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A Clinical Investigation of the Mechanism of Loxoprofen, a Non-steroidal Anti-inflammatory Drug, for Patients with Nocturia

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Abstract

We previously reported the effectiveness of loxoprofen sodium (loxoprofen), a non-steroidal anti-inflammatory drug, for patients with lower urinary tract symptoms (LUTS) complaining of nocturia. In this study, we explored the mechanism of loxoprofen in the treatment of nocturia. Fifty-six patients complaining of nocturia were enrolled. They took a single 60-mg tablet of loxoprofen at bedtime for 14 days. The effects of this treatment were assessed by bladder diaries. Nocturia improved (nocturia decreased $\geq$1 void/night) in 40 patients (71.4%). Nocturnal urine volume was reduced in 31 of 40 (77.5%) without nocturnal single-void volume increase. Nocturnal single-void volume increased in 4 of 40 (10.0%) without nocturnal urine volume reduction. Two of 40 (5.0%) demonstrated both nocturnal urine volume reduction and nocturnal single-void volume increase. Three (7.5%) were exceptions to the above. In conclusion, the main mechanism of loxoprofen is the reduction of nocturnal urine volume for the treatment of nocturia and the second mechanism is the increased bladder capacity.

KEYWORDS: loxoprofen, nocturia, NSAID

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Original Article

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We previously reported the effectiveness of loxoprofen sodium (loxoprofen), a non-steroidal anti-inflammatory drug, for patients with lower urinary tract symptoms (LUTS) complaining of nocturia. In this study, we explored the mechanism of loxoprofen in the treatment of nocturia. Fifty-six patients complaining of nocturia were enrolled. They took a single 60-mg tablet of loxoprofen at bedtime for 14 days. The effects of this treatment were assessed by bladder diaries. Nocturia improved (nocturia decreased ≥1 void/night) in 40 patients (71.4%). Nocturnal urine volume was reduced in 31 of 40 (77.5%) without nocturnal single-void volume increase. Nocturnal single-void volume increased in 4 of 40 (10.0%) without nocturnal urine volume reduction. Two of 40 (5.0%) demonstrated both nocturnal urine volume reduction and nocturnal single-void volume increase. Three (7.5%) were exceptions to the above. In conclusion, the main mechanism of loxoprofen is the reduction of nocturnal urine volume for the treatment of nocturia and the second mechanism is the increased bladder capacity.

Key words: loxoprofen, nocturia, NSAID

Lower urinary tract symptoms (LUTS) are a major health problem for elderly people. Nocturia, a cause of insomnia and thus impaired quality of life, is one of the main problems in LUTS along with urinary incontinence and difficulty in urination. Nocturia is not only a significant bother to patients, but is associated with increases in morbidity, risk of nighttime falls, and mortality [1].

The etiology of nocturia is varied and complex in many patients. However, the pathophysiological basis for nocturia can be divided into 3 categories: (1) Excessive urine output, (2) Sleep-related difficulties and (3) Urinary tract dysfunction [2].

We previously reported that loxoprofen sodium (loxoprofen), a prodrug in the class of short-acting non-steroidal anti-inflammatory drugs (NSAIDs), reduces nocturia in patients with benign prostatic hyperplasia (BPH) and neurogenic bladder [3, 4]. As reported in these papers, nocturia improved or disappeared in 74.2% and 80.6% of the patients with BPH and neurogenic bladder, respectively. Al-Waili reported that indomethacin suppositories (a potent PGs synthesis inhibitor) reduced the frequency of nocturnal voiding and decreased the urine volume in enuresis [5-7]. Other papers have demonstrated that aspirin and diclofenac were also effective for nocturia

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[8, 9]. The main mechanism of NSAIDs for the treatment of nocturia is considered to be the reduction of nocturnal urine volume [5, 10, 11]. However, we observed that nocturia improved in some patients on loxoprofen without reducing the nocturnal urine volume.

We prospectively investigated the mechanism of loxoprofen for nocturia in this study.

Materials and Methods

Between January 2003 and April 2005, 56 patients with LUTS complaining of nocturia were enrolled. Nocturia was confirmed by bladder diary as one or more voids per night on average. The risks and possible adverse effects of loxoprofen were carefully explained to the patients prior to enrollment in the study, and written informed consent was obtained. The patients took a 60-mg tablet of loxoprofen at bedtime for 14 days. The patients were required to keep a bladder dairy. They recorded all micturitions and the time of sleep and rising. The diaries were kept before and during loxoprofen treatment. The effects of this treatment were assessed from the data in the bladder diaries. The differences in data between the baseline and during treatment were investigated in terms of the frequency of voiding, urine volume and single-void volume. The average ratio of the nighttime urine volume was also compared.

All medications before loxoprofen treatment were continued during the loxoprofen treatment. These included α1-blockers, tricyclic antidepressants, anticholinergic medication and sleeping pills. Before the treatment, 48 patients had been treated with α1-blockers, 18 patients with tricyclic antidepressants (imipramine or amytriptyline), 10 patients with anticholinergic medication (propiverine or oxybutynin), and 7 patients with sleeping pills (zolpidem) for nocturia. Twenty-seven patients had been treated with combination therapy. Therefore, none of the patients were on only loxoprofen during this study. The patients had been on these medications for a minimum of 1 month prior to beginning the current study, but were still having 1 or more nocturia episodes per night. The improvement of nocturia was defined as a decrease by at least 1.0 void/night on average. Adverse events were carefully reviewed by an interview at clinic visits including serum creatinine (sCr) and blood urea nitrogen (BUN) abnormality. Patients who had asthma, gastrointestinal disorders, renal dysfunction or allergies to NSAIDs were excluded.

For statistical analyses, the Wilcoxon signed rank test was used to compare the data between before and during treatment in each group, while Mann-Whitney *U*-tests were used for intergroup comparisons. $P<0.05$ was considered significant. Values are reported as the mean $\pm$ standard deviation.

Results

Fifty-six (53 males and 3 females) patients with a mean age of 71.5 years (52–88) were enrolled in this study. Nocturia improved (mean nocturia decreased by at least 1.0 void/night) or disappeared in 40 patients (38 males and 2 females) (71.4%), with a mean age of 72.3 years (52–88). The data from the bladder diaries of the 56 patients are shown in Table 1. Total urine volume, nocturnal urine volume, and total number of nocturnal voids significantly decreased during treatment. However, nocturnal single voided volume did not show a significant change (Table 1). Nocturnal urine volume significantly decreased in both the effective and non-effective groups. However, the nocturnal urine volume was reduced more significantly in the effective group than in the non-effective group. Nocturnal single voided volume was significantly reduced in the non-effective group (Table 1).

We further analyzed the data of the 40 patients in the effective group. We classified them into 4 groups based on 2 factors: 1. Nocturnal urine volume reduction (with or without $\geq$150 ml or $\geq$10% reduction from baseline), 2. Nocturnal single voided volume increase ($\geq$ or $<$150% increase from baseline). Group A (Nocturnal urine volume reduction type) was defined as a nocturnal urine volume reduction of more than 150 ml or $\geq$10% reduction from the baseline with $<$150% nocturnal single voided volume increase. Group B (Nocturnal single voided volume increase type) was defined as an increase of the nocturnal single voided volume by 150% or more from the baseline without nocturnal urine volume reduction. Group C (Mixed type) was defined as an increase of the nocturnal single voided volume by 150% or more from the baseline with nocturnal urine volume reduction. Group D were exceptions to the above.

Thirty-one of 40 (77.5%) were classified as group

Table 1 Nocturia and urine volume before and during the treatment by loxoprofen in 56 patients

		No. voids / night	Urine volume / night (mL)	Urine volume / night (%/day)	Single voided volume / night (mL)	Urine volume / day (mL)
	Baseline	2.8 ± 1.1	776 ± 256	43.4 ± 10.5	226 ± 86.5	1,811 ± 523
	During	1.5 ± 0.9	523 ± 230	32.6 ± 11.4	223 ± 76.4	1,668 ± 569
	*P**	< 0.0001	< 0.0001	< 0.0001	NS	0.0013
Non-effective group (n = 16)						
	Baseline	2.2 ± 1.0	746 ± 253	37.2 ± 9.7	254 ± 115	2,014 ± 552
	During	1.8 ± 1.0	591 ± 250	31.4 ± 8.8	214 ± 80.1	1,893 ± 605
	*P**	0.0040	0.0009	0.0023	0.0494	NS
Effective group (n = 40)						
	Baseline	3.0 ± 1.1	788 ± 260	45.9 ± 9.9	215 ± 70.9	1,730 ± 495
	During	1.8 ± 0.8	508 ± 220	33.1 ± 12.4	226 ± 75.6	1,578 ± 260
	*P**	< 0.0001	< 0.0001	< 0.0001	NS	0.0042
	*P***	< 0.0001	**0.0193**	**0.0013**	0.0370	NS

*P** Comparison between baseline and during treatment: Wilcoxon signed rank test;
*P*** Comparison between effective (mean nocturia decreased by ≧ 1.0 void/night) and non-effective groups (mean nocturia decreased by < 1.0 void/night) groups: Mann-Whitney's *U*-test.
NS, not significant.

A, whose nocturnal urine volume and total nocturnal void significantly decreased during loxoprofen treatment. However, the nocturnal single voided volume did not show any significant change (Table 2). Four (10.0%) were classified as group B. Two (5.0%) were classified as group C. The rest 3 (7.5%) were classified as group D. In groups B, C, and D, nocturnal single voided volume increased during the treatment (Table 2). Table 3 shows the groups B, C, and D cases. Nocturnal single voided volume increased during treatment in these 9 patients (groups B, C and D). Even in group A, nocturnal single voided volume was increased from 7 to 24% (median 11%) in 9 of 31 patients (N. S.) (Table 4). Altogether, bladder capacity was increased in 18 of the 40 effective patients (45.0%) during the treatment. Bladder capacity was also increased from 6 to 18% (median 15%) in 5 of 16 non-effective patients (31.3%) during the treatment (Table 4). A side effect occurred in one patient (1.8%), who complained of gastric discomfort. sCr or BUN did not change in any of the patients.

Discussion

Loxoprofen is a relatively short half-life NSAID pro-drug and inhibits prostaglandin (PG) synthesis via the inhibition of non-selective cyclooxygenase (COX).

Table 2 Nocturia and urine volume before and during the treatment by loxoprofen in the 40 effective patients

Group	No. pts (%)		No. voids / night	Urine volume / night (mL)	Urine volume / night (%/day)	Single voided volume / night (mL)	Urine volume / day (mL)
A	31	Baseline	2.9 ± 1.1	827 ± 254	47.0 ± 9.7	230 ± 69	1,760 ± 438
	(77.5%)	During	1.2 ± 0.8	472 ± 219	30.6 ± 11.2	220 ± 73	1,542 ± 483
		*P**	< 0.0001	< 0.0001	< 0.0001	NS	0.0004
B	4	Baseline	3.4 ± 1.4	626 ± 242	44.1 ± 11.0	157 ± 36	1,463 ± 537
	(10.0%)	During	1.7 ± 0.7	680 ± 158	44.0 ± 14.0	268 ± 78	1,729 ± 804
C	2	Baseline	3.3 ± 1.8	838 ± 392	33.1 ± 5.8	172 ± 24	2,468 ± 746
	(5.0%)	During	1.9 ± 1.2	714 ± 330	31.0 ± 17.0	284 ± 15	2,387 ± 274
D	3	Baseline	3.1 ± 1.0	565 ± 183	44.9 ± 10.3	166 ± 94	1,283 ± 444
	(7.5%)	During	1.8 ± 0.8	522 ± 114	45.0 ± 11.3	208 ± 117	1,210 ± 406

*P** Comparison between baseline and during treatment: Wilcoxon signed rank test.
NS, not significant.

Table 3 Nocturia and urine volume before and during the treatment by loxoprofen in each patient of groups B, C, and D

Patient (Age)		No. voids / night	Urine volume / night (mL)	(%/day)	Single voided volume / night mean (range) (mL)	Urine volume / day (mL)
B1	Baseline	5.0	775	45	138 (100–250)	1,713
(71)	During	2.7	716	42	208 (175–250)	1,697
B2	Baseline	2.0	320	47	115 (70–140)	685
(74)	During	1.0	450	61	200 (190–220)	740
B3	Baseline	2.5	550	29	186 (80–350)	1,895
(65)	During	1.0	740	27	360 (330–380)	2,710
B4	Baseline	4.0	860	55	188 (80–300)	1,560
(82)	During	2.0	810	46	305 (280–310)	1,770
C1	Baseline	2.0	560	29	155 (110–200)	1,940
(82)	During	1.0	480	19	280 (250–310)	2,580
C2	Baseline	4.5	1,115	37	189 (100–310)	2,995
(74)	During	2.7	947	43	287 (180–350)	2,193
D1	Baseline	2.0	770	43	275 (200–340)	1,773
(62)	During	1.0	643	39	343 (260–390)	1,660
D2	Baseline	3.3	417	36	117 (50–250)	1,167
(88)	During	2.0	417	38	150 (100–250)	1,100
D3	Baseline	4.0	509	56	107 (50–150)	908
(85)	During	2.5	505	58	132 (80–240)	870

PGs have various effects on the renal system, vesical, urethral and sympathetic nervous systems, and thus loxoprofen may also act on the same portions as PG synthesis inhibitors. We previously reported that nocturia improved in 74% of patients with BPH by loxoprofen [3]. That was the first report demonstrating the effectiveness of loxoprofen for the treatment of nocturia. Saito *et al.* subsequently reported the effectiveness of loxoprofen for patients with nocturia [10].

Why is loxoprofen effective in reducing nocturia? There are 4 possible sites where loxoprofen may act: 1. Reducing urine volume produced in the kidney, 2. Decreasing detrusor muscle tone, 3. Affecting urinary sensation at the bladder, 4. Affecting sleep in the brain. It is known that PGs contribute to urine production in the kidney. They inhibit sodium tubular reabsorption and anti-diuretic hormone (ADH), decrease aldosterone secretion and cause glomerular vasodilation, natriuresis and diuresis [12]. Therefore, NSAIDs suppress urine production by decreasing glomerular blood flow, particularly in the impaired kidney [13]. Several reports have suggested that the main mechanism of this effect is to decrease urine production during the night [9–11].

In our previous study, however, we found that there were some patients whose nocturia improved with loxoprofen even with increased nocturnal urine volume [4]. This interesting finding led us to investigate the mechanism of loxoprofen for the treatment of nocturia. Actually, several studies have demonstrated the clinical efficacy of PG synthesis inhibitors on detrusor overactivity [14–16]. It has also been suggested that an important physiologic role of PGs on bladder function might be sensitization of the sensory nerves. PGs may indirectly affect bladder activity via effects on neurotransmission as neurotransmitters/modulators [17–19]. Accordingly, it is suspected that loxoprofen might improve nocturia by increasing the threshold of urinary sensation in the central nervous system (CNS) via the suppression of afferent and/or efferent nerve pathways. The levels of PGD_2 and PGE_2 in the brain have been shown to be related to the sleep–wake cycle [19, 20]. It is widely known that NSAIDs suppositories provide patients with good sleep as a secondary effect.

Our data demonstrated that loxoprofen significantly reduced nocturia and nocturnal urine volume. Nocturnal urine volume in particular was reduced by a significantly greater degree in the effective group than in the non-effective group. However, there were no significant differences in nocturnal single voided urine volume during the treatment in 56 patients (Table 1). We then focused on the data of the 40

Table 4 Nocturia, urine volume, and nocturnal single voided volume before and during the treatment by loxoprofen in each patient who demonstrated an increase of nocturnal single voided volume during treatment of group A and the non-effective group (NE)

Patient (Age)		No. voids / night	Urine volume / night (mL)	(%/day)	Single voided volume / night mean (mL) (%/pre)	Urine volume / day (mL)
A6	Baseline	1.0	233	31	125	750
(78m)	During	0.0	155	19	155 (124)	830
A8	Baseline	6.0	1,217	46	174	2,630
(67m)	During	3.8	975	34	206 (118)	2,900
A12	Baseline	2.7	1,175	47	318	2,508
(85f)	During	1.2	850	40	350 (110)	2,133
A15	Baseline	2.5	810	47	233	1,735
(72m)	During	1.0	450	31	250 (107)	1,455
A19	Baseline	2.8	1,103	52	298	2,130
(72m)	During	1.0	770	39	331 (111)	1,979
A20	Baseline	1.5	600	37	217	2,995
(80f)	During	0.0	250	18	250 (115)	1,375
A23	Baseline	2.0	945	42	360	2,265
(57m)	During	1.0	650	29	400 (111)	2,280
A29	Baseline	3.5	783	55	176	1,428
(75m)	During	1.0	400	43	203 (115)	943
A31	Baseline	5.0	1,340	52	221	2,595
(62m)	During	2.0	735	38	255 (115)	1,920
NE42	Baseline	1.3	240	23	102	1,023
(80m)	During	1.0	207	23	117 (115)	893
NE45	Baseline	1.0	497	20	170	2,453
(66f)	During	0.3	428	19	200 (118)	2,223
NE48	Baseline	1.4	814	40	393	2,042
(63m)	During	1.0	730	33	430 (109)	2,180
NE50	Baseline	3.5	893	50	204	1,793
(76m)	During	2.7	787	40	234 (115)	1,980
NE56	Baseline	2.3	665	38	218	1,770
(62m)	During	1.8	635	39	230 (106)	1,620

effective patients. Nocturia was improved mainly due to an increase of the nocturnal single voided volume in 9/40 (22.5%) (groups B, C and D) during loxoprofen treatment. 31/40 (77.5%) demonstrated the reduction of nocturnal urine volume by more than 150 ml or 10% from the baseline (group A). NSAIDs mainly contribute to suppression of urine production in the kidney by decreasing glomerular blood flow. The reduction of urine volume is a major mechanism of loxoprofen, because the nocturnal urine volume reduced significantly, and 77.5% of effective patients demonstrated reduction of the nocturnal urine volume during treatment. However, 4/40 (10.0%) demonstrated increased nocturnal single voided volume during loxoprofen administration without a significant change of the nocturnal urine volume (Group B, Tables 2, 3). 2/40 (5%) demonstrated a reduction of the nocturnal urine volume and an increase of the nocturnal single voided volume (Group C, Tables 2, 3). In 3 patients (7.5%), nocturia was improved despite only a small change of the nocturnal urine volume and/or nocturnal single voided urine volume (Group D, Tables 2, 3), although it is difficult to specify the real mechanism for this improvement. In addition, the nocturnal single voided volume was increased from 7 to 24% (median 11%) in 9 of 31 patients in group A, although the increases were small (Table 4). Altogether, bladder capacity was increased in 18 of 40 effective patients (45.0%) by loxoprofen. Even in non-effective patients, bladder capacity was increased from 6 to 18% (median 15%) in 5 of 16 non-effective patients (31.3%) (N. S.). Therefore, it seems that an increase in bladder capacity is the second mechanism of loxoprofen.

Adverse events of loxoprofen are less frequent than other NSAIDs because loxoprofen is a prodrug of a short-acting NSAID. However, it should be kept in mind that many patients with nocturia are elderly

and may have low thresholds for the development of gastrointestinal ulcers and renal dysfunction, 2 well-known adverse events associated with the long-term administration of NSAIDs [21].

The limitation of this study was the lack of a control group. However, this is the first report elucidating the mechanism of loxoprofen for the treatment of nocturia. Before this treatment, all of our patients were on some medications for nocturia, including α1-blockers, anticholinergic medication, or sleeping pills, suggesting they had refractory nocturia, and they continued their medications during the study. Our data demonstrated that loxoprofen can increase the bladder capacity of patients with refractory nocturia. There have been no reports clearly demonstrating the increased bladder capacity with NSAIDs before. Further investigation is needed to evaluate the effects of PG synthesis inhibitors in the treatment of nocturia and detrusor overactivity. In conclusion, loxoprofen is effective for the treatment of nocturia. The main mechanism of loxoprofen was the reduction of nocturnal urine volume. The second mechanism is the increased bladder capacity. Our results suggest that loxoprofen has an effect on the detrusor muscle or urinary sensation at the bladder and/or CNS.

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