Effect of Imidafenacin before Sleeping on Nocturia

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Objectives: Clinical efficacy, influence on quality of life (QOL), and safety of imidafenacin before sleeping were assessed in patients with overactive bladder (OAB) who suffered from nocturia.

Methods: A total of 60 OAB patients with a mean age of 74 years (45 men and 15 women) who mainly complained of nocturia were enrolled. Imidafenacin (0.1 mg) was administered once daily before sleeping for four weeks. Then the patients were divided into two groups, “a stable-dose group” with sufficient efficacy who remained on 0.1 mg of imidafenacin daily, and “a dose-escalation group” with insufficient efficacy in whom the daily dose of imidafenacin was increased to 0.2 mg before sleeping. Lower urinary tract symptoms and postvoid residual volume (PVR) were examined before treatment and after 4 and 8 weeks of imidafenacin therapy.

Results: In the stable-dose group, nighttime frequency decreased significantly from 3.4 ± 1.1 to 2.3 ± 1.1 and 2.6 ± 2.0 times after four and eight weeks, respectively. In the dose-escalation group, nighttime frequency did not change significantly (from 3.8 ± 1.5 to 3.6 ± 1.8 times) at four weeks, but decreased significantly to 2.8 ± 1.4 times at eight weeks. Daytime frequency, OAB symptom score, and IPSS-QOL index score were significantly improved in both groups at four and/or eight weeks. There was no increase of PVR and no serious adverse events.

Conclusion: Administration of imidafenacin at 0.1–0.2 mg once daily before sleeping was safe and effective for the treatment of OAB with the main symptom of nocturia.

Key words anticholinergic agent, imidafenacin, nocturia, overactive bladder

1. INTRODUCTION

Nocturia is one of the most common urinary symptoms in adults and has a significant impact on both sleep and quality of life (QOL).1–4 According to the definition of the International Continence Society, nocturia is the complaint that an individual wakes one or more times to void urine at night.1 Nocturia is one of the symptoms of an overactive bladder (OAB), being part of a group of storage symptoms that include urgency, frequency and nocturia, with or without urge incontinence.5 The first-line treatment for nocturia without nocturnal polyuria is usually an anticholinergic agent in females and an α1-adrenergic receptor antagonist in males. When α1-adrenergic receptor antagonist therapy shows insufficient efficacy in males, an anticholinergic agent is added. However, the adverse events associated with anticholinergic agents, such as urinary retention, dry mouth and constipation, can prevent the effective treatment of nocturia.6 Imidafenacin is characterized by selective affinity for certain muscarinic receptor subtypes and shows a high affinity for M1 and M3 receptors. It is thought to act by blocking not only M3 receptors on the detrusor muscle of the urinary bladder, but also M1 receptors on the cholinergic nerve terminals, thus reducing acetylcholine release and inhibiting bladder activity.6–8 Imidafenacin is rapidly absorbed, with a maximum plasma concentration at 1.3 h after oral administration and an elimination half-life of approximately 3 h.7 So a dose of 0.1–0.2 mg is administered twice daily for OAB. Therefore, administration of a single dose of imidafenacin before sleeping was thought likely to be effective for the treatment of nocturia. In this study, the efficacy and safety of imidafenacin at a dose of 0.1–0.2 mg before sleeping was evaluated.

2. METHODS

OAB patients with a chief complaint of nocturia were enrolled in this study from July 2010 to March 2011.
Inclusion criteria were as follows: (i) nighttime frequency for urination ≥ 2 times from 1 month or more before enrollment; (ii) an Overactive Bladder Symptom Score (OABSS) ≥ 3 or a score of 2 in patients strongly requesting treatment for OAB; and (iii) a postvoid residual volume (PVR) ≤ 50 mL. Patients with a history of conditions that could possibly affect lower urinary tract function were excluded from this study, including a history of clinically significant bladder outlet obstruction, polyuria (daily urine volume over body weight [kg] × 40 mL), symptomatic urinary tract infection, urethral catheterization, and a prior response to electrostimulation therapy or bladder training. Concomitant treatment with anticholinergic or cholinergic drugs was not permitted during the study.

Patients were given imidafenacin at a dose of 0.1 mg once daily before sleeping for four weeks, and then were divided into two groups. These were a “stable-dose group” with sufficient efficacy who remained on 0.1 mg of imidafenacin before sleeping and a “dose-escalation group” with insufficient efficacy in whom the dose of imidafenacin was increased to 0.2 mg before sleeping (Fig. 1). Administration of imidafenacin was done for eight weeks in total. The frequency of daytime and nighttime urination, OABSS, International Prostatic Symptom Score questionnaire (IPSS) and IPSS-QOL index score (QOL score) were evaluated and PVR was measured by trans abdominal ultrasonography before starting treatment, as well as after four and eight weeks of imidafenacin therapy. Patients with a QOL score ≥ 3 and those with a QOL score of 2 who wished to increase the imidafenacin dosage at four weeks were considered to have “insufficient efficacy” of the 0.1 mg dose.

Results are expressed as mean ± standard deviation (SD). Statistical comparisons of data obtained before and after treatment and between the groups were performed by Wilcoxon signed–rank test and Mann–Whitney U-test, respectively, with \( P < 0.05 \) being considered statistically significant.

3. RESULTS

Of the 67 patients enrolled in the study, seven did not return to hospital. Therefore, efficacy was evaluated in 60 patients aged 52–87 years (mean: 74 years), including 45 men and 15 women. Twenty-four patients (including all of the female patients) had no history of previous treatment for micturition disorders, while 36 male patients had received previous treatment with \( \alpha_1 \)-adrenergic receptor

![Study design](image)

Fig. 1. Study design. Imidafenacin (0.1 mg) was administered before sleeping for four weeks. Then the patients were divided into two groups: a “stable-dose group” with sufficient efficacy who remained on 0.1 mg of imidafenacin and a “dose-escalation group” with insufficient efficacy who received an increased dose of 0.2 mg before sleeping. Patients with a quality of life (QOL) score of 3 or with a QOL score of 2 who wished to escalate the dose at four weeks were considered to show “insufficient efficacy” of imidafenacin at 0.1 mg. The number of daytime and nighttime, Overactive Bladder Symptom Score (OABSS), International Prostate Symptom Score (IPSS), QOL score, clinical improvement, and postvoid residual volume (PVR) were evaluated before starting treatment, as well as after four and eight weeks of imidafenacin therapy.
Table 1. Characteristics of all 60 patients, the stable-dose group, and the dose-escalation group

<table>
<thead>
<tr>
<th>Associated disease (no.)</th>
<th>All (n = 60)</th>
<th>Stable-dose (n = 25)</th>
<th>Dose-escalation (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>40</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Asthma</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

antagonists, including naftopilid at 50 or 75 mg/day (n = 25), tamsulosin at 0.2 mg/day (n = 4), silodosin at 4 or 8 mg/day (n = 6), urapidil at 30 mg/day (n = 1), or phytotherapeutic agents such as cernitin pollen extract (n = 5) or eviprostat (n = 2). Associated diseases were benign prostatic hyperplasia in 40 patients, hypertension in 20 patients, diabetes mellitus in 7 patients, hyperlipidemia in 3 patients, and asthma in 2 patients. The stable-dose group included 35 patients aged 52–86 years (mean: 74 years; 29 males and 6 females), among whom 16 patients had a QOL score of 3 at 4 weeks. The dose-escalation group included 21 patients aged 60–87 years (mean: 75 years; 12 males and 9 females) (Table 1).

In the stable-dose group, the nighttime frequency decreased significantly from 3.4 ± 1.1 to 2.3 ± 1.1 times (P < 0.001) and then to 2.6 ± 2.0 times (P = 0.004) at four and eight weeks, respectively (Fig. 2). In the dose-escalation group, the nighttime frequency was unchanged at four weeks (3.8 ± 1.5 versus 3.6 ± 1.8 times), but was significantly (P = 0.001) decreased to 2.8 ± 1.4 times at eight weeks. There was a significant difference (P = 0.002) in the nighttime frequency between the two groups at four weeks, but not at eight weeks. In both groups combined, nighttime frequency showed a significant (P < 0.001) decrease from 3.5 ± 1.3 to 2.8 ± 1.5 times and then to 2.7 ± 1.8 times at four and eight weeks, respectively. Daytime frequency also decreased significantly (P = 0.019) from 8.6 ± 2.4 to 8.3 ± 2.1 times at four weeks in the stable-dose group. Daytime + nighttime frequency showed significant decrease from 12.0 ± 2.6 to 10.6 ± 2.5 times at four weeks (P < 0.001) and to 10.8 ± 3.8 times at eight weeks (P = 0.004) in the stable-dose group and from 14.0 ± 4.9 to 11.7 ± 3.6 times at eight weeks (P = 0.004) in the dose-escalation group. There was a significant difference (P = 0.018) of daytime + nighttime frequency between the two groups at 4 weeks, but not at 8 weeks.

Assessment with the OABSS showed that symptoms of “nighttime frequency”, “urgency”, and “urge incontinence” were significantly improved at four and/or eight weeks in both groups, while “daytime frequency” was significantly improved (P = 0.049) at eight weeks, in the dose-escalation group (Fig. 3). The total OABSS improved significantly from 6.7 ± 1.9 to 4.6 ± 2.0 at four weeks (P < 0.001) and to 4.6 ± 3.0 at eight weeks (P < 0.001) in the stable-dose group, while it improved from 7.8 ± 2.4 to 6.8 ± 2.9 at four weeks (P = 0.026) and to 5.9 ± 2.8 at eight weeks (P = 0.001) in the dose-escalation group. There were significant differences of “nighttime frequency”, “urge incontinence”, and “total OABSS” between the two groups at four weeks, but not at eight weeks.

Assessment with the IPSS showed that “frequency”, “urgency”, and “nocturia” were significantly improved in both groups at four and/or eight weeks (Fig. 4). The total IPSS also improved significantly from 12.9 ± 4.7 to 10.3 ± 4.8 at four weeks (P < 0.001) and to 11.0 ± 6.8 at eight weeks (P = 0.016) in the stable-dose group, while it improved from 15.1 ± 5.3 to 12.2 ± 5.2 at eight weeks (P < 0.001) in the dose-escalation group. There were significant differences between the two groups with respect to “frequency”, “urgency”, “nocturia”, and “total IPSS” at four weeks, but not at eight weeks. The QOL index improved significantly from 5.1 ± 0.7 to 3.3 ± 1.1 at four weeks (P < 0.001) and to 3.2 ± 1.6 at eight weeks (P < 0.001) in the stable-dose group, while it improved
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Fig. 3 Overactive Bladder Symptom Score (OABSS) before and after administration of imidafenacin in the stable-dose group (dotted line) and dose-escalation group (solid line). Data are expressed as mean ± SD. Wilcoxon signed–rank test: before versus four or eight weeks, #P < 0.05, ##P < 0.01, ### P < 0.001. Mann–Whitney U-test: stable-dose group versus dose-escalation group, *P < 0.05; **P < 0.01.

from 5.2 ± 0.6 to 4.5 ± 0.9 at four weeks (P = 0.003) and to 3.7 ± 1.2 at eight weeks (P < 0.001) in the dose-escalation group. The improvement was more marked in the stable-dose group, and there were significant differences between the two groups at four and eight weeks.

In all patients, PVR did not increase significantly, being 6 ± 11 mL at baseline versus 5 ± 11 mL and 9 ± 20 mL at four and eight weeks, respectively, and there were no significant differences of PVR between the two groups. Adverse events were observed in six patients (10%), including one from the stable-dose group and five from the dose-escalation group. The symptoms were dry mouth (n = 1) and weak urine stream (n = 1) at four weeks, and dry mouth (n = 2), constipation (n = 1), and weak stream (n = 1) at eight weeks. None of these events were serious and resolved promptly after discontinuing imidafenacin. Five patients discontinued treatment, including three patients with lack of efficacy at four weeks and two patients with a weak urine stream at four and eight weeks.

4. DISCUSSION

Imidafenacin (0.1–0.2 mg before sleeping) significantly decreased the number of nighttime frequency from 3.5 ± 1.3 to 2.8 ± 1.5 times (20% decrease) at four weeks and to 2.7 ± 1.8 times (23% decrease) at eight weeks in the 60 patients investigated in this study. OABSS and IPSS parameters showed a significant difference between the stable-dose and dose-escalation groups at four weeks. It was reported that administration of imidafenacin at 0.2 mg twice daily for eight weeks decreased nighttime frequency by 20–24%.13,14 Therefore, the effect of imidafenacin at 0.1–0.2 mg before sleeping on nocturia was similar to that of this drug at 0.2 mg twice daily. In addition, this study showed that if the effect of imidafenacin at 0.1 mg before sleeping is insufficient, increasing the dose to 0.2 mg before sleeping may be effective. As one of the limitations in this study, stable-dose group included male patients with medication with α₁-adrenergic receptor antagonists. The efficacies of combining of α₁-adrenergic receptor antagonists and antimuscarinic agents to treat benign prostatic hyperplasia have been reported.15,16 We could not deny the possibility of the synergic effects of α₁-adrenergic receptor antagonists and imidafenacin.

Imidafenacin decreased the number of daytime frequency. The following mechanisms can be considered in this regard. A decrease of bladder capacity is thought
to be one of the causes of nocturia.\textsuperscript{17} It is possible that administration of imidafenacin before sleeping increases the nighttime capacity of the bladder, and that this in turn improves urine collection during the daytime. Investigation of symptoms related to insomnia has shown that nocturia contributes strongly to abnormal sleep compared with other factors.\textsuperscript{18} Imidafenacin prolongs the hours of undisturbed sleep (the first awakening for urination), and this may improve a patient’s satisfaction with sleep.\textsuperscript{13,14} Control of nocturia leads to improvement of QOL, and may also improve daytime activities and decrease daytime frequency, urgency, and urge incontinence. In the present study, the change of daily or nocturnal urine volume before and after administration of imidafenacin could not be investigated as there were very few examples of voiding diary after administration. However, the increase of bladder capacity at night and/or improvement of QOL after administration of imidafenacin once before sleeping may be related to an effect on collecting function during both daytime and nighttime.

Imidafenacin shows high selectivity for the bladder, which should improve its safety. Administration of oxybutynin hydrochloride or flavoxate hydrochloride once a day before sleeping decreased nocturia without severe adverse events.\textsuperscript{19,20} In the present study, six patients experienced adverse events (dry mouth, weak urine stream, and constipation), but these all resolved promptly after they discontinued imidafenacin. It was reported that the prevalence of adverse events during administration of imidafenacin at 0.1–0.2 mg twice daily was 7–14\%,\textsuperscript{13,14} which is comparable to the present result of 10\%. In the present study, there was no increase of postvoiding residual urine and no serious adverse events. Therefore, administration of imidafenacin at 0.1–0.2 mg before sleeping is safe.

In conclusion, administration of imidafenacin (0.1 mg before sleeping) was safe and effective for nocturia in OAB patients. If the effect of 0.1 mg before sleeping was insufficient, an increase of the dose to 0.2 mg before sleeping was also safe and could improve the response of nocturia.

**Disclosure**

Nothing to disclose.

**REFERENCES**