Impact of Tamsulosin OCAS on Energy of Patients with LUTS/BPH

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1. Introduction

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are very prevalent, particularly among older men. The importance of the management of LUTS/BPH will increase in the near future due to the rapidly ageing population in the Western world [1]. Relief of voiding symptoms such as slow stream and hesitancy used to be the primary treatment goal in LUTS/BPH. However, experts are now becoming increasingly aware that storage symptoms are usually more bothersome for these patients and can more adversely affect quality of life (QoL). Especially nocturia, the complaint that one has to wake up to void several times during the night, is considered to be extremely bothersome for men with LUTS/BPH [2]. This was recently confirmed in a Web survey among 244 practising urologists attending the European Association of Urology (EAU) congress [3]. Most respondents of this survey agreed with the statement that lack of sleep is the main reason for the inconvenience of nocturia.

Abstract

The impact of nighttime lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) such as nocturia has long been underestimated. Lack of sleep because of these symptoms can considerably affect a patient’s performance and his general feeling of well-being. Chronic sleep deficit may lead to increased morbidity and mortality. Therefore, it is important that therapies for LUTS/BPH provide a proper control of nighttime LUTS. Numerous studies in the field of sleep disorders have shown that increasing the length and quality of sleep (QoS) can result in a significant improvement in energy and quality of life (QoL). To relieve nocturnal symptoms of BPH and to improve patients’ QoS and QoL, a new prolonged-release tablet formulation of the $\alpha_1$-adrenoceptor antagonist tamsulosin using the Oral Controlled Absorption System (OCAS) technology was recently developed. Tamsulosin is slowly released from the OCAS tablet throughout the entire gastrointestinal tract, including the colon, and thus provides a relatively stable 24-h plasma concentration of tamsulosin. Due to its advanced delivery system, tamsulosin OCAS is expected to relieve nighttime symptoms of LUTS/BPH and to improve QoS and QoL.

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and that (new) therapies for LUTS/BPH should be evaluated for their effects on nocturia, quality of sleep (QoS), and QoL.

Several studies have shown that lack of sleep can seriously affect a person’s physical and mental well-being and impair performance during the next day [4]. In addition, daytime sleepiness is likely to reduce alertness and hence increase the risk of falls and car accidents [5,6]. In the long run, chronic sleep disorders such as nocturia may even increase the risk of severe metabolic disorders, such as type 2 diabetes or cardiovascular disease [7,8]. Because bed partners can have a significant impact on each other’s sleep, not only the patient with nocturia but also his partner may suffer from disturbed sleep and daytime fatigue [9]. Given the potential consequences of nocturia, questions about sleep quality and quantity should be an integral part of every history and physical examination of patients with LUTS/BPH.

2. Managing sleep disorders: impact on daily life

Although the association between sleep disorders on the one hand and daytime sleepiness and QoL on the other hand is obvious, few clinical data are available showing that successful treatment of sleep disorders has an impact on vitality and health. In the field of LUTS/BPH, several studies showed an improvement of nocturia after surgical or medical treatment for LUTS/BPH [10–12]. However, these studies had rather low power and were not specifically designed to measure the improvement of nocturia. Moreover, none of these studies assessed the impact of nocturia on QoS or QoL. Sleep disorders other than nocturia that are common in the elderly include restless leg syndrome and obstructive sleep apnoea (OSA).

Use of medical therapy to reduce the frequency of periodic leg movements in patients with restless leg syndrome has been shown to significantly increase total sleep time. Various studies in this field showed that this results in significant improvements in QoS and QoL [13,14]. Leg movements in these studies were recorded by actigraphy; QoS was evaluated using modified 50-mm Hamburger Visual Analogue Scales covering domains on life satisfaction (eg, satisfaction with cognitive performance, activities of daily living, leisure activities, and efficacy at work) and burden caused by symptoms (eg, depression, fatigue, and physical symptoms). In one of the studies, the standardised sleep inventory short form-A (SF-A) was used to assess sleep patterns and mood. In another study, QoS was evaluated using polysomnography (PSG) and sleep diaries in which symptoms such as sleep latency and frequency of awakenings were rated. Although PSG data could not objectively show improved QoS in this study, the patients reported a subjective improvement in QoS.

Similarly, treatment of OSA, a condition in which sleep is disturbed because respiration is decreased or stopped repeatedly, significantly reduces daytime sleepiness and improves QoS and QoL of both the patients and their bed partners [15,16]. For QoS and QoL assessment in one of these studies, patients and their bed partners had to complete the Epworth Sleepiness Scale (ESS) questionnaire, the short form health survey (SF-36) and the Calgary Sleep Apnoea Quality of Life Index (SAQLI). Both the patients and their bed partners reported statistically significant improvements in total ESS (p < 0.001 and p = 0.02, respectively) and SAQLI scores (p < 0.001 and p = 0.002, respectively) and in the domains of role-physical, vitality, social functioning, and mental health of the SF-36 questionnaire. In another study, improvements in QoS were recorded using somnographic examinations and sleep quality questionnaires including questions on treatment effectiveness, daytime tiredness, and improvements in QoS. Overall, the data of these studies show that improving QoS can have a major impact on a patient’s and even his partner’s performance and QoL.

3. Managing nocturia in patients with LUTS/BPH

3.1. Initial patient evaluation

Lifestyle changes such as reduced fluid intake or restriction of alcohol or caffeine may help some patients with nocturia, but successful management of nocturia usually implies treatment of its underlying cause. Therefore, patients with nocturia should be adequately evaluated to assess the cause of their complaint. Initial patient screening includes a detailed history and physical examination [17]. The patients are questioned about timing and amount of fluid intake, use of medications, and health problems and undergo physical and neurologic examinations. In addition, the patients have to complete a 24-h diary including information on timing and frequency of voiding and urine volume to distinguish between the different categories of nocturia, that is, polyuria, nocturnal polyuria, and reduced bladder capacity [17–19].
3.2. Treatment of nocturia due to BPH

Patients with nocturia associated with BPH may benefit from drugs affecting either prostate volume or muscle tone in the lower urinary tract (LUT) or from prostate surgery. Currently, $\alpha_1$-adrenoceptor ($\alpha_1$-AR) antagonists such as alfuzosin, doxazosin, and tamsulosin are recommended as first-line pharmacologic therapy for men with LUTS/BPH [20]. The $\alpha_1$-AR antagonists improve urinary flow and other symptoms of BPH by reducing muscle tone in the bladder neck, the urethra, and the prostate. Three distinct types of $\alpha_1$-ARs, the $\alpha_{1A}$-, $\alpha_{1B}$-, and the $\alpha_{1D}$-ARs, exist. Contraction of the muscles of the human LUT is mainly mediated by $\alpha_{1A}$-ARs and $\alpha_{1D}$-ARs, whereas $\alpha_{1B}$-ARs are predominantly present in the vasculature. All currently available $\alpha_1$-AR antagonists are similarly effective in relieving LUTS/BPH, but tamsulosin differs from the other agents because of its greater selectivity for the $\alpha_{1A}$- and $\alpha_{1D}$-ARs [21]. Therefore, it is less likely to cause vasodilation-associated adverse events (AEs) such as dizziness and orthostatic hypotension. Tamsulosin has been available in a modified-release (MR) capsule formulation for many years and several clinical studies have assessed its efficacy and safety versus placebo [22–24]. Drug delivery systems for $\alpha_1$-AR antagonists such as the MR capsule were developed to provide a gradual and continuous drug release but are usually dependent on the presence of water for drug release [25–27]. Unfortunately, whereas the stomach and the small intestine contain enough water to allow drug release in the upper gastrointestinal (GI) tract, water is only

![Graph](image)

**Fig. 1** – (A) The pharmacokinetic (PK) profile of tamsulosin oral controlled absorption system (OCAS) 0.4 mg shows a reduced $C_{\text{max}}$ and a consistent and continued 24-h plasma concentration of tamsulosin (mean PK profile of eight subjects). (B) Scintigraphic analysis shows that tamsulosin is released from the OCAS tablet throughout the entire gastrointestinal tract, including the colon. Reprinted from Stevens et al [30], with permission from Librapharm Limited.
scarcely available in the colon. This means that drug release from these formulations only persists until arrival in the colon, that is, <24 h. Moreover, release from these formulations usually also depends on food intake. Administration of the tamsulosin MR capsule on an empty stomach increases the maximum plasma concentration (C_max) and the area under the curve, which might increase the risk of peak-level associated AEs [28]. Therefore, tamsulosin MR has to be taken after the first meal of the day.

4. Tamsulosin OCAS

Recently, a prolonged-release tablet formulation of tamsulosin using the Oral Controlled Absorption System (OCAS) technology was introduced as an answer to the above-mentioned problems with current α1-AR antagonist formulations. The OCAS formulation is composed of an advanced gel layer that rapidly and completely hydrates during its passage through the upper GI tract. This hydration step is crucial to provide sustained drug release in the colon. Because of its advanced delivery system, the new tamsulosin tablet formulation was expected to have a pharmacokinetic (PK) profile with a lower C_max and a plasma concentration that is consistently maintained above the minimum effective concentration for 24 h, independent of food intake. This improved PK profile should translate into a better control of nighttime symptoms of BPH and a lower risk of peak-associated AEs.

4.1. PK profile and GI transit of tamsulosin OCAS

Two clinical trials provided evidence for the hypothesis that tamsulosin OCAS has an improved PK profile [29]. As expected, the PK profile was flattened with a low C_max and a reduced fluctuation in 24-h plasma concentrations. Plasma concentrations were independent of food intake and the elimination half-life and the time to reach C_max were comparable to those of the MR formulation.

The behaviour of tamsulosin OCAS in the GI tract was recently examined using tandem γ-scintigraphy and PK analysis in a pilot study including eight healthy men [30]. The participants received a single radiolabelled tamsulosin OCAS tablet. Scintigraphic images were taken immediately after dosing, every 15 min until 15 h after dosing and at 24 h after dosing. Blood samples were collected before dosing, hourly until 8 h after dosing, and at 12, 15, and 24 h after dosing. PK data confirmed findings from the above PK studies and the scintigraphic analysis revealed that in all cases where release from the radiolabelled tablet core was observed, this occurred within the colon (Fig. 1). Release time or site from the tablet core was not affected by individual variations in gastric residence, small intestinal transit, or colonic residence. Altogether, the PK and scintigraphic observations strongly suggest that tamsulosin is slowly released from the OCAS tablet throughout the entire GI tract, including the colon, leading to a continuous and consistent 24-h plasma concentration.

4.2. Effect of tamsulosin OCAS on nocturia, QoS, and QoL

A recently published randomised, double-blind, placebo-controlled, proof-of-concept study in 117 patients with LUTS/BPH evaluated the influence of the new tamsulosin OCAS tablet on the severity of nocturia, QoS, and QoL [31]. The investigators introduced “Hours of Undisturbed Sleep” (HUS) as a measure for QoS. The concept of HUS is based on the finding that not only the number of voiding episodes but also the time between falling asleep and the first awakening to void determines performance during the next day. Sleep disruption during slow wave, restorative sleep, which predominates during the first part of the night, is more likely to cause daytime sleepiness than sleep disruption later at night [32].

It was expected that, given its improved PK profile, the new tamsulosin OCAS tablet would provide a better relief of nocturia and a better QoS and QoL (Fig. 2). Indeed, tamsulosin OCAS 0.4 mg improved nocturia and QoL significantly more than placebo (p = 0.028 and p = 0.0087, respectively) and there was a trend towards an increase in the HUS. In
addition, the investigators found a significant relation between the reduction in the number of nocturnal voids on the one hand and the increase in the HUS and the improvement in QoL on the other (Spearman coefficient -0.63 and -0.64, respectively). These findings suggest that improving nocturia can lead to an improved QoS and overall feeling of well-being.

5. Conclusions

Nocturia has long been an underestimated symptom of BPH. Only recently, have urologists recognised the great potential impact of nocturia on the patient’s and his partner’s daily performance and QoL. Unfortunately, currently available treatments are not specifically designed to treat nighttime symptoms of BPH. Most oral drug delivery systems are dependent on the presence of water for drug release, but this is only scarcely available in the colon. The new tamsulosin OCAS tablet formulation is designed to provide a continued release of tamsulosin throughout the entire GI tract, including the colon. This allows a consistent and continued concentration of tamsulosin over a 24-h period.

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References


