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Original Article

Role of Bladder Capacity in Assessing the Effectiveness of Antimuscarinic Agents on Nocturia in Patients with Overactive Bladders

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Abstract

Objective: The aim of this study was to evaluate the effectiveness of oxybutynin in the treatment of nocturia in patients with overactive bladders (OAB) and to assess predictive factors for the responses to oxybutynin.
Patients and Methods: Patients with symptoms of OAB and nocturia for more than 3 months were enrolled. A 2.5 mg dose of oxybutynin was given twice daily for 1 week after a baseline study that included a self-administered nocturia questionnaire, uroflowmetry, and frequency/volume chart. Outcome analysis included changes in nocturia episodes, uroflowmetry, and post-void residual urine. Patients were stratified according to a nocturia index (Ni), nocturnal polyuria index (NPi), and nocturnal bladder capacity index (NBCi).
Results: A total of 59 patients were eligible for analysis. After 1 week of treatment with oxybutynin, the mean number of nocturia episodes had reduced from 2.7 ± 1.3 to 2.3 ± 1.1 ($p < 0.01$). There were no statistically significant differences in the mean reduction of nocturia episodes between the subgroup of patients with NPi ≤ 0.35 and those with NPi > 0.35 (-0.4 *vs.* -0.3, $p = 0.34$, ANCOVA). Reduction in number of nocturia episodes was more significant in patients with Ni ≤ 1.5 than in those with Ni > 1.5 (-0.9 *vs.* -0.2, $p = 0.03$, ANCOVA), and in patients with NBCi > 2 than in those with NBCi ≤ 2 (-1.1 *vs.* -0.2, $p = 0.01$, ANCOVA).
Conclusion: Ni and NBCi are good predicting factors for the effects of antimuscarinic agents on nocturia in patients with OAB. [*Tzu Chi Med J* 2008;20(4):304–308]

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1. Introduction

Nocturia usually coexists with an overactive bladder (OAB). In a survey in the United States [1], 66.8% of OAB cases reported more than one void per night and 42.2% reported more than two voids per night. Nocturia is usually underreported by both patients and clinicians since most people deem nocturia as a

part of the aging process. However, nocturia impairs patients' quality of life and has detrimental effects on health [1]. Incremental increase in the number of voids per night has negative effects on sleep and quality of life, and is a bothersome symptom.

Nocturia can be caused by increased nighttime urine output, decreased nocturnal functional bladder capacity, or a mixed etiology of the two. Despite the fact that many physicians use anticholinergic agents to treat nocturia by increasing bladder capacity and thus decreasing nocturia episodes, there have been few studies on the treatment of nocturia using anticholinergics. The results remain controversial. Chapple et al [2] evaluated the effectiveness of darifenacin, a selective M3 receptor antagonist, in OAB patients in a double-blind, placebo-controlled study. No significant reduction in nocturnal awakenings was observed compared with patients in the placebo control group after 12 weeks of medication. Brubaker and Fitzgerald [3] conducted a randomized, double-blind study to evaluate the effectiveness of solifenacin and concluded that solifenacin improved symptoms only in OAB patients without nocturnal polyuria. Patients with reduced nocturnal bladder capacity were not specified in their study.

Because antimuscarinic agents can suppress voluntary and involuntary bladder contractions and thereby increase functional bladder capacity, we hypothesized that patients with reduced nocturnal bladder capacity will benefit from them. Hence, this study was conducted to evaluate the effectiveness of oxybutynin in treating OAB patients with nocturia, and to assess the predictors for response.

2. Materials and methods

From July 2006 through January 2007, 95 adults presenting with the symptoms of frequency >8 times/day and urgency with or without incontinence for at least 3 months were enrolled. Baselines for the study included results of medical history, physical examination, urine analysis, urine culture, uroflowmetry, and a 2-day frequency/volume chart (FVC). Patients with nocturnal void (urination preceded by sleep) more than once per night were included for analysis. Patients with previous history of major abdominal surgery, neurological disease, and concurrent medication of alpha-blockers, diuretics, and anticholinergics were excluded. Male patients aged >50 years were also excluded since prostatism in aging men may confound the results of oxybutynin response.

After baseline evaluations, patients were treated with 2.5 mg of oxybutynin two times per day for 1 week. Patients completed uroflowmetry and nocturia questionnaire (for example, "How many times do you typically get up at night to urinate?" 0=no nocturia; 1=one time; 2=two times; 3=three times; 4=four times; 5=five times or more) at baseline and at week 1 for evaluation of responses to treatment. Patients were asked to void in private and post-void residual urine was measured using transabdominal ultrasound. Changes in nocturia episodes were determined from the differences at baseline and at week 1.

Definitions used in this study conformed to the standards recommended by the International Continence Society (ICS), except where special cases were noted [4]. Nocturnal urine volume was calculated as the total volume of urine voided during the night and the first void in the morning after waking. Total daily urine volume was calculated as the total urine voided in a 24-hour period. Maximum voided volume (MVV) was the largest volume of urine voided during a single micturition determined from the voiding diary. From the FVC, nocturnal polyuria index (NPi), nocturia index (Ni) and nocturnal bladder capacity index (NBCi) were generated [5]. NPi was calculated as "nocturnal urine volume/total daily urine volume", while Ni was calculated as "nocturnal urine volume/the largest single volume voided in a 24-hr FVC". NBCi was defined as "actual number of nightly voids – predicted number of nightly voids", while the predicted number of nightly voids was calculated as "Ni – 1".

Patients were further divided into subgroups according to NPi (cut-off value=0.35), Ni (cut-off value=1.5), and NBCi (cut-off value=2). Responses to oxybutynin were compared among the subgroups.

Data were expressed as mean±standard deviation or percentages and were analyzed using commercially available statistical software (Medcalc® version 9.3; MedCalc Software, Mariakerke, Belgium). Paired *t* test was used to compare changes in parameters between the end point and baseline. Differences in therapeutic responses between groups were analyzed using analysis of covariance (ANCOVA) using baseline nocturia episodes as covariates. A p value less than 0.05 was considered significant.

3. Results

A total of 59 (62.1%) patients were eligible for analysis in this study after excluding those lost to follow-up (n=5), intolerance of adverse effects (n=1), incomplete records of voiding diaries and symptom scores (n=20), total daily urine volume >3000 mL (n=4), and absence of nocturia (n=6). Demographic data are listed in Table 1. After 1 week of treatment with oxybutynin, the mean number of nocturia episodes reduced from 2.7±1.3 to 2.3±1.1 (p<0.01). There were no significant changes in peak flow rate, voided volume, and post-void residual urine at the end point (all p>0.05). There were no significant differences in reduction in the number of nocturia episodes between

Table 1 — Patient demographics and comparisons of nocturia episodes, peak flow rate (Q_{max}), and post-void residual urine (PVR) between baseline and end point*

Patient characteristics			
Case number	59		
Age, yr (range)	47.9±16.0 (19–82)		
Male/Female	11/48		
Nocturnal urine volume, mL	527.2±323.9		
Total daily urine volume, mL	1721.5±587.3		
Maximal voided volume, mL	319.2±120.6		
	Baseline	End point	*p*
Nocturia episodes	2.7±1.3	2.3±1.1	<0.01
Q_{max}, mL/sec	17.6±1.4	17.5±1.2	0.96
Voided volume, mL	211.0±19.1	243.3±20.4	0.10
PVR, mL	33.5±4.5	37.6±5.8	0.36

*Data presented as *n* or mean±standard deviation.

male and female patients (–0.4 *vs.* –0.2, $p=0.17$, ANCOVA).

Self-reported adverse effects included dry mouth (15/95, 15.8%) and constipation (6/95, 6.3%). No patient complained of cognitive impairment. Most of the adverse events were mild and tolerable, except in one patient who discontinued treatment due to severely dry mouth.

3.1. Subgroup analysis

3.1.1. NPi

As shown in Fig. 1, no statistically significant differences were noted in the mean reductions in number of nocturia episodes between patients with NPi>0.35 and those with NPi>0.35 (–0.4 *vs.* –0.3, $p=0.34$, ANCOVA). The mean number of nocturia episodes in patients with NPi>0.35 ($n=21$) reduced from 2.6±1.3 to 2.3±1.1 ($p=0.30$) after treatment. The mean number of nocturia episodes in patients with NPi≤0.35 ($n=38$) reduced from 2.7±1.3 to 2.3±1.1 ($p<0.01$) after treatment.

3.1.2. Ni

As shown in Fig. 2, a significantly greater degree of reduction in number of nocturia episodes was noted in patients with Ni≤1.5 compared to those with Ni>1.5 (–0.9 *vs.* –0.2, $p=0.02$, ANCOVA). The mean number of nocturia episodes in patients with Ni≤1.5 ($n=18$) reduced from 3.2±1.4 to 2.3±0.9 ($p<0.01$). The mean number of nocturia episodes in patients with Ni>1.5 ($n=41$) reduced from 2.4±1.2 to 2.2±1.1 ($p=0.22$).

3.1.3. NBCi

As shown in Fig. 3, a significantly greater degree of reduction in number of nocturia episodes was found in patients with NBCi >2 compared to those with

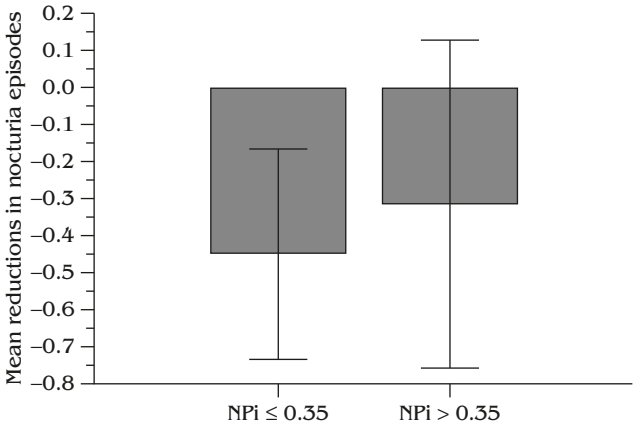

Fig. 1 — Patients with NPi≤0.35 did not have significantly fewer episodes of nocturia at end point compared with those with NPi>0.35 ($p=0.34$).

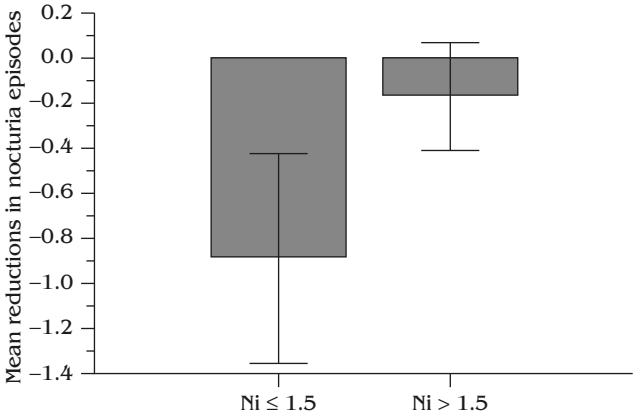

Fig. 2 — Patients with Ni≤1.5 had significantly fewer episodes of nocturia at end point compared with those with Ni>1.5 ($p=0.03$).

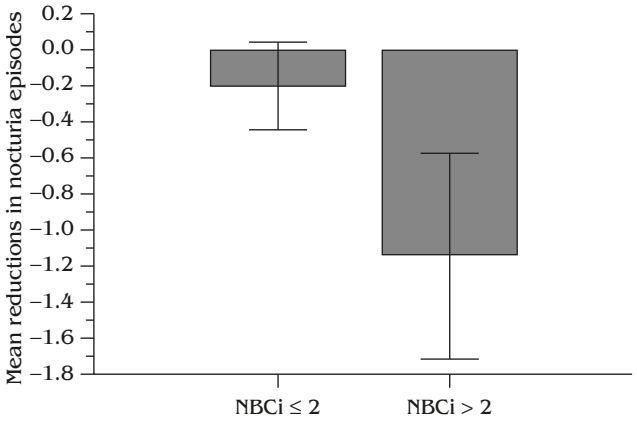

Fig. 3 — Patients with NBCi>2 had significantly fewer episodes of nocturia at end point compared with those with NBCi≤2 ($p=0.01$).

NBCi≤2 (−1.1 *vs.* −0.2, $p=0.01$, ANCOVA). The mean number of nocturia episodes in patients with NBCi>2 ($n=16$) reduced from 3.6±1.5 to 2.5±1.1 ($p<0.01$). The mean number of nocturia episodes in patients with NBCi≤2 ($n=43$) reduced from 2.4±1.1 to 2.2±1.1 ($p=0.20$).

4. Discussion

Ni and NBCi, which take into account MVV and nocturnal bladder capacity, may be the main factors predicting better response to antimuscarinic agents in OAB patients with nocturia. In this study, oxybutynin significantly reduced number of nocturia episodes, particularly in patients with Ni≤1.5 or NBCi>2 ($p<0.05$). Relatively small nocturnal urine volume alone (NPi≤0.35) was not sensitive enough to predict better treatment response to oxybutynin ($p=0.34$).

It has been well established that patients with higher NPi are considered to have excessive nocturnal urine production [4] and have favorable responses to desmopressin [6]. However, NPi≤0.35 is not a good predictor of treatment response to oxybutynin. NPi just indicates nocturnal urine production and does not take bladder capacity into consideration. In fact, when nocturnal urine volume is greater than bladder capacity, nocturia occurs [7]. Patients may wake up in the night to void with either large or small volume, as long as their bladders are full.

In addition, similar to the results of Weiss et al [8], we found that nocturnal polyuria played a minor role in the pathophysiology of nocturia in OAB patients younger than 50 years. The mean age of our patients was 47.9 years, which was lower than the mean age of 56–58 years in the other series. The proportion of studied patients with nocturnal polyuria was 35.6%, which was less than that of previous studies (range, 43–62%) [3,8].

Patients without nocturnal urine overproduction in excess of his/her maximal bladder capacity benefited more from oxybutynin treatment, i.e., patients with Ni≤1.5 had a greater decrease in the episodes of nocturia than those with Ni>1.5. (0.9 *vs.* 0.2, $p=0.03$). Higher Ni values imply nocturnal urine overproduction relative to functional bladder capacity [5]. Rembratt et al [7] evaluated differences in FVC among elderly people with and without nocturia, and proposed that Ni was a statistically significant predictor of nocturia in the elderly. Weiss et al [8] noted that Ni of 1.5 was a threshold, in which higher values meant that nocturia may be attributed to nocturnal urine overproduction in excess of maximal bladder capacity.

Patients with diminished nocturnal bladder capacity can benefit from oxybutynin treatment. Higher NBCi values imply that the underlying pathophysiology of the nocturia is due to decreased nocturnal bladder capacity. Weiss et al [8] proposed NBCi>2 as a highly significant predictor of diminished nocturnal bladder capacity and a major cause of nocturia. We concur that a greater reduction in number of nocturia episodes was noted in patients with NBCi>2 than in those with NBCi≤2 (1.1 *vs.* 0.2, $p=0.01$).

Through antimuscarinic, spasmolytic, and local anesthetic effects, oxybutynin has been widely adopted to treat OAB and nocturia [9]. However, the effects of antimuscarinics on nocturia in OAB patients remain controversial. Kreder et al [10] also reported good responses to tolterodine in OAB patients with nocturia. Johnson et al [11] mentioned that oxybutynin reduced nocturia by a median of 0.30 episodes per night and was significantly more effective than the median reduction (0.00 episode) in the placebo-controlled group ($p=0.07$). Our results demonstrated that oxybutynin also significantly reduced the mean number of nocturia episodes from 2.7±1.3 to 2.3±1.1 ($p<0.01$). It is rapidly absorbed from the gastrointestinal tract after oral intake and has a half-life of 2–3 hours. Its metabolite, N-desethyloxybutynin, also possesses the anticholinergic effects of its parent compound. Thus, the effects of oxybutynin can last for 4–6 hours [12]. Since patients took the second dose of oxybutynin before they slept, oxybutynin had effects on their bladders during their sleep and therefore reduced nocturia episodes. In addition, since oxybutynin is cheaper than tolterodine, it is more cost-effective for treating nocturia.

In the present study, we adopted a 2-day FVC instead of a 7-day FVC. Some authors consider that the wide variability in FVC makes these urinary indices unconvincing and that a 7-day FVC is usually needed to achieve more accurate results [13]. However, the duration of the voiding diary may be related to patient compliance and be burdensome [14]. The reported drop-out rate of the 2-day or 3-day FVC is high and recordings have been complete in only 60% of patients [15]. We adopted the 2-day diary to improve patient compliance, resulting in 78.9% (75/95) completed FVC records. Since both men and women work in our current society, a 7-day diary may not be practical. In addition, the parameters generated from the 2-day FVC provided good information in predicting treatment responses to oxybutynin. Dmochowski et al [16] confirmed that 3-day diaries were as equally effective as 7-day diaries and may have better accuracy due to increased patient compliance.

There were several limitations in the study. First, due to the limited number of cases enrolled, patients without nocturnal polyuria did not demonstrate statistically significant responses to oxybutynin compared with those with nocturnal polyuria. Second, nocturia was not an initial inclusion criterion of the study. Nocturia in patients with OAB may not be representative of nocturia in the general population. Third, the

study duration was only 1 week due to the rapid onset of responses to oxybutynin therapy. Finally, we admit that there was little improvement in reductions in the number of nocturia episodes (–0.4) among these patients. With such a small degree of reduction in the number of nocturia episodes (despite statistical significance), patients will not see any improvement to their quality of life. Of course, the effects may be partly due to the placebo effect, and placebo effect on lower urinary tract symptoms will tend to wear off after long-term therapy. Future placebo-controlled study with a longer duration of observation is warranted to confirm the therapeutic effects of oxybutynin. Therefore, the main purpose of the present study was to find out which factors could predict better responses to anticholinergic agents. In our study, we used Ni and NBCi as predictors and showed that patients with reduced nocturnal bladder capacity may benefit more from treatment with anticholinergic agents.

5. Conclusion

Ni and NBCi are predictive factors for the effects of antimuscarinic agents in the treatment of nocturia in OAB patients. Nocturnal urine volume alone is not a reliable predicting factor.

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