Effectiveness of Non Steroidal Anti Inflamatery Drug "Diclofenac Sodium" in Treatment of Nocturia in Benign Prostatic Hyperplasia Patien

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ABSTRACT:

BACKGROUND:

We explored the effectiveness of enteric coated diclofenac sodiumfor patients with benign prostatic hyperplasia (BPH) complaining of nocturia. A total of 30 BPH patients aged 50-75 years were enrolled in the study. They each took a single 50-mg tablet of diclofenac sodium prior to sleeping at night for 14 days in addition to their BPH treatments In the questionnaire ,21 of 30 patients (70%) felt more satisfaction than previous treatments.

OBJECTIVE:

In this study, we attempted to investigate the role of enteric coated diclofenac sodium (voltaren) in the therapeutic management of BPH patients with nocturia.

METHODS:

Thirty patient with BPH (63.6± 6.56 years old) more than two episodes of nocturia per night were involved. These patients had received standard drug therapy. Although these patients had received standard drug therapy for more than half a year, they had still three or more episodes of nocturia. The patients took a single dose of 50 mg of diclofenac sodium enteric coated at night prior to sleep. Before and 2 week after the initiation of this therapy, the effects of this treatment were assessed by frequency volume chart and a questionnaire.

RESULT:

In the questionnaire ,21 of 30 patients (70%) felt more satisfaction than previous treatments. Patients were grouped into a diclofenac sodium-effective (n = 23) and ineffective groups (n = 7) based on the results of the frequency-volume chart. In the effective group, interestingly, night-time urine volume showed significant reduction ($P < 0.001$). On the other hand, the average single voided volume at night showed no significant change. There was a statistically significant difference in the night-time urine volume after treatment between groups ($P < 0.05$). In frequency volume chart, total void per day, total void per night, total urine volume per day, total night urine volume per day and single voided volume in the night before and after this treatment were 9.9±0.56and 10.1±0.69per day, 3.9±0.87 and 2.3±1.1 per night, 1500.2±106.9 and1508.7±107.3 mL per day, 580.2±136.9 and 350.4±169.3 mL per night, and 150±7.2 and 150.4±7.05mL, respectively, in a diclofenac sodium-effective group.

CONCLUSION:

Diclofenac sodium can be effective and useful for BPH patients with nocturia.

KEYWORDS: BPH,diclofenac, nocturia, NSAIDs, overactive bladder

INTRODUCTION :

Nocturia is a major health problem for benign prostatic hyperplasia (BPH) and overactive bladder (OAB) patients.[1]. Nocturia is a symptom which interrupts sleep by the urge to void. Nocturia is thought to be caused by volume-related reasons (age-related, excess intake of alcohol or diuretics, endocrine or metabolic disorders, peripheral edema), sleep-related reasons (insomnia, pain, dyspnea, depression, drugs) and lower urinary

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tract-related reasons (small bladder capacity, detrusor hyperactivity, prostate-related, overflow incontinence, decreased bladder compliance, sensory urgency).[1]. Nocturia impairs quality of life, and is one of the main problems in these BPH/OAB patients along with urinary incontinence and difficulty in urination.[1]Recently, there have been some reports indicating that non-steroidal anti-inflammatory drugs (NSAIDs) are effective for patients with nocturia.[2,3]. Araki and his associates reported that loxoprofen sodium, the most common NSAID in Japan, reduces nocturia in the patients with BPH.[3]. But the mechanisms of this effect are not fully understood. Prostaglandins (PG) have various effects on the kidney, bladder, urethra and sympathetic and parasympathetic nervous systems. PG inhibit Na tubular reabsorption and ADH. In addition, PG decrease aldosterone secretion and cause glomerular vasodilatation, natriuresis and diuresis. PG are reported to increase the detrusor tone, relax the urethra and reduce intraurethral pressure. In particular, prostaglandin E (PGE) and prostaglandin F (PGF) increase the tone of the detrusor smooth muscle and enhance micturition. PG increase a release of acetylcholine from nerves and activate capsaicin-sensitive afferents in urinary bladder.[4,5,6]. In this study, we attempted to investigate the effectiveness of diclofenac for BPH patients with nocturia. In addition, we also investigated a possible mechanism underlying the relief of nocturia by this drug. Loxoprofen sodium (loxoprofen) is a potent PG synthesis inhibitor. Loxoprofen is a non-selective cyclooxygenase(COX) inhibitor, and has fewer side-effects in the stomach compared to other NSAIDs. Loxoprofen's active metabolite inhibits PGE2 production in leukocytes three times more strongly than indomethacin.[7,8] Furthermore, loxoprofen is also reported to have relatively short half-life among NSAIDs.[7,8]

METHODS:

Thirty men aged 50–75 years(mean 63.6 ± 6.56), complaining of BPH with nocturia and other LUTS at the outpatient urology clinic of medical city from june 2008 to, January 2009 were enrolled in this prospective study. Explaining the purpose and methods before the study, since this drug was not usually used for patients complaining of BPH with nocturia in iraq. The International Prostate Symptom Score(IPSS) of 8 or more was required for study entry. Estimated prostatic volume > 30 g using ultrasonography . All patients had more than two episodes of nocturia per night and were all bothered by nocturia, which resulted in sleep disturbance. Patients with asthma, gastrointestinal diseases, renal failure, urinary tract infection or allergies to NSAIDs and who had previously received other NSAIDs for nocturia were excluded from the study. Various treatments including behavioral modification such as fluid restriction or medical treatments such as alpha1-blockers, including tamsulosin and alfuzosin, had been unsuccessful in all cases. All patients received a 50 mg enteric coated diclofenac sodium tablet prior to sleeping at night for 14 days. After 14-day diclofenac sodium treatment, patients were asked whether they had obtained a more satisfactory result than any previous treatment. Patients were also requested to record a frequency-volume chart for 3 days before and after diclofenac sodium(collected urine is measured by urine bag). The frequency-volume chart included voiding volume and time of urination. Changes from baseline to 14-day treatment in daytime, and night-time urine volume, daytime and night-time frequency, single voided volume at night and percentage night-time urine volume (defined as night-time urine volume/24-h urine volume × 100), respectively, were evaluated using the frequency-volume chart before and after diclofenac sodium. Night and day were defined according to the ICS standardization of urological terms report. Baseline patient characteristics are in table(V). Statistical analysis was carried out using the T test. $P < 0.05$ was regarded as the level of significance.

Table IV: Baseline characteristics of patients complaining of BPH with nocturia treated with diclofenac sodium .

Age (years)	63.6 ± 6.56
Frequency of urination	
Daytime	9.9 ± 0.58
Night-time	3.9 ± 0.85
Urine volume (mL)	
Daytime	1516.8 ± 106.9
Night-time	588 ± 135.8
Average single voided volume (mL)	
Night-time	150.6 ± 7.4

RESULT :

In the questionnaire ,21 of 30 patients (70%) felt more satisfaction with diclofenac sodium treatment than previous treatments. We evaluated the objective outcome of these patients using the frequency-volume chart. The average night-time frequency in 23 of 30 (76.6%) patients decreased after a 2-week diclofenac sodium treatment, and the patients were satisfied with this treatment. Patients were grouped into a diclofenac sodium-effective group (n = 23) and ineffective group (n = 7) based on the results of the frequency-volume chart. The effective group was defined as patients in whom the average night-time frequency decreased by more than one time per night after 14-day diclofenac sodium treatment. The ineffective group was defined as patients in whom the average night-time frequency increased or decreased less than one time per night after treatment. There was no difference in baseline frequent-volume chart parameters between the two groups. Night-time frequency showed a statistically significant reduction from baseline by treatment in the diclofenac sodium-effective group ($P < 0.001$; from 3.9±0.87 to 2.3±1.1 times), although there was no significant change from baseline in the ineffective group (4±0.5 to 3.8±1.1 times). There was statistically significant difference in night-time frequency after treatment between effective and ineffective groups ($P < 0.01$). On the other hand, there was no significant difference in daytime frequency between the two groups (Table V) . Night-time urine volume (ml) showed a statistically significant reduction from baseline by treatment in the diclofenac sodium-effective group ($P < 0.001$; from 580.2±136.9 to 350.4±169.3 ml), and between effective and ineffective groups ($P < 0.05$) In the diclofenac sodium-effective group, percentage night-time urine volume significantly reduced after diclofenac sodium treatment ($P < 0.001$) from [27.4 ± 4.1%] to [18.2 ± 6.4%]). The average single voided volume at night showed no significant change (from150±7.2 mL to150.4±7.05 mL,). In the ineffective group, on the other hand, no frequency-volume chart parameters significantly changed after diclofenac sodium treatment. There was a statistically significant difference in night-time urine volume and percentage night-time urine volume between effective and ineffective groups ($P < 0.05$),($P < 0.01$) respectivly.Table V

No serious adverse events occurred during the study, but mild events were observed in three of 30 (10%): two patients had gastric discomfort and one had nausea.

Table V: Change from baseline to 14 days of treatment in frequency volume chart parameters for diclofenac sodium-effective and ineffective patients

	Effective group			Ineffective group			Between two groups
	Before	After	P-value	Before	After	P-value	P-value
Frequency of urination							
24-h	13.9±0.99	12.4±1.3	<0.001 s.	14.2±0.48	13.6±1.4	0.31 n.s.	0.15 n.s.
Day time	9.9±0.56	10.1±0.69	0.16 n.s.	10.2±075	9.7±048	0.17 n.s.	0.17 n.s.
Night time	3.9±0.87	2.3±1.1	<0.001 s.	4±0.5	3.8±1.1	0.8 n.s.	0.01 s.
Urine volume (mL)							
Day time	1500.2±106.9	1508.7±107.3	0.76 n.s.	1497.1±68.5	1564.3±140.6	0.26 n.s.	0.36 n.s.
Night time	580.2±136.9	350.4±169.3	<0.001 s.	587.8±83.9	572.8±168.8	0.86 n.s.	0.03 s.
Average single voided volume (mL)							
Night time	150±7.2	150.4±7.05	0.8 n.s.	149.3±8.4	150±8.6	0.9 n.s.	0.7 n.s.
Percentage urine volume over night							
	27.4±4.1	18.2±6.4	<0.001 s.	28.01±3.5	27.4±3.2	0.7 n.s.	<0.01 s

DISCUSSION :

Nocturnal frequency of micturition caused by nocturnal polyuria is a very common symptom in elderly population effecting 3–4% of the population older than 65 years of age. Nocturia is associated with impaired health, decrease in quality of life, disturbed night sleep with increased daytime sleepiness. [9] It is associated with Benign Prostatic Enlargement (BPE) but is known to persist following treatment for BPE suggesting other causes for nocturnal polyuria symptoms [10]. The average 24 h urine volume in adults of 1600 ±300 ml does not change dramatically with age [11]. In contrast, the distribution of urine out put between day and night changes markedly with increasing age [11]. The effect of NSAIDs, especially indomethacin on an obstructed kidney has been extensively studied in animals and in human beings [12,13]. It is mediated through cyclooygenase enzymes, which are responsible for the production of prostaglandin H2, the first step in prostaglandin biosynthesis. In normotensive subjects with fluid homeostasis, there is minimal role for prostaglandins in maintaining renal plasma flow [14]. Kinn et al. studied the effect of diclofenac sodium on unobstructed normal functioning kidneys in 8 subjects with a mean age of 42 years (range 35–59) for 4.5 h. They showed that the urine output decreased within 10 min of injection. Renal plasma flow and glomerular filtration rate was noted to decrease by 35% with nadir at 2 h and evidence of start of recovery by 3 h. The most predominant and persistent effect was noticed on tubular resorption of sodium and water [15]. In the present study the patients received the medication only once a day at 2100 h, so that this effect on the renal function could be limited to fluid redistribution from night to day, rather than fluid retention [16].

The existence of two isoforms of cyclooygenase (COX) enzymes has been known since early 1990s, with marked differences between different NSAIDs with respect to COX enzyme selectivity. There is a predominance of COX 2 isoform in the renal vasculature suggesting the feasibility of better efficacy with COX 2 selective inhibitor like celecoxib. [17]

In this study, we attempted to investigate the effect of diclofenac sodium on patients with nocturia. Of 30 patients, 21 patients answered this treatment as excellent or improved. Satisfaction of the patients for this treatment was relatively high. Our data indicated that there are significant reductions in total void per night and total urine volume per night, and that there are no significant changes in

total void per day, total urine volume per day and one voided volume in night before and after this treatment.

There are some reports indicated that NSAIDs are effective for patients with nocturia. Larson reported that indomethacin relieves symptoms of BPH.[5] Le Fanu reported that aspirin is effective for symptoms of nocturnal polyuria.[2] Al-Waili reported that indomethacin markedly reduced bed-wetting episodes and decreased the frequency of voiding in enuretics with small or normal functional bladder capacity. [18].

The author suggests the mechanisms are by decreasing the urine volume, clearance of free water and urinary electrolytes and through possible effects on bladder and urethral contraction, by inhibiting NO and PG synthesis.[19] Recently, Araki et al . reported that the effectiveness of loxoprofen for patients with BPH complaining of refractory nocturia.[3] Investigation of the mechanisms of this beneficial effect is important. PGs have various effects on many systems in vivo , i.e. renal and urinary tract system. [7,8] NSAIDs are reported to reduce GFR and urine volum to decrease detrusor muscle tone and increase urethral tone.. [7,8 In this study, we demonstrated that diclofenac sodium significantly reduces nocturia and urine volume during the night's sleep. Furthermore, there are no significant differences in single voided volume at night between before and after diclofenac sodium medication. Our data indicated that the mechanism of this effect is caused by decrease in urine volume at night. In this study, we also demonstrated that diclofenac sodium does not reduce total urine volume during daytime. In the present study, side-effects of this therapy are gastric discomfort. However, as NSAIDs have serious side-effects in many systems, careful observation is required.

CONCLUSION:

NSAIDs in the form of diclofenac sodium 50 mg enteric coated tablet are effective in the treatment of nocturia. There was a decrease in nocturnal frequency from 3.9±0.85to 2.3±1.1($p < 0.001$). 76.6% of patients noticed improvement in their symptoms. The effect of the once a day medication is shown to be due to fluid redistribution between day and night rather than fluid retention. Diclofenac sodium can be effective and useful for patients with nocturia. Our data suggest that the main mechanism of this effect is to decrease urine production during a night's sleep.

REFERENCES :

1. Resnick NM, Yalla SV. Geriatric incontinence and voiding dysfunction. In: Walsh PC, Retik AB, Vaughan ED dysfunction. In: Walsh PC, Retik AB, Vaughan ED Jr et al. (eds). Campbell's Urology, 8th edn. WB Saunders, Philadelphia, 2002;1224.
2. Le Fanu J. The value of aspirin in controlling the symptoms of nocturnal polyuria. BJU Int. 2001;88: 126–27.
3. Araki T, Yokoyama T, Kumon H. Effectiveness of a nonsteroidal anti-inflamatory drugs for nocturia on patients with benign prostatic hyperplasia: a prospective non-randomized study of loxoprofen sodium 60 mg once daily before sleeping. Acta Med. Okayama2004;58: 45–49.
4. Herbert L, Jacson R, Fredin Det al. Evidences that separate PGE2 receptor modulate water and sodium transport rabbit cortical collecting ductAm. J. Physiol. 1995;265: F643–52.
5. Larsen GK. Indomethacin and symptomatic relief of benign prostatic hyperplasia. JAMA1995;273: 347.
6. Maggi A. Prostanoids as local modulator of reflex micturition. Pharmacol. Res. 1992;25:13–20.
7. Matsuda K, Tanaka Y, Ushiyama S et al. Inhibition of prostaglandin synthesis by sodium2-[4-(2-oxocyclopentylmethyl) phenyl]propionate dihydrate (CS-600), a new anti-inflamatory drugs, and its active metabolite in vitro and in vivo. Biochem. Pharmacol. 1984;33: 2473–78.
8. Sugimoto M, Kojima T, Asami M et al. Inhibition of prostaglandin production in the inflamatory tissue byloxoprofen-Na, an anti-inflamatory prodrug.Biochem.Pharmacol.1991;42: 2363–8.
9. Asplund R. Nocturia, nocturnal polyuria, and sleep quality in the elderly. J Psychosom Res 2004;56:517–25.
10. Homma Y, Yamaguchi T, Kondo Y, Horie S, Takahashi S, Kitamura T. Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia. J Urol 2002;167:172–76.
11. Kirkland JL, Lye M, Levy DW, Banerjee AK. Patterns of urine flow and electrolyte excretion in healthy elderly people. Br Med J 1983;287:1665–67.

12. Allen JT, Vaughan Jr ED, Gillenwater JY. The effect of indomethacin on renal blood flow and uretral pressure in unilateral ureteral obstruction in a awake dogs. Invest Urol 1978;15:324–27.

13. Persson AE, Wahlberg J, Sjodin JG. The effect of indomethacin on glomerular capillary pressure and renal pelvic pressure in ureteral obstruction. Scand J Urol Nephrol Suppl 1983;75:31–34.

14. Dilger K, Herrlinger C, Peters J, Seyberth HW, Schweer H, Klotz U. Effects of celecoxib and diclofenac on blood pressure, renal function, and vasoactive prostanoids in young and elderly subjects. J Clin Pharmacol 2002;42:985–94.

15. Kinn AC, Elbarouni J, Seideman P, Sollevi A. The effect of diclofenac sodium on renal function. Scand J Urol Nephrol 1989;23:153–57.

16. Sanjai K. Addla et al. Diclofenac for Treatment of Nocturia Caused by Nocturnal Polyuria. european urology 2006;49:720–26.

17. Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. Faseb J 2004;18:790–80.

18. Van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardization of terminology in nocturia: Report from the standardization subcommittee of the International Continence Society. BJU Int 2002;90:11–15.

19. Coyne KS, Zhou Z, Bhattacharyya SK, et al. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003;92:948–54.