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Effectiveness of a nonsteroidal anti-inflammatory drug for nocturia on patients with benign prostatic hyperplasia: a prospective non-randomized study of loxoprofen sodium 60 mg once daily before sleeping.

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Abstract

We explored the effectiveness of loxoprofen sodium (loxoprofen), which is the most common non-steroidal anti-inflammatory drug (NSAID) in Japan, for patients with benign prostatic hyperplasia (BPH) complaining of nocturia. A total of 93 BPH patients aged 49-84 years were enrolled in the study. These patients had received standard drug therapy with alpha1-blocker for BPH, followed by anticholinergic drugs, hypnotics, tricyclic antidepressants, and/or antiduretic hormone, but they still complained about 2 or more episodes of nocturia. They each took a single 60-mg tablet of loxoprofen prior to sleeping at night for 14 days in addition to their BPH treatments. The effects were assessed by questionnaire before and after treatment as excellent (nocturia disappeared or decreased by 2 or more voids/night), improved (nocturia decreased by 1 void/night), unchanged, or worsened (nocturia increased). Nocturia improved or disappeared in 74.2% of patients: excellent, improved, unchanged, and worsened results were obtained in 37.6%, 36.6%, 21.5%, and 4.3% of patients, respectively. The effects were better in patients whose baseline nocturia was $>$ 2 times than in those with a lesser frequency at enrollment (P = 0.04). Loxoprofen can be an effective and useful treatment option for patients with BPH complaining of refractory nocturia.

KEYWORDS: nocturia, loxoprofen sodium, non-steroidal anti-inflammatory drugs (NSAIDs)

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Original Article

Effectiveness of a Nonsteroidal Anti-inflammatory Drug for Nocturia on Patients with Benign Prostatic Hyperplasia: A Prospective Non-Randomized Study of Loxoprofen Sodium 60 mg Once Daily before Sleeping

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We explored the effectiveness of loxoprofen sodium (loxoprofen), which is the most common non-steroidal anti-inflammatory drug (NSAID) in Japan, for patients with benign prostatic hyperplasia (BPH) complaining of nocturia. A total of 93 BPH patients aged 49-84 years were enrolled in the study. These patients had received standard drug therapy with α1-blocker for BPH, followed by anticholinergic drugs, hypnotics, tricyclic antidepressants, and/or antiduretic hormone, but they still complained about 2 or more episodes of nocturia. They each took a single 60-mg tablet of loxoprofen prior to sleeping at night for 14 days in addition to their BPH treatments. The effects were assessed by questionnaire before and after treatment as excellent (nocturia disappeared or decreased by 2 or more voids/night), improved (nocturia decreased by 1 void/night), unchanged, or worsened (nocturia increased). Nocturia improved or disappeared in 74.2% of patients: excellent, improved, unchanged, and worsened results were obtained in 37.6%, 36.6%, 21.5%, and 4.3% of patients, respectively. The effects were better in patients whose baseline nocturia was > 2 times than in those with a lesser frequency at enrollment ($P = 0.04$). Loxoprofen can be an effective and useful treatment option for patients with BPH complaining of refractory nocturia.

Key words: nocturia, loxoprofen sodium, non-steroidal anti-inflammatory drugs (NSAIDs)

Lower urinary tract symptoms (LUTS) are becoming a major health problem for elderly people. Nocturia, a cause of insufficient sleep and thus impaired quality of life, is one of the main problems in LUTS along with urinary incontinence and difficulty in urination. The etiology of nocturia is various, being complex and obscure in many patients, although LUTS, insomnia, and nocturnal polyuria due to cardiovascular or renal hypofunction and disorders of the central nervous system (CNS) may be among the causes [1]. Nocturia is a well-recognized symptom of benign prostatic hyperplasia (BPH), which is commonly treated by α1 blockers or/and 5α-reductase inhibitors. However, the effectiveness of these drugs for nocturia is reported to be only 25-39 % [2].

Prostaglandins (PGs) have various effects on the kidney, urinary bladder, urethra, and sympathetic nervous system [3]. In particular, PGE and PGF increase the tone of the detrusor muscle and enhance micturition [4]. Al-Waili reported that indomethacin suppositories (a

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potent PGs synthesis inhibitor) reduced the frequency of voiding and decreased the urine volume in enuresis [5]. Recently, we experienced by chance a patient being treated for BPH in whom nocturia suddenly decreased from a usual 4 voids to one void/night when he took a 60-mg tablet of loxoprofen prescribed for his shoulder pain.

In this study, we explored the effectiveness of loxoprofen, a prodrug in the class of short-acting nonsteroidal anti-inflammatory drugs (NSAIDs) usually prescribed at a dosage of 60 mg t.i.d. for the management of pain, in patients with BPH complaining of nocturia.

Materials and Methods

Between January 2001 and December 2001, 93 consecutive BPH patients with 2 or more voids per night (estimated prostatic volume >20 g using transrectal ultrasonography) aged 49–84 (mean 69.8) years were enrolled in the study. The International Prostate Symptom Score (IPSS) score of 8 or more was required for study entry. Although α1-blockers were prescribed initially for 2 or 3 months, study patients' incidence of nocturia remained 2 or more voids per night. Moreover, anticholinergic drugs, hypnotics, tricyclic antidepressants, and/or antidiuretic hormome were prescribed for at least 1 month. Some patients received 2 or 3 kinds of medications at the same time. However, the number of nocturia incidences did not change after administration of these medications and they still had 2 or greater voids per night. Patients who had asthma, gastrointestinal disorders, renal dysfunction, or allergies to NSAIDs were excluded. Written informed consent was obtained from the patients to participate in this study.

Beginning on the day when we judged that the effect of standard medications was not sufficient, patients took a single 60-mg loxoprofen tablet prior to sleeping at night for 14 days in addition to their BPH treatments. The main outcome measure was occurrences of nocturia, which was defined as the score on the IPSS nocturia question before and after treatment as either excellent (nocturia disappeared or decreased by 2 or more voids/night), improved (nocturia decreased by 1 void/night), unchanged or worsened (nocturia increased). Statistical analysis was performed using Fisher's exact test with $P<0.05$ considered significant.

Results

Nocturia improved or disappeared in 74.2% of the patients overall: excellent, improved, unchanged and worsened results were obtained in 37.6%, 36.6%, 21.5% and 4.3% of patients, respectively (Table 1).

We analyzed the effect of loxoprofen on the basis of the frequency of nocturia at baseline (Table 1). The effects were better in patients whose baseline frequency was >2 voids/night than in those with less-frequent nocturia: when the patients were divided into 2 groups, 31 with 2 episodes of nocturia and 62 with more frequent nocturia, the excellent responder rates were 22.6% and 45.2% in each, respectively ($P=0.04$, Fisher's exact test). The excellent responder rates were slightly reduced with increased age of the patients: excellent responses were observed in 46.3% of patients aged 49–69 years, 35.9% in those aged 70–79 years, and 15.4% in those aged 80–84 years (Table 2). However, there was no significant difference among the age groups. The mean number of nocturia occurrences in those aged 49–69 years, 70–79 years, and 80–84 years were 2.77, 3.05, and 3.30, respectively. There was a significant difference in the occurrence rate between participants aged 49–69

Table 1 Effects of loxoprofen *vs*. frequency of nocturia at baseline

Frequency at Baseline	No. of Patients	Excellent	Improved	Unchanged	Worsened
2	31	7*(22.6%)	12 (38.7%)	11 (35.5%)	1 (3.2%)
$2<\leqq 3$	29	14 (48.3%)	12 (41.4%)	3 (10.3%)	0 (0 %)
$3>$	33	14 (42.4%)	10 (30.3%)	6 (18.2%)	3 (9.1%)
Total	93	35 (37.6%)	34 (36.6%)	20 (21.5%)	4 (4.3%)

*The percentage of patients showing excellent response was significantly lower than in the other frequency-at-baseline groups ($P=0.04$, Fisher's exact test).

Table 2 Efficacy of loxoprofen on nocturia with patients' age distribution

Age	No. of Patients	Excellent	Improved	Unchanged	Worsened
49–69	41	19 (46.3%)	12 (29.3%)	8 (19.5%)	2 (4.9%)
70–79	39	14 (35.9%)	15 (38.5%)	10 (25.6%)	0 (0 %)
80–84	13	2 (15.4%)	7 (53.8%)	2 (15.4%)	2 (15.4%)

years and those aged 80–84 years ($P = 0.017$). Table 3 shows the effects of loxoprofen in patients who did not respond to previous treatments for nocturia concurrently with therapy for BPH. Since these patients had bladder outlet obstruction (BOO), anticholinergic drugs or tricyclic antidepressants such as 2 mg oxybutynin or 10 mg imipramin had been administered prior to sleeping. In 32 patients who did not respond to anticholinergic drugs, the excellent and improved rates of loxoprofen were 44% and 38%, respectively, and the rates were 39% and 37%, respectively, in 76 non-responders to tricyclic antidepressants. In 42 patients who did not respond to hypnotics, the excellent and improved rates following loxoprofen therapy were 31% and 38%, respectively. However, excellent effects were obtained in only one of nine patients who were previously refractory to antidiuretic hormone (desmopressin acetate, administered as a nasal drop).

Adverse events. Adverse events were reported by 10 patients (10.7%) (Table 4). Gastric discomfort was the most common, occurring in 6 patients (6.4%). Closed throat sensation, leg edema, urinary frequency in the morning after drug administration, decreased urine volume during the night and weak urinary stream were seen in one patient each. All adverse events disappeared after discontinuing loxoprofen.

Discussion

The etiology of nocturia is still obscure in many patients. It appears that there are many factors involved, including pathologic conditions such as cardiovascular disease, diabetes mellitus, lower urinary tract obstruction, sleep disorders, and environmental factors [6]. Nocturia may be attributed to nocturnal polyuria and /or diminished nocturnal bladder capacity. Anticholinergic drugs, hypnotics, and antidiuretic hormone, either alone or in combination, are usually administered for nocturia in addition to treatments for BPH. In the present study, nocturia either improved or disappeared in 74.2% of patients following loxoprofen treatments. Considering their nocturia did not improve sufficiently after α1-blockers, anticholinergic drugs, antiduretic hormone, and/or hypnotics, the effectiveness of loxoprofen is highly encouraging.

Why is loxoprofen effective in reducing nocturia? Al-Waili reported that in an open trial a 100-mg indomethacin suppository improved nocturia in all 15 patients [7]. With regard to loxoprofen, inhibition of prostanoids (PGs) synthesis via the inhibition of cyclooxygenase may play a role in its effects on nocturia. It remains unknown which subtype of cyclooxygenase (COX) inhibitor was effective against nocturia, although Yokoyama *et al.* reported that a COX-2 inhibitor might play a more important role in inhibiting an overactive bladder than a COX-1 inhibitor experimentally [8]. There are 4 possible sites where loxoprofen's action may occur: by reducing urine volume produced at the kidney; by affecting urinary sensation at the bladder; increasing the threshold of urinary sensation at the CNS, including afferent and efferent neuro-pathways between the CNS and bladder; or by affecting sleep at the brain. PGs contribute to urine production in the kidney, and NSAIDs suppress urine production by decreasing glomerular blood flow, particularly in the impaired kidney [9]. PGE_2, $PGF_{2\alpha}$, PGE_1 and thromboxane A_2 cause contraction of the isolated detrusor muscle of the human

Table 3 Efficacy of loxoprofen among non-responders to previous treatments for nocturia

Previous Treatments	No. of Patients	Excellent	Improved	Unchanged	Worsened
Anticholinergics*	32	14 (44 %)	12 (38 %)	6 (19 %)	1 (3%)
TCA†	76	30 (39 %)	28 (37 %)	17 (22 %)	4 (5%)
Hypnotics$^+$	42	13 (31 %)	16 (38 %)	11 (26 %)	2 (5%)
Antidiuretic hormone‡	9	1 (11.1%)	5 (55.6%)	3 (33.3%)	0 (0%)

*, Non-responders to 2 mg oxybutynin hydrochloride or 10 mg propiverine hydrochloride administered before sleeping. No patients took both medications simultaneously. However, some patients received each medication at different time. †, Non-responders to 10 mg imipramine hydrochloride or 10 mg amitriptyline hydrochloride administered before sleeping. No patients took both medications simultaneously. However, some patients received each medication at different time. TCA, tricyclic antidepressants. ‡, Non-responders to desmopressin acetate, nasal drop. $^+$, Non-responders to hypnotics: zolpidem tartrate.

Table 4 Adverse events following administration of loxoprofen for nocturia

Adverse Event	No. of patients
Gastric discomfort	6 (6.5%)
Closed throat sensation	1
Leg edema	1
Frequent urination in mornings following administration	1
Decrease of urine volume and weak urinary stream during the night	1

bladder [10, 11]. NSAIDs have sedative actions on irritable symptoms caused by cystitis or following lower urinary tract surgery [12, 13] and beneficial effects of these drugs have also been demonstrated in bladder instability without inflammation; however, side effects have limited their clinical use for the latter indication [14–17]. Recently, it has been suggested that an important physiologic role of PGs on bladder function might be sensitization of the sensory nerves [18] and that PGs may indirectly affect bladder activity via effects on neurotransmission as neurotransmitters/modulators [18–20]. Accordingly, it is suspected that loxoprofen might improve nocturia by increasing the threshold of urinary sensation in the CNS via the suppression of afferent and/or efferent nerve pathways. The NSAIDs indomethacin and diclofenac suppository have also been reported effective in the treatment of nocturnal enuresis [21, 22]. The levels of PGD_2 and PGE_2 in the brain have been shown to relate to the sleep-wake cycle [23, 24]. Administration of NSAIDs in suppository formulations is usually effective in providing good sleep for patients. In this study, patients whose nocturia improved generally reported noticeable improvements in their quality of life through having sound sleep. Even in the unchanged group, some patients reported sleeping better than they did prior to treatment because the time to first voiding was delayed by several hours (data not shown). These findings suggest that the effects of loxoprofen might help provide more restful sleep.

Although the patients' PG levels were not measured in this study, it seems likely from the results that the 4 mechanisms discussed above are complexly involved in each individual patient. Further investigations are necessary to substantiate these suggestions.

Adverse events caused by loxoprofen are less frequent than those associated with other NSAIDs because loxoprofen is a prodrug in the family of short-acting NSAIDs. However, it should be kept in mind that many patients with nocturia are elderly and may have a low threshold for the development of gastrointestinal ulcer and renal dysfunction, 2 well-known adverse events associated with long-term administration of NSAIDs [9, 25, 26]. Adverse events such as edema or respiratory distress suggest decreases in urine production in the kidney. In our study, one patient complained of edema after treatment. In the present study, patients received only 60 mg of loxoprofen q.d.; the usual dosage prescribed in Japan for the management of pain is 60 mg 3 times daily. Nevertheless, the authors recommend that older patients switch from continuous to intermittent administration as required, once symptoms improve.

Our patients were selected randomly from among patients with BPH complaining of nocturia in whom α1-blockers, anticholinergic drugs, hypnotics, tricyclic antidepressants, and other medications did not demonstrate sufficient effectiveness against nocturia. In particular, patients younger than 70 years old who are bothered by nocturia of >2 episodes per night showed a good response by prostaglandin synthesis inhibition. Additionally, one of the main merits of loxoprofen for the treatment of nocturia is that it does not decrease voiding potency even in patients with BOO (data not shown) and does not produce side effects such as dry mouth and constipation, even in the elderly.

One of the limitations of this study is the lack of a control group. Johnson *et al.* reported that the improvement rate of nocturia was 22% in the control group in their study [2]. Improvement rates of our study of 74.2 % were significantly higher than rates in previously reported placebo groups.

Our study is preliminary, and prospective randomized control study including long-term follow-up of the effects of loxoprofen is warranted to validate these data.

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