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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.