Nocturia and Tamsulosin OCAS

Philip Van Kerrebroeck*

University Hospital Maastricht, Department of Urology, P. Debyelaan 25, 6202 AZ Maastricht, The Netherlands

1. Introduction

In its latest standardisation report, the International Continence Society (ICS) defined nocturia as “the complaint that an individual has to wake at night one or more times to void, with each void preceded and followed by sleep” [1]. There is still some debate among this definition because it does not consider the number of nocturnal voids, which implies that, although many people may consider one voiding episode per night to be normal, they are still diagnosed with nocturia [2]. A recent study evaluated nocturia and several health parameters of about 3000 elderly men aged 55–75 yr visiting general practitioners in Maastricht [3]. Evaluation of the prevalence of nocturia in this population revealed that as much as 78.7% of the participants responded to the ICS definition of nocturia, including 45.8% with one...
nocturnal void and 32.9% with two nocturnal voids. A recently published population-based survey among 19,165 men and women ≥18 yr in five countries showed that nocturia is the most prevalent lower urinary tract symptom (LUTS), with 48.6% of men responding to the ICS definition of nocturia [4].

It is well documented that the prevalence of nocturia increases with age [5]. However, a telephone survey of 1271 Dutch men conducted in 2001 revealed that even in younger age groups (18–34 and 35–54 yr), one voiding episode per night is quite common, affecting 15% and 29% of men, respectively. Two percent of the men aged 18–34 yr and 5% of those within the age category of 35–54 yr even had at least two nocturnal voids.

2. Benign prostatic hyperplasia and nocturia

In view of the bothersomeness of nocturia and its impact on QoS and QoL, proper treatment is warranted. Nocturia may be the expression of various disorders, but the most common cause of nocturia in elderly men is benign prostatic hyperplasia (BPH). In BPH patients, nocturia is usually due to a low bladder capacity caused by a high postvoid residual volume and/or detrusor overactivity. Besides nocturia, typical complaints of patients with LUTS suggestive of BPH (LUTS/BPH) are urgency, daytime frequency, obstruction, pain, and terminal dribbling. A quantitative market research study conducted in 2003 among 150 general practitioners and 150 urologists revealed that nocturia is the most bothersome LUTS of BPH (data on file). More than 60% of the respondents selected nocturia as the most bothersome symptom, and an additional 15% considered it as the second most bothersome symptom of BPH.

3. Consequences of nocturia

Obviously, frequent nocturnal awakenings can have a profound impact on a patient’s quality of sleep (QoS). Indeed, a survey conducted among male and female residents ≥50 yr in The Netherlands revealed that nocturia is the most common cause of disturbed sleep among the 705 male participants of the survey [6].

During a closed expert meeting in Marbella, urologists were questioned on their opinion on different aspects of nocturia secondary to BPH. Interactive voting revealed that 66% of the participating urologists agreed that sleep disturbance is the major reason why nocturia is so bothersome. Another 24% more or less agreed with this statement (Fig. 1).

Sleep studies have shown that sleep is not a uniform state, but rather a succession of cycles of deep and shallow sleep [7,8]. Periods of rapid eye movement sleep (REM sleep) alternate with periods of non-REM sleep. REM sleep is characterised by a high activity of the brain and is thought to contribute to an individual’s psychological and emotional well-being and rebolstering of the memory [8]. A person usually has about four to five periods of REM sleep, which are quite short at the beginning of the night and longer at the end. Non-REM sleep is composed of four different stages. Many of the restorative functions of sleep occur during stages three and four of non-REM sleep, also referred to as slow-wave sleep (SWS) or deep sleep. SWS predominates in the first 3–4 h of sleep and gradually shortens when sleep continues. One will typically feel more groggy when awoken during SWS, and mental performance is somewhat impaired relative to awakenings from other stages [9,10]. Therefore, sleep disturbance during the first part of sleep should be avoided as much as possible. Recently the hours of undisturbed sleep (HUS), or the time from falling asleep until the first wakening to void, have been suggested as a measure for QoS [11]. It was suggested that not only the frequency of nocturnal awakenings but also the length of the HUS determines an individual’s QoS and daytime performance. According to this theory, HUS should be at least 3 h to ensure a good night’s sleep and to prevent a person from feeling weary during the following day [12]. Interrogation of the audience at the closed meeting in Marbella revealed that 63% of the attending urologists agreed, and 30% more or less agreed with the statement that nocturia is the most bothersome urinary symptom because it affects quality of sleep (Fig. 2). In addition, 45%
agreed and 36% more or less agreed that HUS should be a key parameter for evaluating the effects of LUTS/BPH treatment on sleep (Fig. 3). According to 69% of the urologists, LUTS/BPH treatment should be evaluated for their effects on QoS and QoL (Fig. 4).

4. Tamsulosin oral controlled absorption system

Most currently available $\alpha_1$-adrenoceptor (AR) antagonist formulations rely on the presence of water for drug release. As the colon is practically devoid of water, drug release is essentially limited to the upper gastrointestinal (GI) tract (ie, stomach and small intestine). Consequently, these formulations have a rather high peak/trough plasma concentration and do not produce consistent drug levels over a 24-h period. Moreover, the pharmacokinetics (PK) of these formulations is usually food-dependent, giving a higher maximum plasma concentration ($C_{\text{max}}$) when taken under fasting conditions than under fed conditions [13].

To overcome the limitations of the classic $\alpha_1$-AR antagonist formulations, a prolonged release tablet formulation of tamsulosin was recently developed. The tamsulosin tablet is based on the oral controlled absorption system (OCAS) technology, which consists of a gel-forming and a gel-enhancing component. The advanced gel layer of the tablet has the ability to rapidly absorb water during its passage through the stomach and the small intestine, attaining complete hydration by the time the tablet reaches the colon. The water that is stored in the gel layer allows continued drug release in the colon. Convincing evidence for continued release from the tablet in the colon comes from a recent study combining $\gamma$-scintigraphy and PK analysis [14]. Radiolabeled tamsulosin OCAS tablets were given to eight healthy volunteers, and the transit of the tablet throughout the GI tract and release from the tablet core were monitored by means of $\gamma$-scintigraphy. In addition, blood samples for PK analysis were taken at regular time points after dosing. The scintigraphic images indeed showed persistent drug release in the colon. Individual PK profiles varied considerably between subjects, but these variations did not considerably affect the time and site of drug release from the tablet. Tamsulosin OCAS showed a favourable PK profile with a low $C_{\text{max}}$ and a continuous 24-h plasma concentration, independent of food intake [14,15]. Safety analysis showed that tamsulosin OCAS is associated with a slightly lower risk of the most commonly reported treat-
ment-emergent adverse events (dizziness and abnormal ejaculation) than the conventional modified release formulation of tamsulosin [16].

5. Tamsulosin OCAS and nocturia

The improved PK profile of tamsulosin OCAS was believed to result in a low risk of peak-associated adverse events and a good control of day- and nighttime symptoms of BPH. The latter was tested in a randomised, double-blind, placebo-controlled, 8-wk proof-of-concept study including 117 patients with LUTS/BPH and at least two voids per night [17]. The objective of this pilot study was to evaluate the role of HUS as a novel tool for assessing the impact of treating nocturia on QoS and to measure the impact of tamsulosin OCAS on nocturia, sleep, and QoL. After a run-in period of 2 wk, the patients were randomised to either placebo (N = 56) or tamsulosin OCAS 0.4 mg once daily (N = 61) for 8 wk. The increase from baseline to end point in the mean HUS was 60 min for placebo and 80 min for tamsulosin OCAS (analysis of covariance, p = 0.198). Tamsulosin OCAS reduced the number of nocturnal voids and the nocturia questions of the International Prostate Symptom Score (IPSS) significantly more than placebo (p = 0.099 and p = 0.028, respectively) (Fig. 5). Tamsulosin OCAS also significantly improved the IPSS QoL versus placebo (p = 0.0087). Correlation analysis showed a correlation between the reduction of nocturnal voids and the HUS (Spearman coefficient = −0.63) and between the reduction of the IPSS nocturia and the improvement in IPSS QoL (Spearman coefficient = 0.64), suggesting that an improvement of nocturia indeed increases the HUS, which may lead to a better QoL.

6. Conclusions

Nocturia is one of the most bothersome symptoms of LUTS/BPH and the major cause of sleep disruption in the elderly. Therefore, treatments for LUTS/BPH should be evaluated for their impact on QoS and QoL. As the first 3–4 h of sleep are critical for feeling refreshed and lucid during the next day, the HUS may be an appropriate tool for measuring the impact of treatment on QoS and QoL.

The new tablet formulation of tamsulosin uses the advanced OCAS technology to achieve drug release throughout the entire GI tract, including the colon. Because of its favourable PK profile, with a consistent and continuous 24-h plasma concentration, tamsulosin OCAS was believed to provide a good relief of nocturia, an increase in the HUS, and a better QoL than placebo.

Conflicts of interests

The author has nothing to disclose.

References


