with matching placebo and tamsulosin MR capsules 0.4 mg with matching placebo were produced under European Union Good Manufacturing Practices. Dosing of fasted subjects took place between 8.00 and 10.00 in the morning of the study day with 200 ml of water.

2.6. Study procedures

After they passed screening, subjects were admitted to the unit for a placebo run-in phase on days -1 to 0, after which they were randomised to a specific treatment sequence, with each period consisting of one study day. For the placebo run-in phase and each double-blind study day subjects were admitted to the unit the afternoon of the day before dosing and were served a standard meal (2 slices of wholemeal bread, marmalade and a glass of orange juice) at 22:00 hours. Baseline assessments (including vital signs, orthostatic stress testing and AEs) were done the following morning 30 minutes before dosing. Orthostatic stress tests were performed at 4, 6 and 8 hours post-dose, before blood samples were taken. Other post-dosing study assessments were done at 2, 4, 6, 8 and 10 hours following administration of the investigational medicinal product. Subjects were not allowed to smoke while in the unit.

Three hours after dosing a glucose-containing sport drink (without caffeine: Extran®) was provided and a standard light meal (2 slices of wholemeal bread, marmalade and a glass of orange juice) was given 9 hours after dosing. Subjects remained one more night in the unit. A light meal was served at 22:00 hours.

2.7. Orthostatic stress tests and vital signs

Orthostatic stress tests were performed according to the following protocol. Subjects were asked to lie down for at least 5 minutes after which vital signs (blood pressure and pulse rate) were measured. Subsequently subjects were asked to sit for 2 minutes after which vital signs were measured and finally subjects were asked to stand up and vital signs were measured after 3 minutes of relaxed standing. The definition of a positive orthostatic stress test is provided in Table 1.

Vital signs were measured using an automated device (Dinamaps). In every subject the same arm and the same device were used and if possible the person making the measurement was the same.

2.8. Pharmacokinetics

Samples of venous blood for the measurement of tamsulosin in plasma were collected before and after dose intake at the following time points: 1 hour pre-dose and at 2, 4, 6, 8 and 10 hours post-dose. Blood samples were collected into standard polyethylene tubes containing lithium-heparin as anti-coagulant. Samples were kept on ice for maximal 30 minutes until centrifuged at 2500*g* for 10 minutes at 4 °C. The resulting plasma was frozen at -70 °C within 30 minutes after centrifugation and stored at that temperature until analysis. 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 × 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.

PK analysis was done using WinNonlin software (version 4.1, Pharsight Corp., Mountain View, CA, USA). Only C_{max} and time to C_{max} (t_{max}) were evaluated as data had only been collected over 10 hours.

2.9. Assessment of safety/tolerability

AEs were assessed at specific time points (pre-dose, and at 2, 4, 6, 8 and 10 hours post-dose) during the placebo run-in day and on the double-blind study days. All observed or spontaneously reported AEs during the study were recorded and evaluated for severity and causality. They were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system.

2.10. Statistical methods

A test of the difference between active treatments in the proportion of subjects demonstrating a positive orthostatic stress test was performed using an exact McNemar test, using PROC

Table 1
Definition of a positive orthostatic stress test

1	Symptoms such as light-headedness, dizziness, faintness, etc. upon standing, AND/OR
2	A decrease in systolic blood pressure $\geq$20 mmHg between supine and standing, AND/OR
3	A decrease in diastolic blood pressure $\geq$10 mmHg between supine and standing and/or a standing diastolic blood pressure $<$60 mmHg, AND/OR
4	An increase in standing pulse rate $\geq$20 bpm between supine and standing and/or a standing pulse rate $\geq$100 bpm

FREQ in SAS® version 8.2; only those observations which demonstrated a discordant test result between treatments at a particular time point were used [13]. A discordant test result for a subject at a particular time point implies that the test was positive on tamsulosin OCAS 0.4 mg but not on tamsulosin MR 0.4 mg or that the test was negative on tamsulosin OCAS 0.4 mg but positive on tamsulosin MR 0.4 mg at that time point. This implies that any time point for which there was a positive test result on both the OCAS and MR formulation was excluded from the analysis.

The sample size for this study was derived from the study by Michel et al. [9]. In this study the proportion of patients with a positive orthostatic stress test at 6 hours post-dose was 67% for subjects dosed with tamsulosin MR 0.4 mg and 42% for subjects dosed with placebo. For the present study it was assumed that tamsulosin OCAS 0.4 mg would have a positive orthostatic test incidence similar to that of placebo. Using a McNemar's test of equality of paired proportions with a 0.05 two-sided significance level, the chosen sample size ($n = 40$) had a power of >80% to detect a difference in proportions of 24% when the proportion of discordant pairs was 33%. To support this primary analysis the Mainland-Gart test for treatment differences adjusting for period was also performed [14].

The change from baseline to 2, 4, 6, 8 and 10 hours post-dose in vital signs was subjected to an analysis of covariance (ANCOVA) including treatment, period and sequence as fixed factors, subject as a random factor and baseline as a continuous covariate.

3. Results

3.1. Number of subjects

A total of 40 elderly male subjects (39 Caucasian, 1 Asian) meeting inclusion and exclusion criteria were enrolled in the study and randomised to either treatment sequence, with the following demographic characteristics: mean age 66.9 years (range 60–78 years), mean weight 81.5 kg (range 57–97 kg), mean height 1.75 m (range 1.63–1.91 m) and a mean body mass index of 26.6 kg/m^2 (range 21.4–30.4 kg/m^2). All subjects completed the study: there were no discontinuations.

3.2. Orthostatic test results

During the placebo run-in period, one subject (2.5%) had a positive orthostatic test at pre-dose. Of the 120 post-dose tests (40 subjects tested at 4, 6 and 8 hours), none was positive. During the double-blind treatment period, the incidence of positive orthostatic stress tests, by treatment group, is provided in Fig. 1. Both tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg caused a higher proportion of positive tests compared to pre-dose. Across all post-dose time points, 17.5% of tests for tamsulosin OCAS treated subjects were positive compared to 31.7% of tests for tamsulosin MR treated subjects. Fewer subjects on tamsulosin OCAS had a positive orthostatic test at each post-dose time point, with the largest treatment difference (=20%) observed at 4 hours post-dose. Two of the positive orthostatic stress tests were accompanied by symptoms (dizziness, light-headedness or fainting): both were on tamsulosin MR 0.4 mg, one at 4 hours and one at 6 hours.

Fig. 2 shows the analysis of the paired orthostatic stress test results and its statistical analysis using the exact McNemar test. Of the total of 35 discordant pairs observed for the pooled post-dose time points, 26 (74.3%) had a positive test for tamsulosin MR and 9 (25.7%) had a positive test for tamsulosin OCAS; this difference was statistically significant ($p = 0.006$). As shown in Fig. 2, the largest difference between treatments was observed at 4 hours post-dosing with 10% of the discordant pairs having a positive test for

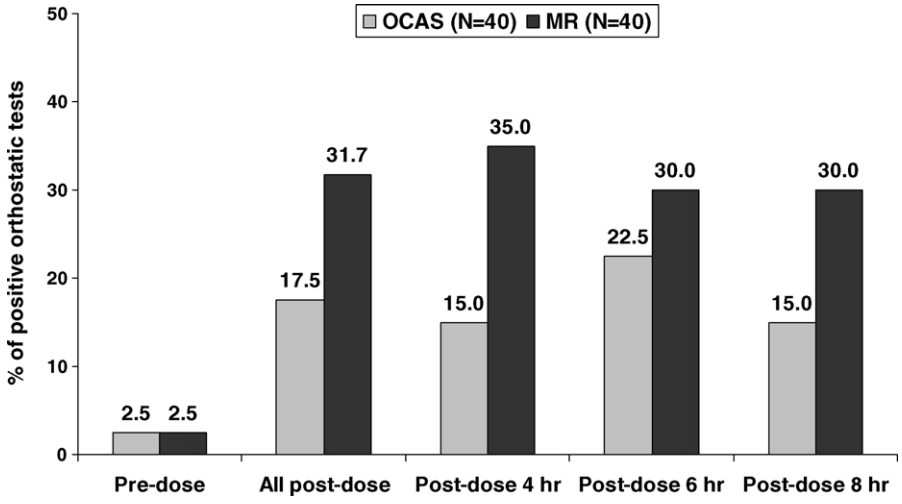

Fig. 1. Proportion of positive orthostatic stress tests following dosing of tamsulosin OCAS 0.4 mg or tamsulosin MR 0.4 mg in elderly volunteers in the fasted state.

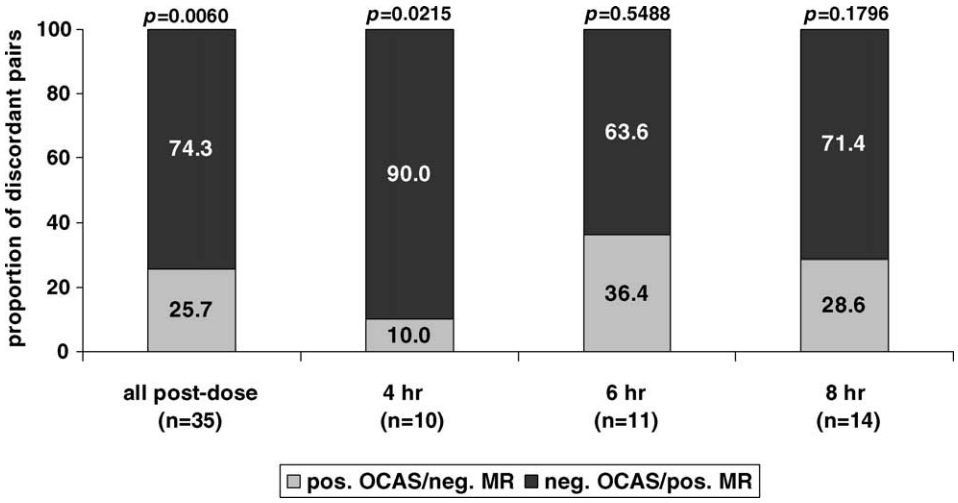

Fig. 2. Proportion of discordant pairs showing a positive orthostatic stress test comparing treatment of fasted elderly volunteers with tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg.

tamsulosin OCAS and 90% having a positive test for the MR formulation; this difference was statistically significant ($p = 0.0215$). The differences at later time points continued to demonstrate that fewer subjects had a positive orthostatic test on tamsulosin OCAS though none of these differences were statistically significant. Analysis of the orthostatic test outcomes using the Mainland-Gart test to adjust for period supported these findings.

3.3. Vital signs

Figs. 3(a)–(c) show the mean changes in vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) from baseline following dosing with tamsulosin OCAS 0.4 mg or tamsulosin MR 0.4 mg. At all time points, the change from baseline was larger for the MR than for the OCAS formulation; tamsulosin MR demonstrated larger decreases in diastolic and systolic blood pressure than tamsulosin OCAS and larger increases in pulse rate. The mean differences were statistically significant at the 2, 4 and 10 hour time points for systolic blood pressure, at the 4 hour time point for diastolic blood pressure and at the 2, 4 and 6 hour time points for the pulse rate.

3.4. Pharmacokinetics results

The plasma concentration time curve and PK are presented in Fig. 4 and Table 2, respectively. It shows that under these fasted conditions, tamsulosin MR 0.4 mg was gradually absorbed. The mean C_{max} was 17.9 ng/mL. It was reached at a median value of 6.1 hours, after which the plasma concentration started to decline immediately. With tamsulosin OCAS 0.4 mg, the mean C_{max} was lower (6.8 ng/ml) but was reached at approximately the same time (median t_{max}: 6.2 hours), although for the majority of subjects (26 out of 40) the t_{max} was reached slightly later with tamsulosin OCAS than tamsulosin MR. Compared with the MR formulation, the plasma concentration of OCAS also showed a much slower decline after C_{max} in accordance with the improved prolonged release character of tamsulosin OCAS. Inter-subject variability was similar for both formulations.

3.5. Safety/tolerability results

All subjects completed the study and there were no serious AEs. Seven subjects on tamsulosin OCAS 0.4 mg (17.5%) reported one or more treatment emergent AEs (TEAE), while 9 subjects on tamsulosin MR 0.4 mg (22.5%) reported one or more TEAEs. Nearly all TEAEs were mild; only one was moderate (headache). These numbers include the patients with a symptomatic orthostatic stress tests (2 patients receiv-

Table 2
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	5.68	17.92
	SD	1.16	6.21
	Min	4.1	8.3
	Max	8.2	39.9
	Median	6.13	17.07
	N	40	40
Tamsulosin OCAS 0.4 mg	Mean	6.83	6.75
	SD	1.92	2.54
	Min	4.1	2.1
	Max	10.0	15.5
	Median	6.17	6.22
	N	40	40

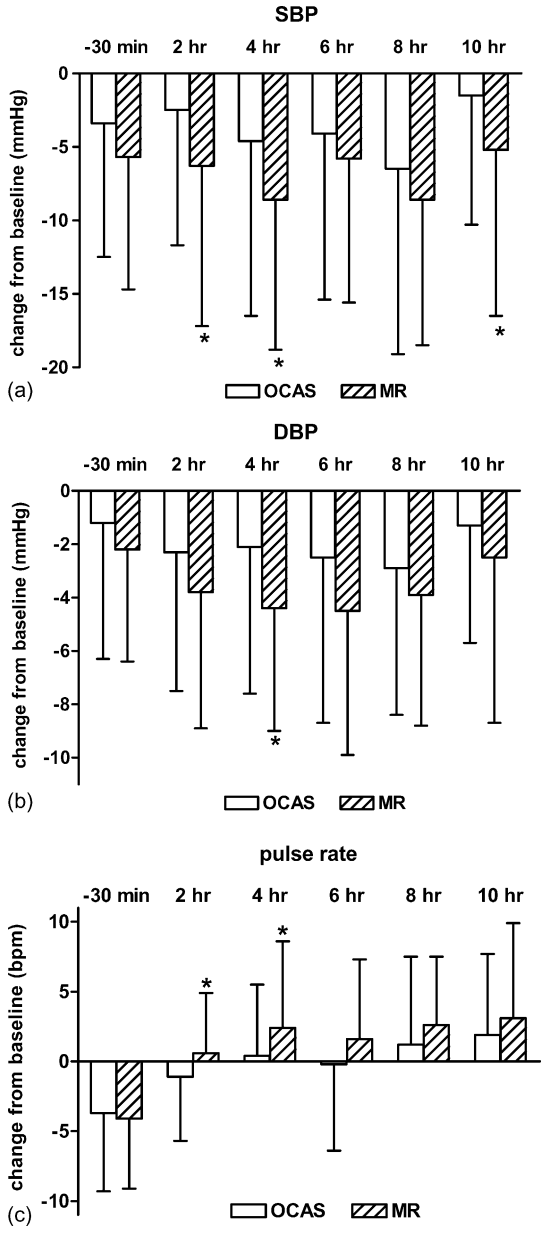

Fig. 3. Effect on vital signs following dosing with either tamsulosin OCAS 0.4 mg or tamsulosin MR 0.4 mg. The mean change from baseline ± standard deviation of 40 subjects has been plotted for systolic blood pressure (SBP) (a), diastolic blood pressure (DBP) (b) and pulse rate (PR) (c). *$p < 0.025$.

ing tamsulosin MR 0.4 mg) but not the patients with an asymptomatic orthostatic stress test.

4. Discussion

Tamsulosin OCAS tablets 0.4 mg are a new formulation of tamsulosin, that has a different PK profile from the well-known MR capsules 0.4 mg formulation, displaying a lower C_{max}, a slightly later t_{max} and an improved C_{max}/C_{24h} ratio, i.e. superior controlled release characteristics [11,15]. In addition the PK profile of the new formulation is not affected by concomitant food intake [11]. The lower C_{max} with tamsulosin OCAS was confirmed by the data from the present single dose study when both products were administered under fasting conditions. Although in the present study there was no difference between the two formulations for the median t_{max}, this was reached slightly later in the majority of subjects receiving tamsulosin OCAS 0.4 mg compared to tamsulosin MR 0.4 mg.

The present data show that, in line with its improved PK profile, tamsulosin OCAS 0.4 mg is associated with a significantly lower incidence of positive orthostatic stress tests in elderly subjects in the fasted state than the commercially available MR 0.4 mg formulation. Similarly, we have also found that tamsulosin OCAS 0.4 mg tablets produce significantly less inhibition of phenylephrine-induced, α_1-AR-mediated vasoconstriction than tamsulosin MR 0.4 mg capsules [15].

Tamsulosin MR 0.4 mg displays a significant food effect resulting in an increased C_{max} and increased area under the curve (AUC) when it is taken in the fasted state as compared to taking the drug after breakfast [8]. In a previous study it was demonstrated that this food effect increases the risk of orthostatic hypotension when tamsulosin MR is not dosed according to the labelling recommendations and therefore has the potential to increase the incidence of vasodilatation-related AEs to posture change when fasted [9]. The data presented in Figs. 1 and 2 confirm these earlier observations in the elderly and show a significantly lower sensitivity of subjects to orthostasis after tamsulosin OCAS than tamsulosin MR. These data are supported by the effect on vital signs of both formulations in Fig. 3. 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 [15] and reduced tendency for orthostatic hypotension by tamsulosin OCAS. 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 clinical study [16]. Taken together these data demonstrate that the OCAS formulation maintains the therapeutic efficacy of tamsulosin in LUTS/BPH patients while further reducing cardiovascular effects.

Drug-induced orthostatic hypotension increases with age and has a high prevalence in the elderly

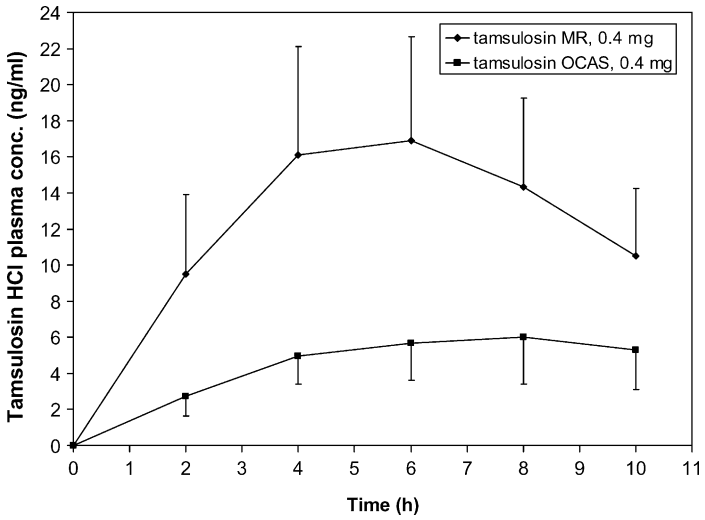

Fig. 4. Plasma concentration time curve of single doses of tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg under fasting conditions ($N = 40$). The error bars denote the standard deviation.

[10]. It is frequently mentioned as an important risk factor in the occurrence of syncope and falls [2] and postural hypotension in geriatric clinical practice is often drug-induced [17]. Since polypharmacy is common in the elderly, it is important to combine drugs with utmost care in this age group. It is therefore important to use combinations of drugs that have a minimal interference with each other as well as with physiological mechanisms. The present study and a previous study directly measuring vascular α_1-AR antagonism [15] show that tamsulosin OCAS 0.4 mg has an excellent profile in this respect.

Chapple et al. [16] have shown that the clinical efficacy of tamsulosin OCAS 0.4 mg is similar to tamsulosin MR 0.4 mg, but that there was a tendency for improved cardiovascular tolerability (and a lower incidence of abnormal ejaculation) for tamsulosin OCAS 0.4 mg compared to tamsulosin MR 0.4 mg. The present study shows that tamsulosin OCAS 0.4 mg is indeed associated with a lower sensitivity to orthostasis in the elderly when administered under comparable fasting conditions which stresses the cardiovascular system. These results support the view that tamsulosin OCAS 0.4 mg shows a small but clinically relevant improvement in cardiovascular safety compared to the MR 0.4 mg formulation due to the absence of a food effect. Furthermore, the patients included in the present study were selected for not being vulnerable to orthostatic hypotension (e.g. subjects with cardiovascular disease or who had symptomatic orthostatic hypotension during the screening or placebo run-in period were excluded). Therefore, in real life practice where also the very elderly and 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. [2,12]) are treated, the difference may even be larger.

5. Conclusions

Tamsulosin OCAS 0.4 mg shows a lower incidence of positive orthostatic tests following single dosing in fasting healthy elderly subjects compared to tamsulosin MR 0.4 mg. Also the effects on vital signs are in favour of the OCAS formulation. This is in line with improved controlled release characteristics of the OCAS compared with the MR formulation.

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