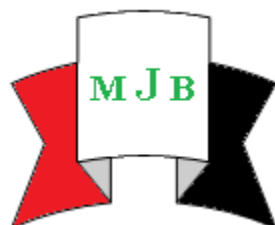


The Role of Celecoxib for Treatment of Refractory Nocturia Caused by Benign Prostatic Hyperplasia

Mohammed Bassil Ismail Adil Hefdhil Al.soufi Hasanin Farhan Hasan
Urology Clinic of Medical City, Baghdad General Directory of Health, Baghdad,
IRAQ.



Received 31 December 2013

Accepted 24 February 2014

Abstract

Objective: Nocturia is a well-recognized symptom in patient with benign prostatic hyperplasia (BPH), which is commonly treated by alpha- blocker and/ or 5 alpha - reductase inhibitors. However, the effectiveness of these drugs for nocturia has been reported to be only 25%- 39%. The aim of this study was to investigate the efficacy of celecoxib, a cyclooxygenase -2 inhibitor, in the treatment of patient with BPH complaining of nocturia.

Patients and methods: A prospective study of 50 men with signs tract symptoms and BPH of refractory nocturia to alpha- blocker and/ or 5 alpha reductase inhibitor more than two episodes of nocturia per night were involved for nocturia. Although these patients had received standard drug therapy for more than one month , they had still three or more episodes of nocturia. The patients took a single dose of 100 mg of celecoxib at night prior to sleep. and 2 week after the initiation of this therapy, the effects of this treatment were assessed by frequency chart and a questionnaire.

Results: In the questionnaire ,32 of 50 patients (64%) had an excellent response with celecoxib treatment than previous treatments, 14 of 50 patients (24%) had an improvement with celecoxib treatment than previous treatments, 4 of 50 patients (8%) had no response with celecoxib treatment, Nocturnal frequency showed a statistically significant reduction from, baseline after two weeks treatment with celecoxib ($P < 0.01$), International Prostate Symptom Score(IPSS) showed a statistically significant reduction from baseline after two weeks treatment with celecoxib ($P < 0.01$), peak flow rate showed a statistically no response from baseline after two weeks treatment with celecoxib ($P < 0.05$).

Conclusion: Celecoxib is effective in the treatment of patients with BPH complaining of refractory nocturia. The results suggest a novel treatment option for this common condition.

Keywords: nocturia, celecoxib, benign prostatic hyperplasia.

الخلاصة

الهدف: ان هدف الدراسة هو لتحديد فعالية عقار السيليكوكسب في معالجة التبول الليلي عند مرضى تضخم البروستات الحميد. **منهج الدراسة:** اشتملت الدراسة على ٥٠ مريضاً يعانون من التبول الليلي لأكثر من مرتين نتيجة لتضخم البروستات الحميد تتراوح اعمارهم بين (٥٠-٧٥). وقد جمع المرضى من الاستشارية البولية في مدينة الطب في بغداد للفترة من شهر حزيران ٢٠١٠ الى شهر اب ٢٠١١. علماً ان هؤلاء المرضى مستمرين على علاج تضخم البروستات الحميد التقليدي لأكثر من شهر وبالرغم من ذلك الا انهم ضلوا يعانون من التبول الليلي لأكثر من مرتين.

اعطي هؤلاء عقار السيليكوكسب ١٠٠ ملغم مرة واحدة يومياً قبل النوم. وقمنا باحتساب عدد مرات التبول الليلي قبل وبعد اسبوعين اعطاء المرضى عقار السيليكوكسب اظهرت النتائج بان ٣٢ من المرضى (٦٤%) كانت فعالية العقار عندهم ممتازة.

نتائج الدراسة: حسب المقياس الشخصي اظهرت النتائج بان ٣٢ (٦٤%) من المرضى كانت فعالية العقار لديهم ممتازة و ١٤ (٢٨%) من المرضى كانت فعالية العقار لديهم مقبولة و ٤ (٨%) ليس لديهم اي استجابة للعقار.

الاستنتاج: اثبتت الدراسة فعالية عقار السيليكوكسب في علاج التبول الليلي لدى المرضى الذين يعانون من تضخم البروستات الحميد.

Introduction

The International Continence Society (ICS) defined nocturia as waking at night to void[1]. Nocturia is associated with a number of putative conditions or circumstances [10] including aging, overactive bladder (OAB), and BPH in men.

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. There have been some reports indicating that non-steroidal anti-inflammatory drugs (NSAIDs) are effective for patients with nocturia.[2,3].

But the mechanisms of this effect are not fully understood. Prostaglandins (PG)inhibit Na⁺ tubular reabsorption and ADH. In addition, PG decrease aldosterone secretion and cause glomerular vasodilatation, natriuresis and diuresis. 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].

Medication usage (including diuretics, and analgesics), diabetes mellitus, diabetes insipidus, anorexia nervosa, and sleep disturbance can also cause nocturia. [10]. The causes of nocturia fall into three categories: diurnal polyuria, nocturnal polyuria, and low nocturnal bladder capacity [10]. Diurnal polyuria is recognized when an individual produces more than 4 mL of urine per kg of body weight over a 24-hr period.[9]. The causes of polyuria include sources of osmotic and free water diuresis, such as diabetes mellitus and diabetes

insipidus of both central and nephrogenic origins.[10,11] Nocturnal polyuria refers to a condition in which the rate of urine

Production is excessive only at night; the total 24-hr output being within normal limits. Nocturnal polyuria from the ICS is a nocturnal urine volume (NUV) of at least one - third that of the total daily urine production.[9]. Abnormality in secretion of arginine vasopressin may, as with diurnal polyuria, play a role in the etiology of nocturnal polyuria. [10,12]. Reduced Nocturnal Bladder Capacity; Bladder storage problems may be caused by a reduction in the functional capacity of the bladder, for example as a result of cancer of the bladder,prostate, or urethra.[10].Storage problems may also arise through bladder irritation as a result of infection, interstitial cystitis, calculi, and bladder hypersensitivity.[10]. In order to diagnose nocturia properly, it is necessary first to establish whether the individual has awoken at night to void, or voids because he or she is already awake. Several medical issues, such as pain and anxiety, may interrupt sleep[13] A thorough patient history and physical examination are central to the diagnosis of nocturia and are the primary means of establishing whether a treatable underlying condition such as diabetes mellitus, obstructive sleep apnea, diabetes insipidus, OAB, BPH, or congestive heart failure is present.[14].

Benign prostatic hyperplasia (BPH) also known as nodular hyperplasia, It is characterized by hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete

nodules in the periurethral region of the prostate [15].

Benign prostatic hyperplasia symptoms are classified as storage or voiding.

Storage symptoms include urinary frequency, urgency (compelling need to void that cannot be deferred), urgency incontinence and voiding at night (nocturia). Voiding symptoms include weak urinary stream, hesitancy (needing to wait for the stream to begin), intermittency (when the stream starts and stops intermittently), straining to void, dysuria (burning sensation in the urethra), and dribbling. These storage and voiding symptoms are evaluated using the International Prostate Symptom Score (IPSS) questionnaire, designed to assess the severity of BPH. [16].

The International Prostate Symptom Score (IPSS) is an 8question (7 symptom questions + 1 quality of life question) written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of the disease Benign Prostatic Hyperplasia (BPH). Additionally, the IPSS can be performed multiple times to compare the progression of symptoms and their severity over months and years [17,18].

Celecoxib is a sulfa NSAID and selective COX-2 inhibitor celecoxib is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is C₁₇H₁₄F₃N₃O₂S, and the molecular weight is 381.[18]. Celecoxib inhibits COX-2 without affecting COX-1. COX-1 is involved in synthesis of PGs and thromboxane (TXA₂), but COX-2 is only involved in the synthesis of PGs. Therefore, inhibition of COX-2 inhibits only PGs synthesis without affecting TXA₂ and thus offers no cardioprotective effects of non-

selective NSAIDs. [19] Inhibition of PGE₂ synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE₂ appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.[20]

Patients and Method

Fifty 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 2010 to, august 2011 were controlled 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.

Inclusion criteria:

- 1- Patients with BPH and > 2 voids per night.
- 2- International prostate symptom score of > 0 or = 8
- 3- Prostate volume > 30 ml.
- 4- Alpha -blocker or alpha blocker and finasteride were prescribed initially
- 5- Patient has negative urine culture findings and normal renal function

Exclusion criteria:

- 1- Patients that have other pathologic conditions that may cause nocturia.
- 2- Patients with previous prostate surgery.
- 3- Patients with prostate cancer or patients with prostate - specific antigen level > 10 ng/mL

Various treatments including behavioral modification such as fluid restriction or medical treatment such as alpha1-blockers, including tamsulosin and alfuzosin, had been unsuccessful in all cases.

All patients received a 100 mg of celecoxib at 9 p.m. for 14 days.

After 14-day of celecoxib treatment, patients were asked whether they had obtained a more satisfactory result than any previous treatment. The baseline parameters at the start of the study and at the end of two weeks (end of the study) for patients whose matched the included criteria were assessed, which include:

1. IPSS
2. Nocturia frequency
3. Measurement of peak flow rate (Qmax)
4. Measurement of prostatic volume
5. Measurement of serum PSA

The main outcome measure was the occurrences of nocturia, which was defined as the score on the International Prostate Symptom Score nocturia question before and after treatment as either excellent (nocturia disappeared or decreased by >2 voids/

night), improved (nocturia decreased by ≤ 2 void/night), or unchanged.

Results

In the questionnaire, 32 of 50 patients (64%) had an excellent response with celecoxib treatment than previous treatments, 14 of 50 patients (24%) had an improvement with celecoxib treatment than previous treatments, 4 of 50 patients (8%) had no response with celecoxib treatment. Nocturnal frequency showed a statistically significant reduction from baseline after two weeks treatment with celecoxib ($P < 0.01$). IPSS showed a statistically significant reduction from baseline after two weeks treatment with celecoxib ($P < 0.01$). Peak flow rate showed a statistically no response from baseline after two weeks treatment with celecoxib ($P < 0.05$).

Table 1 Descriptive statistics for each parameter in groups

Groups	Parameter	Sample size	Mean	SD	SE	Min.	Max.
Baseline	Nocturnal Frequency	50	5.18	1.16	0.16	3	7
	Peak Flow Rate	50	12.28	1.34	0.19	10	15
	International prostate system score	50	18.58	1.86	0.26	14	22
After therapy	Nocturnal Frequency	50	2.64	1.54	0.22	0	7
	Peak Flow Rate	50	12.68	1.39	0.20	10	16
	International prostate system score	50	15.40	1.95	0.28	11	20

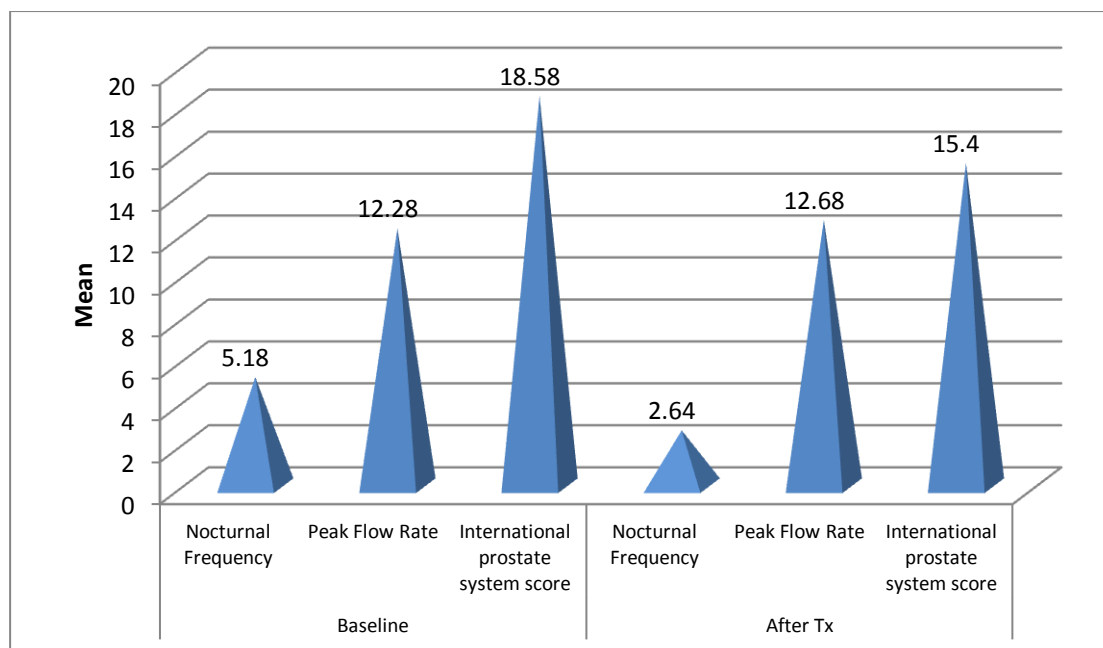


Figure 1 Mean for each parameter in groups

Table 2 Comparison between Baseline and after therapy for Nocturnal Frequency

Groups	Mean	±SD	t-test	P-value	Signi ficance.
Baseline	5.18	1.16	9.35	0.000	HS
After therapy	2.64	1.54			

HS: High significant $P < 0.01$

Table 3 Comparison between Baseline and after Therapy for Peak Flow Rate

Groups	Mean	±SD	t-test	P-value	Signi ficance.
Baseline	12.28	1.34	1.46	0.150	NS
After therapy	12.68	1.39			

NS: Non significant $P > 0.05$

Table 4 Comparison between Baseline and after therapy for International prostate system score

Groups	Mean	±SD	t-test	P-value	Signi ficance.
Baseline	18.58	1.86	8.34	0.000	HS
After therapy	15.40	1.95			

HS: High significant $P < 0.01$

Discussion

Nocturnal frequency of micturition caused by nocturnal polyuria is a very common symptom in elderly population effecting 34% 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. [21]

It is associated with Benign Prostatic Enlargement (BPE) but is known to persist following treatment for BPE suggesting other causes for NPS [22]. The average 24 h urine volume in adults of 1600 ± 300 ml does not change dramatically with age [23]. In contrast, the distribution of urine output between day and night changes markedly with increasing age [23].

The effect of NSAIDs, especially indomethacin on an obstructed kidney has been extensively studied in animals and in human beings [24, 25].

It is mediated through cyclooxygenase 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 [26].

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 hours and evidence of start of recovery by 3 h. The most predominant and persistent effect was noticed on tubular resorption of sodium and water [27].

In the present study the patients received the medication only once a day at 9 p.m., so that this effect on the renal function could be limited to fluid redistribution from night to day, rather than fluid retention [28].

The existence of two isoforms of cyclooxygenase (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.[29]

PGs by virtue of their action on the afferent arteriole of the kidney and on the detrusor muscle[7] of the bladder are said to have a role in the pathogenesis of nocturia.

PGs cause vasodilatation of the afferent arteriole resulting in an increase in the glomerular filtration rate and ultimately in the amount of urine produced. Further, prostaglandins E and F increase the tone of the detrusor muscle and enhance micturition.[7]

The above-mentioned role of prostaglandins forms the basis of the use of NSAIDs in the treatment of nocturia in patients in whom this symptom is poorly controlled by medical therapy prescribed for BPH. NSAIDs block the COX-1 and COX-2 enzymes, which convert arachidonic acid to PGs. Reduced PGs synthesis, in part explains the clinical benefit that is seen with this class of drugs.[7]

Another additional benefit that NSAIDs may provide in patients with BPH is that by virtue of their anti inflammatory properties, the pathogenesis of BPH may be altered in a positive fashion since chronic inflammation is believed to be an etiological factor in patients with BPH. Studies have shown that focal upregulation of COX-2 takes place in the glandular epithelium of patients with BPH.[53]

In this study, we attempted to investigate the effect of celecoxib on patients with nocturia. Of 50 patients, 24 patients answered this treatment as excellent . Satisfaction of the patients for this treatment was relatively high. Our data indicated that there are significant reductions in total void per night Although the number of patients in this study was small, celecoxib can be effective and useful treatment for patient with nocturnal polyuria.

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. [1]

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.[35]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 volume, to decrease detrusor muscle tone and increase urethral tone.

loxoprofen reduced the PGE2 in the urine, leading to change in the volume of urine, which contributed to a reduction in the frequency of the micturition reflux in non-anesthetized rats.[34] Wang et al.[31] reported that chronic inflammation in BPH is associated with focal upregulation of COX-2 in the glandular epithelium. The COX-2 isoform is predominant in the renal vasculature,[31] and several studies have demonstrated the expression of COX-2 mRNA in human prostatic tissue,[32,33] suggesting the feasibility of better efficacy with COX-2-selective inhibitors such as celecoxib.

The side effects, such as mild gastric discomfort, dizziness and diarrhoea occurred more in patients who were given celecoxib, no significant side-effects was detected so as to require exclusion of a patient from the study,

and medical intervention was not performed in any of the patients because of side-effects. COX-2 promotion of cell growth and modification of phenotype has been linked to its ability to increase PG production, promote angiogenesis, inhibit apoptosis, and modulate inflammation in the microenvironment around cells[30]

Conclusion

COX-2 inhibitors in the form of celecoxib (100-mg capsule) are effective in the treatment of nocturia due to BPH. The effect of the once a day medications shown to be due to fluid redistribution between day and night rather than fluid retention. Celecoxib can be effective and useful for patients with nocturia.

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- 5.
- 2- Le Fanu J. The value of aspirin in controlling the symptoms of nocturnal polyuria. BJU Int. 2001; 88: 126- 7.
- 3- Araki T, Yokoyama T, Kumon H. Effectiveness of nonsteroidal anti-inflammatory drugs for nocturia in patients with benign prostatic hyperplasia: a prospective non-randomized study of loxoprofen sodium 60 mg once daily before sleeping. Acta Med. Okayama 2004; 58: 45- 9.
- 4- Herbert L, Jacson R, Fredin Det al. Evidences that separate PGE2 receptor modulate water and sodium transport in rabbit cortical collecting duct. Am. J. Physiol. 1995; 265: F643- 52.
- 5- Larsen GK. Indomethacin and symptomatic relief of benign prostatic hyperplasia. JAMA 1995; 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 sodium 2-[4-(2-oxocyclopentylmethyl) phenyl]propionate dihydrate (CS-600), a new anti-inflammatory drugs, and its active metabolite in vitro and in vivo. *Biochem. Pharmacol.* 1984; 33: 2473- 8.
- 8-Sugimoto M, Kojima T, Asami M et al. Inhibition of prostaglandin roduction in the inflammatory tissue byloxoprofen-Na, an anti-inflammatory prodrug. *Biochem. Pharmacol.*1991;42: 2363- 8.
- 9- 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- 5.
- 10- Weiss JP, Blaivas JG. Nocturnal polyuria versus overactive bladder in nocturia. *Urology* 2002;60:28- 32, discussion 32.
- 11- Asplund R. Nocturia in relation to sleep, health, and medical treatment in the elderly. *BJU Int* 2005;96:15- 21.
- 12- Matthiesen TB, Rittig S, Norgaard JP, et al. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. *J Urol* 1996;156:1292-9.
13. Partinen M. Epidemiology of obstructive sleep apnea syndrome. *Curr Opin Pulm Med* 1995;1:482- 7.
14. Weiss JP, Blaivas JG, Stember DS, et al. Evaluation of the etiology of nocturia in men: The nocturia and nocturnal bladder capacity indices. *Neurourol Urodyn* 1999;18:559- 65.
- 15-eMedicine - Transurethral Microwave Thermotherapy of the Prostate (TUMT) :Article by Jonathan Rubenstein
- 16-Barry MJ, Fowler FJ Jr, O'Leary MP, et al . The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* (1992)148(5): 1549-57. PMID 1279218
- 17-Patel AK, Chapple CR. Benign prostatic hyperplasia: treatment in primary care. *BMJ.* 2006 Sep 9;333(7567):535-9. Review.
- 18-McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg LM Jr, Clarke HS, Crawford ED, Diokno A, Foley JP, Foster HE, Jacobs SC, Kaplan SA, Kreder KJ, Lieber MM, Lucia MS, Miller GJ, Menon M, Milam DF, Ramsdell JW, Schenkman NS, Slawin KM, Smith JA; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003 Dec 18;349(25):2387-98.
- 19- Shi S and Koltz U. Clinical use and pharmacological properties of selective COX-2 inhibitors. *European Journal of Clinical Pharmacology.* Nov 13, 2007
- 20- DiPiro, Joseph T., Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, and L. Michael Posey. *Pharmacotherapy A Pathophysiologic Approach (Pharmacotherapy (Dipiro) Pharmacotherapy (Dipiro))*. New York: McGraw-Hill Medical, 2008.
- 21- Asplund R. Nocturia, nocturnal polyuria, and sleep quality in the elderly. *J Psychosom Res* 2004;56:517- 25.
- 22- 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- 6.

- 23- 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- 7.
- 24- Allen JT, Vaughan Jr ED, Gillenwater JY. The effect of indomethacin on renal blood flow and uretral pressure in unilateral ureteral obstruction in awake dogs. *Invest Urol* 1978;15:324- 7.
- 25- 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- 4.
- 26- 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
- 27- Kinn AC, Elbarouni J, Seideman P, Sollevi A. The effect of diclofenac sodium on renal function. *Scand J Urol Nephrol* 1989;23:153- 7.
- 28- Sanjai KA, Adebajji BA, Neilson D, et al. Diclofenac for treatment of nocturia caused by nocturnal polyuria. *Eur Urol.* 2006;49: 720-726
- 29- Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *Faseb J* 2004;18:790- 80
- 30- Di Silverio F, Gentile V, De Matteis A, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: A retrospective analysis. *Eur Urol.* 2003;43:164-175.
- 31- Wang W, Berg A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2 and cell proliferation in glandular epithelium. *Prostate.* 2004;61:60-72.
- 32- O'Neill GP, Ford AW. Expression of mRNA for cyclooxygenase 1 and 2 in human tissues. *FEBS Lett.* 1993;330:156-160.
- 33- Hussain T, Gupta S, Mukhtar H. Cyclooxygenase 2 and prostate carcinogenesis. *Cancer Lett.* 2003;191:125-135
- 34- Schatzl G, Temml C, Schmidbauer J, et al. Cross-sectional study of nocturia in both sexes: Analysis of a voluntary health screening project. *Urology* 2000;56:715.
- 35- 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.