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Gabapentin: A novel drug as add-on therapy in cases of refractory overactive bladder in children

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Abstract *Objective:* To determine the effectiveness of gabapentin as an add-on therapy in children presenting with overactive bladder (OAB) not responding to conventional anticholinergics.
Materials and methods: Children with refractory OAB were included prospectively from March 2009 to February 2010. The inclusion criterion was persistence of symptoms while on conventional anticholinergics for 6 months. Gabapentin was prescribed as an add-on therapy. The patients were followed 4 weekly with bladder diary and urodynamic study was repeated at 3 months.
Results: There were 31 children, 26 of neurogenic OAB and 5 of non-neurogenic origin. Mean ± SD age was 8.5 ± 5.3 years. Data were analyzed in 30 patients as treatment was terminated in 1 due to adverse effects. Continence improved in 16 (53.3%) patients. Voiding volume improved from 175 ± 90 to 320 ± 110 ml ($p < 0.03$). Objective assessment of OAB symptom relief showed marked improvement ($p < 0.05$). Mean maximum cystometric bladder capacity improved from 210 ± 94 to 360 ± 110 ml ($p < 0.02$). The maximal detrusor contraction decreased from 75 ± 35 to 25 ± 15 cm H_2O ($p < 0.02$). Fourteen patients (46.7%) failed to respond to gabapentin therapy. These patients had baseline maximum cystometric bladder capacity <60% for age and maximum detrusor contractions >50 cm of water ($p < 0.03$).
Conclusions: Gabapentin gives moderate results in children with OAB refractory to conventional anticholinergics. In general, the drug is well tolerated with fewer adverse effects.

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Introduction

Overactive bladder (OAB) is a common and distressing urological disorder that not only adversely affects quality of life but also imposes a significant financial burden. The current standard of care is to decrease detrusor overactivity (DO) via blockade of bladder M_3 muscarinic receptors, the primary cholinergic receptors responsible for detrusor contraction [1,2]. However, systemic antimuscarinic adverse effects, such as dry mouth and constipation, limit the tolerability of antimuscarinic treatment in many children. Even the most recent group of uroselective antimuscarinics are not totally free from these side effects [2]. Furthermore, 30–40% of children do not respond to these conventional anticholinergics [2,3].

Gabapentin, an antiepileptic drug that is free from antimuscarinic adverse effects, was approved by the Food and Drug Administration in 2000 for pediatric use [4]. The drug has recently been explored for the treatment of OAB [5–10]. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not interact with GABA receptors, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation [5]. The drug has been used for various types of neuropathic pain as it appears to have inhibitory activity on afferent C nerve fiber activity (Fig. 1a) [8,11]. The same mechanism has been exploited to treat various lower urinary tract disorders such as OAB and interstitial cystitis, mainly in adults [12,13].

Data on gabapentin and its use in children with lower urinary tract symptoms (LUTS) are sparse. Herein we present our data on the effectiveness of gabapentin in children with LUTS.

Materials and method

From March 2009 to February 2010, we studied 31 children with OAB (neurogenic and non-neurogenic) who continued to have LUTS in spite of taking conventional anticholinergics for at least 6 months. The inclusion criteria were: patients presenting with LUTS such as frequency, urgency or urge incontinence with urodynamically proven DO ± low compliance in cases of neurogenic OAB and/or at least 8 micturitions every 24 h and at least 2 urge incontinence episodes per week in cases of non-neurogenic OAB. An informed consent was obtained from the patients or parents (in the case of small children). Basic work-up included: complete history, focused neurological examination, examination of bladder diary, urine analysis (routine examination and culture sensitivity), renal function test, micturating cystourethrogram (MCU), and a urodynamic study for the confirmation of DO especially in cases of neurogenic bladder. During urodynamic study the bladder was initially filled at a low rate, i.e. 2 ml/min, which went up to maximum 10% of the expected bladder capacity for age, i.e. age [years] + 2 × 30 ml. The patients received oral gabapentin 10–20 mg/kg/day divided into three doses for a period of at least 12 weeks [10].

The patients were followed up every 4 weeks for the first 3 months and 3 monthly thereafter. The follow-up included a detailed history, physical examination and review of 3-day bladder diary. Urodynamic study was repeated at 3 months from the date of start of gabapentin. Patients/parents were questioned about adverse reactions, which were classified as: mild = did not interfere with child's routine activities (playing, schooling), moderate = interfered to some extent, and severe = interfered significantly [14].

The results were evaluated on the basis of the improvement in OAB symptoms. Subjective assessment was based on changes in bladder diary data and objective assessment was done on the basis of a 6-point patients/parents perception of bladder condition (PPBC) scale (Table 1) and changes in urodynamic indices according to the International Children's Continence Society classification [14,15]. The definitions were taken as: complete cure = with no episode of leak, improvement = at least a 90% decrease in incontinence episodes, partial improvement = 50–89% decrease in incontinence episodes, and failure = a less than 50% decrease. The urodynamic indices studied were: compliance, maximum cystometric bladder capacity for age, detrusor contractions and end filling pressure.

The patients with proven urinary tract infection and bladder stones were excluded from the study. Statistical analysis was done with the application of SPSS (Version 11.5) software and P value < 0.05 was considered as statistically significant. The Student t-test and Wilcoxon Mann–Whitney tests were used for statistical analysis.

Results

Thirty-one children with OAB were enrolled in the study, 26 being neurogenic OAB (Table 2) and 5 being of non-neurogenic origin. The mean ± SD age at enrollment was 8.5 ± 5.3 years. Mean ± SD gabapentin treatment duration was 14.5 ± 7.5 months. Data were analyzed in 30 patients, as in 1 patient treatment was terminated because the patient complained of intolerable adverse effects. At a mean follow-up of 10.5 months [7–22], 16 (53.3%) patients had achieved spontaneous voiding, while 14 (46.7%) patients required clean intermittent self-catheterization to ensure complete emptying of bladder. Of the 16 patients with spontaneous voiding, 11 belonged to the neurogenic group and the other 5 were the non-neurogenic group. Both groups had post-void residual urine less than 10% of expected bladder capacity for age.

Continence improved in 16 (53.3%) patients overall. Of these, 3 (10%) were completely dry, 6 (20%) showed significant improvement and 7 (23.3%) had a partial response.

On the PPBC scale, patients/parents reported a significant improvement in bladder condition ($p < 0.05$) (Fig. 1b and Table 3). Similarly, in the 3-day voiding diary, the mean ± SD voiding volume improved from 175 ± 90 to 320 ± 110 ml ($p < 0.03$). Mean ± SD maximum cystometric bladder capacity improved from 210 ± 94 to 360 ± 110 ($p < 0.02$). The mean ± SD maximal detrusor contraction decreased from 75 ± 35 to 25 ± 15 cm H_2O ($p < 0.02$). The mean ± SD number of urge incontinence episodes improved from 4.1 ± 0.9 to 1.8 ± 0.4 per day ($p < 0.05$).

Fourteen patients (46.7%) required clean intermittent self-catheterization before treatment, while after treatment with gabapentin this number increased to 16 (53.3%)