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Efficacy of tolterodine in children with overactive bladder

Aşırı aktif mesane tanısı alan çocuklarda tolterodine kullanımının etkisi

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The known about this topic

Overactive bladder (OAB) is characterized by urgency and increased voiding frequency with or without incontinence and mostly seen in school-age children. The first-line pharmacologic therapy of OAB in children consists of anticholinergic drugs such as oxybutynin, tolterodine, propiverine, and solifenacin. Oxybutynin is the only drug approved but it has adverse effects that limit its use. Tolterodine has fewer adverse effects and is tolerated better.

Contribution of the study

Tolterodine remarkably ameliorates the clinical symptoms of OAB in a short time with no adverse effects. The effects of tolterodine on bladder capacity and post-void residual volume are similar to those of oxybutynin but superior to oxybutynin in terms of reducing bladder wall thickness.

Abstract

Aim: Tolterodine is an anticholinergic drug used for the treatment of overactive bladder. We evaluated the effects of tolterodine on clinical symptoms and compared its efficacy with that of oxybutynin in terms of bladder capacity, bladder wall thickness, and post-void residual volume in children with overactive bladder.

Material and Methods: Twenty-six patients who were treated with tolterodine for overactive bladder (20 girls, mean age 8.0±2.2 years) were evaluated retrospectively. Twenty patients with overactive bladder who had undergone oxybutynin treatment (15 girls, mean age 7.6±1.8 years) served as the control group. Dysfunctional voiding symptom scoring was used to evaluate the clinical response to tolterodine. To investigate the effect of treatment on the bladder, ultrasonographic data at baseline and the third month were compared with the oxybutynin group.

Results: The dysfunctional voiding symptom scores significantly decreased after the third month of tolterodine treatment ($p<0.001$). Bladder capacity significantly increased ($p<0.001$), and filled bladder wall thickness decreased ($p=0.007$); however, post-void residual volumes significantly increased ($p<0.001$) at the third month. No serious adverse effects were recorded during tolterodine treatment. The increase in bladder capacity at the third month in the tolterodine group was similar to that

Öz

Amaç: Tolterodine, aşırı aktif mesanenin tedavisinde kullanılan antikolinerjik bir ilaçtır. Bu çalışmada, aşırı aktif mesane tanısı almış çocuklarda tolterodinin klinik bulguları üzerindeki etkileri ile mesane kapasitesi, mesane duvar kalınlığı ve post-miksiyonel rezidü üzerindeki etkileri oksibutininin ile karşılaştırıldı.

Gereç ve Yöntemler: Aşırı aktif mesane tanısı alıp tolterodin ile tedavi edilen 26 hasta (ortalama yaş 8,0±2,2 yıl) geriye dönük olarak değerlendirildi. Oksibutinin tedavisi alan aşırı aktif mesaneli 20 hasta (15 kız, ortalama 7,6±1,8 yıl) kontrol grubu olarak alındı. Klinik yanıtı değerlendirmek için disfonksiyonel işeme semptom skorlaması kullanıldı. Tedavi sonrası mesanedeki değişikliklerin değerlendirilmesi amacı ile başlangıçtaki ve üçüncü aydaki ultrasonografik veriler oxybutinin grubu ile karşılaştırıldı.

Bulgular: Tolterodin tedavisinin üçüncü ayında, disfonksiyonel işeme semptom skorları anlamlı olarak azaldı ($p<0,001$). Ultrsanografik değerlendirmede ortalama mesane kapasitesi anlamlı olarak artarken ($p<0,001$), ortalama dolu mesane duvar kalınlığı anlamlı olarak azaldı ($p=0,007$) ve ortalama post-miksiyonel rezidü anlamlı olarak arttı ($p<0,001$). Herhangi bir yan etki kaydedilmedi. Tolterodin ve oksibutinin grupları arasında anlamlı bir fark yoktu, ancak tedaviden sonra ortalama

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in the oxybutynin group (p=0.77), but the decrease in filled bladder wall thickness was significantly greater in the tolterodine group (p=0.019).

Conclusion: Tolterodine remarkably ameliorates the clinical symptoms of overactive bladder in a short time, and seems to be as effective as oxybutynin for the treatment of overactive bladder in children. Its effect on reduction of bladder wall thickness appears to be superior to that of oxybutynin.

Keywords: Children, overactive bladder, tolterodine

dolu mesane duvar kalınlığındaki azalma, tolterodin grubunda anlamlı olarak daha yüksekti (p=0,019).

Çıkarımlar: Tolterodin, aşırı aktif mesaneye bağlı klinik bulguları kısa sürede iyileştirir. Overaktif mesaneli çocuklarda oksibutinin kadar etkili bir tedavi olarak görünmektedir. Mesane cidar kalınlığını azaltması, oksibutininden daha iyi gibi gözükmektedir.

Anahtar sözcükler: Aşırı aktif mesane, çocuk, tolterodin

Introduction

Overactive bladder (OAB) is a form of lower urinary tract dysfunction caused by involuntary detrusor contractions during the filling phase. It is characterized by urgency and increased voiding frequency with or without incontinence. Overactive bladder occurs mostly in school-age children and more frequently in girls than in boys (1).

The diagnosis of OAB is made based on clinical findings according to the International Children's Continence Society (ICCS) (1). Children with OAB generally have a small bladder capacity (BC). Therefore, they consume little fluid to avoid the social burden of urgency and increased voiding frequency. Constipation and encopresis are observed frequently in these children because of embryologic, anatomic, and functional interactions between the bladder and bowel (1).

Overactive bladder occurs as a result of stimulation of cholinergic receptors (2). Therefore, the first-line pharmacologic therapy consists of anticholinergic drugs. These drugs mainly act by inhibiting the efferent neurons in the detrusor muscle. In addition, an animal study implied that they also act by way of sensory afferent neurons (3). Oxybutynin, tolterodine, propiverine, and solifenacin are used for the treatment of OAB in children (4). Oxybutynin is the first-line treatment and is the only drug approved for OAB. The anticholinergic effect of oxybutynin is not selective for the bladder; therefore, its use is limited by adverse effects. Tolterodine is another anticholinergic drug that is effective against OAB. It is more selective for the bladder, has fewer adverse effects, and is better tolerated. Few studies have addressed the use of tolterodine in children, which has the same activity as oxybutynin but fewer adverse effects (5).

We assessed the clinical efficacy of tolterodine compared with oxybutynin in terms of bladder capacity (BC), bladder wall thickness (BWT), and post-void residual (PVR), urine volume in children with OAB.

Material and Methods

Study group

In this single-center study, children who were diagnosed as having pure OAB and who received tolterodine (0.1 mg/kg/day, maximum 2 mg/day) as a first-line therapy were retrospectively evaluated. The diagnosis of OAB was made based on clinical findings. The inclusion criteria were: age 5–18 years, having had a clinical evaluation involving dysfunctional voiding symptom (DVS) scoring (6), having been treated only with tolterodine, and available ultrasonography data at the initiation of tolterodine therapy (baseline) and after the third month of treatment. Patients who had dysfunctional voiding, neurologic findings or bladder outlet obstruction were not included in the study. Patients who did not have regular follow-up were excluded. Ultimately, a total of 26 patients (20 girls) were enrolled (tolterodine group).

The control group consisted of 20 patients (15 girls) with OAB who received oxybutynin treatment (0.15–0.4 mg/kg/day) and had available ultrasonography data at baseline and after the third month of treatment (oxybutynin group).

The study was approved by the ethics committee of Cerrahpasa Faculty of Medicine (02.06.2009-16990). Informed consent was obtained from the parents of all children in accordance with the Declaration of Helsinki.

Clinical assessment

The demographic data, duration of therapy, and medication dosage were recorded from the medical records. Dysfunctional voiding symptom scoring was used to evaluate the clinical response to tolterodine. The scores at baseline and after the first and third months of treatment were recorded. Adverse effects that occurred during treatment and treatment compliance data were obtained from medical records.

Ultrasonography

All ultrasonographic examinations were performed in the Department of Pediatric Radiology at Istanbul University Cerrahpasa Medical Faculty. The ultrasonographic BC, BWT, and PVR values at baseline and after the third month of treatment were recorded.

Children were encouraged to drink fluid as much as possible. The measurements were performed when the children said that they were full and wanted to empty their bladder. The measurements were performed in the standard supine position. All measurements were performed

at the same bladder points. Bladder wall thickness was measured in three places: perpendicular to the luminal surface of the bladder at the thickest part of the trigone, at the dome of the bladder, and at the anterior wall of the bladder, and the mean measurement was recorded. All measurements were taken post-micturition.

For each patient, the age-appropriate expected BC was calculated using the formula: expected BC = [age (years) + 1] × 30 mL (7), and the baseline BC was expressed as a percentage of the expected capacity. A measured BC of <65% of the expected capacity for age was defined as a small capacity. The increase in BC compared with baseline was calculated separately for each patient to evaluate treatment response at the end of the third month and was expressed as a percentage. The change in BWT was calculated in the same way. A BWT of ≥3 mm in a filled bladder was considered an increase. Post-void residual urine volume at the end of the third month of treatment was expressed as a percentage of the BC. A PVR volume >10% of the BC or >20 mL was defined as an increased volume.

Statistical analysis

The SPSS 15.0 software for Windows was used for statistical analyses. The Shapiro-Wilk test was used to evaluate the normality of the data distribution. Continuous variables are presented as median [interquartile range (IQR)]. Non-parametric tests were used due to the small sample size and the presence of non-normally distributed data. The changes in BC, BWT, and PVR were compared using Wilcoxon signed-rank tests. The tolterodine and oxybutynin groups were compared using the Mann-Whitney U-test and Chi-square test. A p value <0.05 was considered indicative of statistical significance.

Results

Clinical and ultrasonographic response to tolterodine

Dysfunctional voiding symptom scores at baseline and after the first and third months of treatment were compared to evaluate the efficacy of tolterodine. The median (IQR) DVS score at the baseline was 15.5 (11.8; 22.0), and significantly decreased to 8.0 (4.0; 10.0) at the first month, and to 3.0 (2.0; 4.0) at the third month of the treatment (p<0.001, for both) (Fig. 1).

The median BC at the baseline was significantly lower than the median expected BC for age [205 (123; 265) mL vs. 255 (210; 334) mL; p= 0.008]. A total of 11 patients (42%) had a small BC. The median BC significantly increased to 285 (230; 363) mL after the third month of treatment (p<0.001) (Fig. 2a). The median increase in BC after the third month of treatment was 47% (27%; 91%).

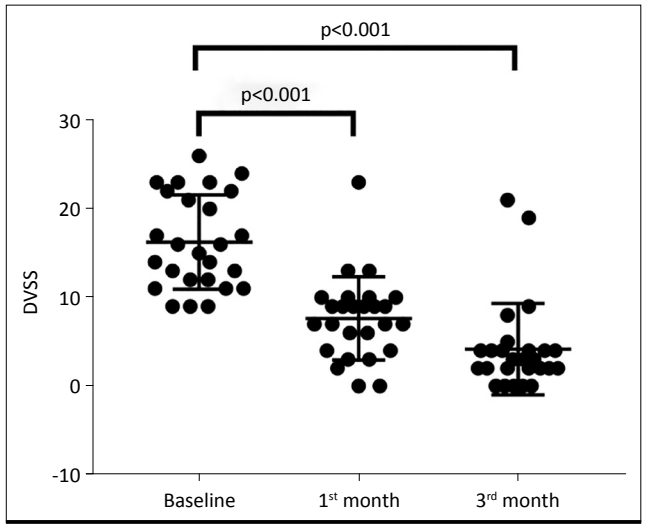

Figure 1. Dysfunctional voiding symptom scoring (DVSS): comparisons of the baseline with the 1st month and 3rd month of tolterodine treatment (Wilcoxon signed rank test)

A total of 20 patients (77%) had a higher BWT at baseline. The median micturition BWT significantly decreased at the end of the third month of treatment compared with baseline [3.9 (3.0; 4.3) mm vs. 3.2 (2.5; 4.0) mm; p=0.007] (Fig. 2b). The median decrease in BWT at the third month was 7.8% (1.6%; 19.4%).

The median PVR volumes at baseline significantly increased from 0.0 (0.0; 15.0) mL to 25.5 (15.0; 37.8) mL at the end of the third month of treatment (p<0.001) (Fig. 2c). After the third month of treatment, the median PVR volume was 8.8% (4.8%; 14.5%) of the BC and the PVR was higher in 16 patients (61.5%).

There were no serious adverse effects that required discontinuation of therapy, such as flushing, dry mouth, headache, constipation, hyperpyrexia or dizziness.

Comparison of tolterodine and oxybutynin

There were no significant differences between the two groups in terms of change in BC or PVR after the third month of treatment, whereas the decrease in the mean filled BWT was significantly greater in the tolterodine group than in the oxybutynin group after treatment (p=0.019). The bladder data are summarized in Table 1.

Discussion

Our data indicate that tolterodine treatment for 3 months significantly decreases DVS scores, significantly increases BC, and significantly decreases BWT in children with OAB. An elevated PVR volume was an unfavorable effect of tolterodine. Moreover, the effects of tolterodine on BC

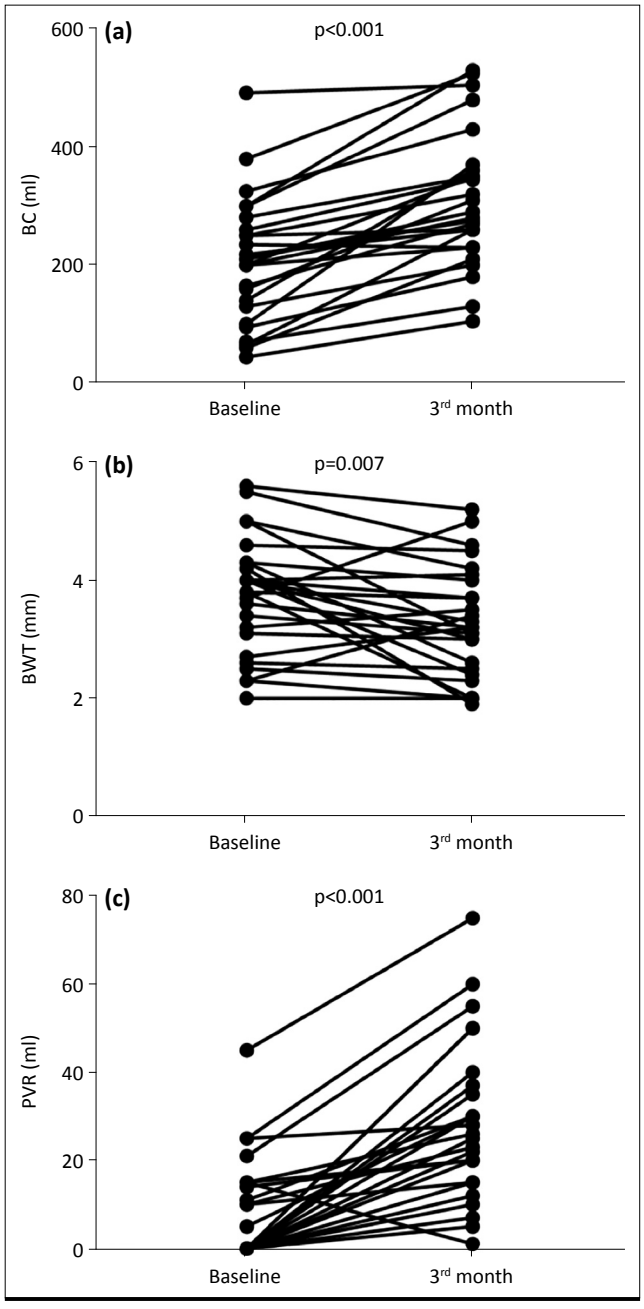

Figure 2. The effect of tolterodine on the bladder (differences from the baseline to the 3rd month) (Wilcoxon signed rank test) (a) bladder capacity (BC) (b) bladder wall thickness (BWT) (c) post-void residual urine volume (PVR)

and PVR were similar to those of oxybutynin but superior to oxybutynin in terms of reducing BWT.

We evaluated the clinical effects of tolterodine based on the DVS scores. The scores were significantly lower after the first and third months of treatment than at baseline. This is consistent with previous studies that evaluated treatment outcomes using this scoring system to evaluate non-neurogenic bladder disorders (8–10). These studies have reported that tolterodine significantly reduced DVS scores in a short time.

In the present study, the effects of tolterodine on BC, BWT, and PVR were also evaluated using ultrasound. In all, 42% of patients had a small BC (less than 65% of the expected capacity). A significant increase in BC (median 47%) was observed after 3 months' treatment. This finding is compatible with previous reports (10–12). In one previous study, tolterodine was used as a first-line therapy in 12 pediatric patients and after oxybutynin treatment in 10 pediatric patients; the authors found that tolterodine increased BC and the compliance rate and significantly decreased detrusor pressure (11). Indeed, urodynamic tests suggest that oxybutynin and tolterodine significantly increase BC and compliance (13, 14). Therefore, tolterodine has a favorable effect on BC.

Patients with OAB frequently exhibit an increased BWT caused by thickening of the detrusor muscle (15, 16). The BWT is increased in children with posterior urethral valve, dysfunctional voiding, and neurogenic bladder (16–18). This finding is related to the increase in detrusor activity against the closed external sphincter (19). In a study of adult women, tolterodine significantly decreased BWT after 12 weeks (20). However, the effects of tolterodine on BWT in children with OAB are unclear. In this study, the median BWT in filled bladders was 3.9 mm at the baseline, and 77% of patients had an increased BWT. After the third month of tolterodine treatment, BWT was reduced by 8% compared with baseline. In contrast, BWT was not reduced after the third month of oxybutynin therapy. Therefore, tolterodine seems to be superior to oxybutynin in reducing BWT.

In adults, tolterodine reportedly induces a dose-dependent increase in PVR urine volume (19–22); however, other studies have reported no such effect (11, 23). In this study, tolterodine led to a significantly larger PVR at the end of the third month of treatment. This may be a negative effect of tolterodine because a greater residual urine volume increases the risk for urinary tract infection. However, our study involved a limited number of subjects and the relationship between tolterodine and urinary tract infection was not evaluated. Therefore, more comprehensive and prospective studies of this issue are warranted.

Oxybutynin has a high incidence of adverse effects, and so is not well tolerated by some patients. In adults, dry mouth, constipation, blurred vision, and feelings of warming are adverse effects of oxybutynin; these are considerably less frequent with tolterodine (24–28). No pediatric studies have reported any serious adverse effects of tolterodine, but non-serious adverse effects including constipation,

Table 1. Comparisons of the clinical and ultrasonographic findings between the tolterodine and oxybutynin groups

	Tolterodine group n=26	Oxybutynin group n=20	p[a]
Age, years	7.5 (6.0; 9.8)	7.5 (6.0; 10.1)	0.52
Sex (female), n (%)	20 (77)	15 (75)	0.89
Expected BC, mL	255 (210; 334)	255 (210; 323)	0.52
Baseline BC, mL	205 (123; 265)	150 (99; 200)	0.08
Baseline BCb, %	71.5 (39.5; 108)	61 (44; 72.5)	0.18
BC at the 3rd month, mL	285 (230; 363)	250 (181; 338)	0.13
Increase in BC, %	47 (27; 91)	69 (17; 147)	0.77
Baseline BWT, mm	3.9 (3.0; 4.3)	3.3 (2.6; 5.0)	0.55
BWT at the 3rd month, mm	3.2 (2.5; 4.0)	3.6 (2.6; 5.0)	0.27
Change in BWT, %	-7.8 (-19.4; -1.6)	11.7 (-13.4; 29.8)	0.019
Baseline PVR, mL	0.0 (0.0; 15.0)	10.5 (0.6; 21.5)	0.09
PVR at the 3rd month, mL	25.5 (15; 38)	10.0 (25; 40)	0.75
PVR at the 3rd monthc, %	8.8 (4.8; 14.5)	9.5 (5.9; 11.4)	0.89
Pts with increased PVR at the 3rd monthd, n (%)	16 (61.5)	11 (55)	0.77

BC: Bladder capacity; BWT: Bladder wall thickness in filled bladder; PVR: Post-void residual urine volume; a: Continuous data presented as median (25th p; 75th p), and Mann-Whitney U test and Chi-square test were used for the comparisons; b: % of the initial bladder capacity to the expected capacity; c: % of the PVR to BC at the end of 3rd month; d: Number of patients with a PVR >20 mL or >10% BC at the end of 3rd month

dry mouth, and heat stroke have been mentioned (11, 29). In our study, no adverse effects that required discontinuation of tolterodine were documented. This suggests that tolterodine is well tolerated in children; however, the retrospective design of this study means that the records of some patients may not have been available.

This is one of few studies on the effects of tolterodine on BWT in children with OAB. This study was limited by the small sample size, its retrospective and non-randomized design. Additionally, another limitation is not having urodynamic studies.

Conclusion

Tolterodine is effective against OAB in children. It provides significant clinical improvement, increases BC, and reduces BWT in such patients. Tolterodine is superior to oxybutynin in terms of its effect on BWT. A greater PVR volume was the only unfavorable effect of tolterodine observed in this study. Prospective studies are needed to confirm our findings.

Ethics Committee Approval: The study was approved by the ethics committee of Cerrahpaşa Faculty of Medicine (02.06.2009-16990).

Informed Consent: Informed consent was obtained from the parents of all of the children.

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