CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 22, NO. 12, 2006, 2323–2328

0300-7995
doi:10.1185/030079906X154051

ORIGINAL ARTICLE

Behaviour and transit of tamsulosin Oral Controlled Absorption System in the gastrointestinal tract

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Key words: **Gamma scintigraphy – Gastrointestinal tract – Oral Controlled Absorption System – Tamsulosin OCAS – Transit**

ABSTRACT

Objective: To assess the *in vivo* behaviour, gastric emptying time and gastrointestinal transit of the new tablet formulation of tamsulosin which uses the Oral Controlled Absorption System (OCAS) technology and to relate gastrointestinal transit parameters to the profile of the plasma concentration time curve.

Research design and methods: After breakfast, 8 healthy male subjects received a single tamsulosin OCAS* 0.4 mg tablet labelled with 4MBq technetium-99m. Scintigraphic images were taken immediately after dosing, every 15 min until 15 h post-dose and at 24 h post-dose. Blood samples for pharmacokinetic analysis were taken up to 24 h after dosing. Safety was assessed by physical examinations, vital signs, laboratory safety evaluations and adverse events monitoring.

Results: A mean C_{max} of 7.84 ± 2.54 ng/mL was achieved after 5.13 ± 1.25 h (t_{max}). The mean gastric emptying time for the tablet was 4.1 ± 2.5 h. Mean transit time through the small intestine was 3.6 ± 2.9 h; the mean colonic arrival time 7.7 ± 2.9 h post-dose and the mean release time (spread of the technetium-99m label from the tablet core) 12.3 ± 1.7 h post-dose. In all cases where release of the radiolabelled tablet was observed, this occurred within the colon. Variations in gastric residence, small intestinal transit or colonic residence did not apparently influence release time or site.

Conclusions: The results suggest that tamsulosin is released from the OCAS formulation throughout the entire gastrointestinal tract, including the colon, indicating consistent and continued 24-h drug release. This correlates with a more consistent pharmacokinetic profile.

Introduction

Benign prostatic hyperplasia (BPH) is a prevalent condition in older men, which is associated with lower urinary tract symptoms (LUTS) related to voiding (e.g. slow stream, hesitancy, intermittency) and storage (e.g. daytime frequency, urgency, nocturia)[1]. Since its introduction in the 1990s, medical therapy has become increasingly important for the treatment of LUTS suggestive of BPH (LUTS/BPH) and has obviated the need for surgery in many patients. Today, treatment with α_1-adrenoceptor (α_1-AR) antagonists is recommended as first-line medical therapy for LUTS/BPH[2]. α_1-AR antagonists exert their effect by relaxing smooth muscle in the bladder neck, urethra and prostate, which results in an improvement of LUTS[3].

* Tamsulosin OCAS is a registered trade name of Astellas Pharma Europe

Of all currently available α_1-AR antagonists (alfuzosin, doxazosin, tamsulosin, terazosin), tamsulosin has the most favourable tolerability/efficacy ratio[3]. This is probably due to its greater selectivity for α_1-AR subtypes that are predominantly present in the lower urinary tract (α_{1A}-AR and α_{1D}-AR) over those in the blood vessels (predominantly the α_{1B}-AR subtype)[4,5]. Nonetheless, the pharmacokinetic (PK) profile of the conventional tamsulosin modified release capsule has some drawbacks. Like most currently available α_1-AR antagonists, the tamsulosin capsule is based on a technology depending on the presence of water in the gastrointestinal (GI) tract to release its active ingredient. Consequently, drug release is impeded during passage of the formulation through the colon where water is poorly available[6,7]. Furthermore, the tamsulosin capsule must be taken after the first meal of the day because its release is food-dependent[4,5]. If taken in the fasted state, the maximum plasma concentration (C_{max}) and the area under the curve (AUC) rise by about 70% and 30% respectively, increasing the risk of adverse events (AE) related to vasodilatation (e.g. dizziness, headache, orthostatic hypotension)[8,9].

Recently, a prolonged-release formulation of tamsulosin has been developed in order to overcome the above mentioned limitations of the conventional tamsulosin capsule. This so called Oral Controlled Absorption System (OCAS) technology consists of a gel matrix, containing a gel-forming and a gel-enhancing component[6,10]. It was expected that, due to its composition, the tamsulosin OCAS* tablet would undergo substantial hydration in the stomach and the small intestine, so that complete hydration occurs prior to arrival at the colon. The gel matrix then has sufficient gel strength to allow drug release in the colon. Consequently, the drug would be released at a constant rate throughout the GI tract, independent of food intake. Pharmacokinetic studies demonstrated that tamsulosin OCAS indeed has an improved PK profile showing a lower C_{max}, a more continuous and consistent 24-h plasma concentration and does not depend on food intake[6]. Moreover, there is growing evidence that this improved PK profile translates into a better cardiovascular safety profile and ensures daytime and night time symptom control[11–13].

However, to date, there is no direct evidence that the smoother PK profile of tamsulosin OCAS is the result of constant drug release throughout the entire GI tract, including the colon. The present study was designed to demonstrate the direct link between the position of the OCAS tablet in the GI tract and its PK profile by determination of the location of the tamsulosin OCAS tablet through gamma scintigraphy and concurrent PK measurements. Gamma scintigraphy is a non-invasive technique which has repeatedly been used in evaluating the *in vivo* release properties of drug formulations[14]. It is often combined with PK analysis to provide information concerning sites of release and absorption[15].

Patients and methods

This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Tayside Medical Research Ethics Committee and the Administration of Radioactive Substance Advisory Committee. Informed written consent was obtained from all participants prior to the start of the study.

Study design

The present study was a single-centre, open-label, single-dose study. All participants underwent medical screening within 21 days before the start of the study including the assessment of vital signs, serum biochemistry, urinalysis, hepatitis B and C screening, 12 lead ECG screening and interrogation on medical history, demographics and drug abuse. After a light breakfast, 15 min prior to dosing, all subjects received a single tamsulosin OCAS tablet 0.4 mg labelled with technetium-99m (99mTc) with 240 mL water. Tamsulosin OCAS 0.4 mg tablets were supplied by Astellas Pharma Europe. The tablets (Batch No 04028000084, Expiry 02/2006) were manufactured at the manufacturing site of Astellas Pharma Europe in Meppel, the Netherlands. For radioactive labelling, a hole was drilled into the edge of each tablet and the cavity was filled with approximately 3 mg of charcoal, containing a maximum of 4 MBq ^{99m}Tc. The remainder of the hole was filled with tablet granulate and sealed with a drop of gelatin mixture. To compare dissolution behaviour of labelled and unlabelled tablets, the paddle method using the Ph. Eur dissolution test apparatus was performed. Samples were collected at 3, 7 and 12 h and analysed using HPLC-UV detection. The position of the tablet in the GI tract and the PK profile were measured simultaneously through gamma scintigraphy and concurrent PK measurements. For a proper evaluation of release, it should be considered that the radioactivity is located in the centre of the tablet, which implies that dispersion of radioactivity in the GI tract reflects the final stages of erosion of the tablet. The PK data on the other hand also provide information on release and absorption of tamsulosin from the outer layers of the tablet. During the study,

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the subjects maintained a normal feeding pattern. Subjects remained in the study centre until 24 h post-dose. Medical assessment (excluding screening of drug abuse and virology) was repeated within 10 days after completion of the dosing visit. The total duration of the study was approximately 4 weeks from screening to follow-up.

Study population (inclusion/exclusion criteria)

The study included healthy male volunteers aged between 18 and 60 years, with a Body Mass Index within the range 18.0–29.9 kg/m^2 and a body weight ≥ 50 kg. Subjects with an allergy to a drug or any component of the dosage form or with any other allergy, which in the opinion of the investigator contraindicates their participation, were excluded from the study. Other exclusion criteria were abnormal heart rate or blood pressure, hepatitis B or C, any clinical history of upper gastrointestinal symptoms in the 3 weeks prior to inclusion, acute diarrhoea or constipation in the 14-day period before initiation of the study. Also, gastrointestinal surgery in the last 12 months, use of prescribed medication within 14 days or over-the-counter medication within 48 h prior to inclusion, vegetarian, drug abuse, alcohol abuse, smoking or any clinical condition, including gastrointestinal, cardiovascular, respiratory, renal, hepatic, neurological, dermatological, psychiatric or metabolic, which, in the opinion of the investigator, would not allow safe completion of the study.

Assessment of efficacy

Scintigraphic images were collected immediately after dosing, then every 15 min until 15 h after dosing and at 24 h post-dose. All scintigraphic images were taken with subjects in a standing position. Blood samples for pharmacokinetic analysis were collected into 6 mL Vacuette tubes containing lithium-heparin before dosing and 1, 2, 3, 4, 5, 6, 7, 8, 12, 15 and 24 h after dosing. Blood samples were centrifuged at 2500 *g* for 10 min and plasma fractions were removed and stored at –20°C until shipment to Cephac Europe s.a.s. where they were analysed using a validated method. Briefly, the method involved a liquid/liquid extraction using ethyl/cyclohexane followed by reverse phase liquid chromatography with tandem mass spectrometric detection. The analytical procedure in human plasma was shown to be linear from 0.10 to 50.00 ng/mL using 0.2 mL of the sample. AEs were registered before dosing, hourly until 15 h after dosing and 24 h post-dose. Release time, tablet gastric emptying time and GI transit parameters were determined by qualitative assessment of the scintigraphic images by two skilled persons independent of each other.

Assessment of safety/tolerability

Safety was assessed by physical examination, assessment of vital signs, laboratory safety evaluations (blood chemistry, haematology and urinalysis) and monitoring of AEs. Subjects were actively questioned on AEs before dosing, throughout the study visit (hourly to 15 h post-dose and at 24 h post-dose) and at follow-up. AEs spontaneously reported by the subjects were also recorded.

Results

Demographics and other baseline characteristics

The study enrolled 8 healthy male volunteers. Demographics of all subjects are shown in Table 1. All participants completed the study.

Efficacy results

Scintigraphy analysis

The dissolution studies comparing labelled and unlabelled tablets show that the modified tablets have a similar dissolution behaviour as unlabelled tablets at all time points. Scintigraphic data (release time, tablet gastric emptying time and GI transit parameters) were analysed using the WebLink image analysis programme. Transit parameters of all subjects are presented in Table 2. Transit parameters are provided for intact tablet cores only as accurate assessment is not possible once activity has been released. The mean gastric emptying time for the tablet was 4.1 ± 2.5 h; subject 3 had a prolonged gastric emptying time of 10.1 h. The mean transit time through the small intestine was 3.6 ± 2.9 h. Residence at the ileocaecal junction (ICJ) was observed in 4 of 8 subjects; 2 subjects (subjects 2 and 4) had a prolonged ICJ residence. The mean colonic arrival time was 7.7 ± 2.9 h post-dose. In 3 subjects (subjects 2, 3 and 4), colonic arrival was slightly delayed, which could be

Table 1. *Summary of subject demographics*

Number of subjects enrolled and completed	8
Age of subjects (mean ± SD, range)	42.0 ± 5.9, 34–53 years
Race of subjects	Caucasian
Height (mean ± SD)	1.74 ± 0.06 m
Weight at screening (mean ± SD)	77.6 ± 6.9 kg

attributed to the prolonged gastric or ICJ residence time of the tablet.

The mean release time (spread of the ^{99m}Tc label from the tablet core) was 12.3 ± 1.7 h post-dose and in all cases where release of radiolabel from the tablet was observed, this occurred within the colon (Figure 1). Variations in gastric residence, small intestine transit or colonic residence did not apparently influence release time or site. In 2 cases, the tablet core was excreted during the imaging period. However, it should be noted that the core of the tablet could have been broken up so that release of activity could not be excluded.

Pharmacokinetic analysis

Individual plasma tamsulosin concentration profiles are depicted in Figure 2. C_{max} and time to attain C_{max} (t_{max}) were directly obtained from the individual profiles. Analysis of the mean plasma tamsulosin concentration profile revealed that a mean C_{max} of 7.84 ± 2.54 ng/mL was achieved after 5.13 ± 1.25 h (t_{max}). The shapes of the individual profiles varied considerably between subjects (Figure 2).

Correlation between scintigraphy and pharmacokinetic analysis

Combined analysis of scintigraphy and PK suggest that erosion of the tablet starts in the small intestine and is continued after its arrival in the colon, where radiolabel is released from the tablet core. Although the PK profiles varied considerably between subjects, there was no correlation between these variations and the patterns of transit through the GI tract. The range of release times of the radiolabel from the tablet core was quite narrow, i.e. 9.1–13.9 h after dosing. There was no evidence for any premature release from the tablet core in tablets with extended residence in any section of the GI tract. Subject 8 has a low C_{max} and a

Table 2. *Individual transit parameters of a tamsulosin OCAS tablet 0.4 mg labelled with ^{99m}Tc as determined by means of gamma scintigraphy. The times presented represent the midpoint between the image at which release of radiolabel from the tablet core or transit to a specified region of the intestine was observed and the previous image (NR: no residence observed)*

Subject	Gastric emptying (h post-dose)	Small intestine transit time (h)	Colonic arrival (h post-dose)	Time of release (h post-dose)	Site of release
1	3.9	2.2	6.1	9.1	Colon
2	2.4	10.0	12.4	13.1	Colon
3	10.1	1.4	11.5	13.9	Colon
4	3.4	5.7	9.1	13.1	Colon
5	2.8	2.8	5.6	11.9	Colon
6	3.4	2.5	5.9	NR	No release observed (void at 11.4 h)
7	3.9	1.2	5.1	12.4	Colon
8	2.9	3.2	6.1	NR	No release observed (void at 19.3 h)
Mean	4.1	3.6	7.7	12.3	
SD	2.5	2.9	2.9	1.7	

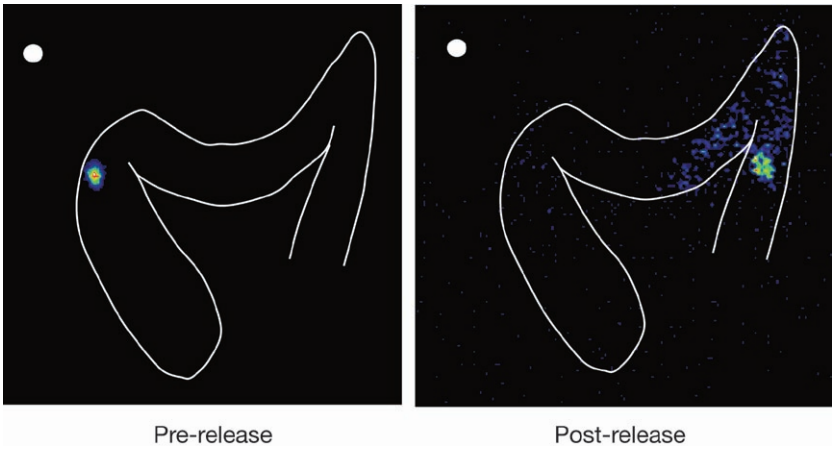

Figure 1. *Scintigraphic images from subject 7 before and after release of radiolabel from a single tamsulosin OCAS tablet 0.4 mg labelled with ^{99m}Tc. Both images are anterior views. The external marker is indicated by a white circle, the colon wall is provided as ROI as a guide to colonic transit*

low absorption of tamsulosin. In this person the tablet core was excreted intact at 19.3 h post-dose, so this low PK profile might be attributed to a lower erosion of the tablet and poorer absorption.

Safety/tolerability results

No clinically significant changes in vital signs or laboratory results were registered between pre- and post-dose. One subject reported dizziness, which was possibly related to the study medication. The AE resolved spontaneously after 10 min.

Discussion

The newly developed controlled release (OCAS) formulation of tamsulosin consists of an improved gel-layer which is designed to absorb water within the small intestine. As drug release is highly dependent on the presence of water, hydration of the gel-layer is believed to be critical for the release of tamsulosin in the lower GI tract where water is poorly available. The current pilot study investigated the behaviour and gastrointestinal transit of the new tamsulosin OCAS 0.4 mg tablet in 8 healthy subjects under fed conditions by means of gamma scintigraphy and concomitant PK analysis of blood samples.

As expected, PK analysis of the blood samples confirmed the results of previous PK studies with tamsulosin OCAS showing a flattened tamsulosin concentration profile[6]. The shape of this profile, with a reduced C_{max} and a more continuous and consistent 24-h plasma concentration of tamsulosin suggests that the drug is being released throughout the entire GI tract, including the colon. Certainty on this issue was obtained by the analysis of the scintigraphic data, providing information on deposition, dispersion and movement of the tablet. It was found that the tablet entered the small intestine within 4 h in 7 subjects; only 1 subject had a prolonged gastric emptying time. Transit times through the small intestine and colonic arrival times were more variable; most likely, this was due to prolonged residence at the ICJ in 2 subjects. Nevertheless, the range of release times of the radiolabel from the tablet core was quite narrow; indicating that extended residence in any section of the GI tract does not elicit premature release from the tablet core. In all cases where release from the tablet core could be demonstrated, this occurred within the colon. There was significant absorption of tamsulosin prior to observed release of the ^{99m}TC label which supports a model of tablet erosion from the outside, leaving the labelled core intact. These findings indicate that the improved PK profile of the tamsulosin OCAS tablet can indeed be accounted for by the fact that the gel layer carries sufficient water into the colon to allow drug release. As a result, tamsulosin is slowly released throughout the entire GI tract, which results in a more consistent and continuous plasma concentration of the drug. It was assumed this would generate a better control of night-time LUTS/BPH. Direct evidence on this issue was recently provided by a pilot study showing that tamsulosin OCAS 0.4 mg increases the patient's hours of undisturbed sleep (HUS), referring to the time from falling asleep until the first awakening to void[13]. As a good sleep during the first part of the night is critical for feeling refreshed during the next day, an increase of HUS may improve the patient's quality of life. Another advantage of the flattened PK profile of tamsulosin OCAS 0.4 mg is that C_{max} consistently remains below the maximum tolerated concentration,

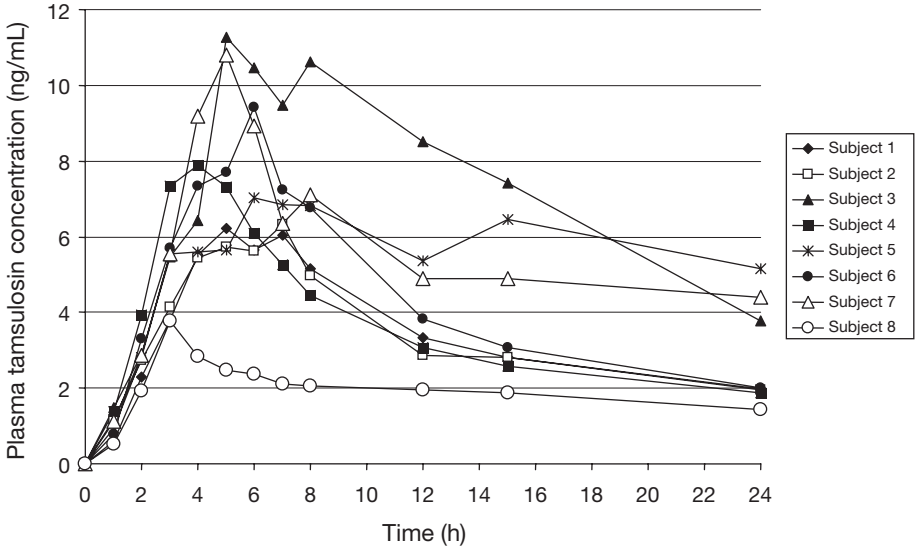

Figure 2. *Individual plasma concentration time curves of single doses of tamsulosin OCAS 0.4 mg under fed conditions*

which was previously shown to translate into a better cardiovascular safety[9,16,17]. In line with these findings, the safety results of the present study show that tamsulosin OCAS 0.4 mg has no significant impact on vital signs or laboratory results (blood chemistry, haematology and urinalysis). Moreover, none of the participants of the study experienced severe side effects.

Parallel analysis of PK and scintigraphy data revealed that the time of drug release from the tamsulosin OCAS tablet and the resultant PK profile do not correlate with differences in individual transit parameters like gastric residence, small intestine transit and colonic residence. This implies that, although transit parameters may differ considerably between subjects, this has no significant impact on the tamsulosin plasma concentration profile. Only excretion of the intact tablet, probably due to low erosion and poor absorption, might translate into an aberrant PK profile with a very low C_{max}. However, the latter phenomenon appears to be rather uncommon as it was only observed in 1 out of 8 participants.

Conclusion

Taken together, the results of the current study suggest that tamsulosin OCAS is being released throughout the entire gastrointestinal tract, including the colon, indicating consistent and continued 24-h drug release. This is the first study that assessed the direct link between the behaviour of tamsulosin OCAS in the GI tract and its PK profile.

Acknowledgements

This study was sponsored by Astellas Pharma Inc., Middlesex, UK. The authors are grateful to Dr B. O'Mahony, Dr B. Lindsay and Miss J. Band for their contribution to the study and to Ismar Healthcare NV for their assistance in editing of the manuscript.

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Paper CMRO-3655_3, *Accepted for publication*: 29 September 2006
Published Online: 30 October 2006
doi:10.1185/030079906X154051