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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%)

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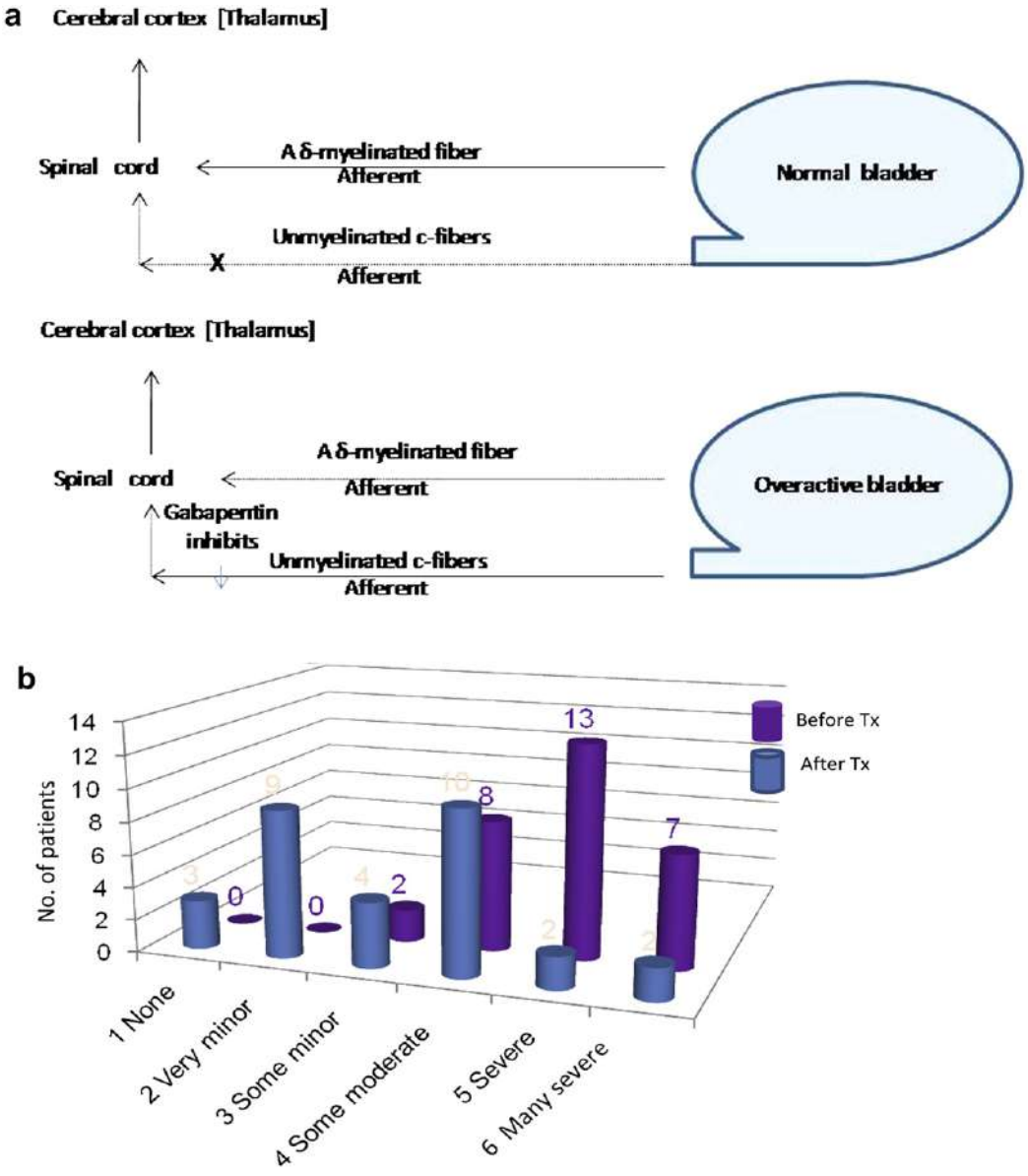

Figure 1 a. The mechanism of pathway for gabapentin. b. Patients/parents perception of bladder condition scale before and after treatment.

(p = NS). Similarly, the 3-day voiding diary showed improved OAB symptoms which correlated well with the changes in urodynamic indices and PPBC score (Table 3).

Fourteen patients (46.7%) failed to respond to gabapentin therapy. Their urodynamic factors were analyzed to determine any correlation to the failure. The patients who failed gabapentin add-on therapy had baseline maximum cystometric bladder capacity less than 60% for age and maximum detrusor contractions >50 cm of water ($p < 0.03$).

Table 1 Patients/parents perception of bladder condition (PPBC) scale.

1. Does not cause me any problem at all
2. Causes me some very minor problems
3. Causes me some minor problems
4. Causes me [some] moderate problems
5. Causes me some severe problems
6. Causes me many serious problems

Most of the patients, 24 (80%), experienced mild (concentration problems, mood swings, hyperactivity) and 5 (16.7%) of the patients had moderate (somnolence, anxiety) adverse reactions but both groups continued with the medicine. Serious (drowsiness, dizziness, headache, fatigue) side effects were noted in 1 patient (3.3%) in whom the drug had to be stopped.

Discussion

OAB is defined by its symptoms, consisting of urgency with or without urgency incontinence, frequency and nocturia

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Table 2 Etiology of neurogenic bladder.

Etiology	No./%
Spinabifida	22 [84.61%]
Tethered cord	3 [11.54%]
Sacral agenesis	1 [3.85%]

[1]. Neurogenic OAB occurs as a result of detrusor muscle overactivity, referred to as neurogenic detrusor overactivity, secondary to known neurologic disorders. Children with spinal cord lesions/myelodysplasia often suffer from neurogenic OAB. In contrast, non-neurogenic OAB occurs as a result of detrusor muscle overactivity and can arise from non-neurological abnormalities, such as bladder stones, muscle disease, urinary tract infection or drug side effects, or can be idiopathic [16,17].

Current treatments for OAB include medication, diet modification, programs in bladder training, electrical stimulation, and surgery [21,22]. Muscarinic receptor antagonists, including oxybutynin, tolterodine, trospium chloride, darifenacin, and solifenacin, are front-line therapies for OAB, with an efficacy of 65–75% in reducing major symptoms [2,3,18]. Of these, oxybutynin is the only drug approved by the Food and Drug Administration. Treatment with antimuscarinics is not free of side effects, such as dry mouth, dry eyes, blurred vision, drowsiness, constipation, and cardiac side effects such as palpitations and arrhythmia, which have proven difficult for some individuals to tolerate, especially in the pediatric age group [19,20]. Because of these inherent side effects, which are often ignored in the light of the benefits of these drugs, there has been ongoing research to find novel drugs that are devoid of these side effects. In addition, 30–40% of children fail to respond to these conventional anticholinergics and may need more cumbersome, costly and invasive procedures such as intravesical botulinum toxin, neuromodulation and augmentation cystoplasty [2,3]. The facility for the former may not be available at many centers.

Due to the enormous complexity of micturition, the exact mechanism of OAB is not known [16–18]. The condition can result from hypersensitivity of sensory neurons of the urinary bladder, arising from various factors including inflammatory conditions, hormonal imbalances, and bladder outlet obstruction. Destruction of the sensory nerve fibers, either due to an injury to the sacral region of the spinal cord or from a disease that causes damage to the dorsal root fibers as they enter the spinal cord, can also lead to OAB. In addition, damage to the spinal cord or brainstem causing interruption of transmitted signals can lead to abnormalities in micturition. Therefore, both peripheral and central mechanisms can be involved in mediating the altered activity in OAB [16,17].

In spite of the uncertainty regarding whether central or peripheral mechanisms, or both, are involved in OAB, many proposed mechanisms implicate neurons and pathways that mediate non-painful visceral sensation. The bladder afferent pathways, which carry somatosensory information from the bladder, consist of myelinated Aδ-fibers and unmyelinated C-fibers. These fibers enter the spinal cord via the dorsal root ganglion and project to the brainstem and thalamus via second or third order nerve fibers. Aδ-fibers transmit signals from mechanoceptors that initiate the normal micturition reflex, while C-fibers are not essential for normal voluntary voiding. However, various pathological conditions, such as spinal cord injury and chronic bladder irritation, induce sensitization and/or recruitment of C-fibers, resulting in an overall increase in the C-fiber contribution to mechanotransduction and bladder overactivity (Fig. 1) [8,11,23]. Currently, there are no clinically approved applications of central nervous system oriented pharmacotherapies for treating lower urinary tract disorders, such as OAB. However, recent animal studies have suggested potential targets in the central nervous system for modulating urinary tract functions [7,21].

Gabapentin, a second-generation anticonvulsive drug, was formed by the addition of a cyclohexyl group to gamma-aminobutyric acid (GABA), which allowed this form of GABA to cross the blood–brain barrier. Despite its structural similarity to GABA, gabapentin does not bind to GABA receptors in the central nervous system. Its precise mechanism of action is unknown, but it has been hypothesized that it may involve enhanced neuronal GABA synthesis or inhibition of afferent C-fiber activity [8,11,23]. Gabapentin is not metabolized, and does not induce or inhibit hepatic metabolism, and is mainly excreted through the kidneys. The half-life is 4–9 h; therefore, it is usually

Table 3 3-day voiding diary, urodynamic indices and PPBC scale.

	Before	After	*p* value
3-day voiding diary			
Mean + SD Voiding volume [ml]	175 ± 90	320 ± 110 ml	$p < 0.03$
Mean + SD number of urge incontinence/day	4.1 ± 0.9	1.8 ± 0.4	$p < 0.05$
Post-void residual urine [>10% of expected bladder cap. for age] No.	14	16	NS
Urodynamic indices			
Mean + SD maximum cystometric bladder capacity [ml]	210 ± 94	360 ± 110	$p < 0.02$
Mean + SD maximal detrusor contraction [cm H_2O]	75 ± 35	25 ± 15	$p < 0.03$
PPBC Scale			
Mean + SD PPBC Scale	5 ± 0.8	2.1 ± 0.9	$p < 0.05$

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given three times a day. The drug has been extensively used in partial seizures, neuralgia and various types of neuropathies. Although side effects from gabapentin are not common, they can occur and include: somnolence, drowsiness, headache, fatigue, blurred vision, ataxia, tremors and anxiety [11,12]. Gabapentin was first used in urology for the treatment of refractory interstitial cystitis [8,12]. The possible pathogenesis of interstitial cystitis in this regard was proposed as up-regulation of afferent C-fiber sensory neurons. In this study, 10 of 21 interstitial cystitis patients reported subjective improvement of their pain. It has been hypothesized that certain cases of OAB share this pathophysiology of up-regulation of afferent C-fiber sensory neurons (Fig. 1a) [8,12]. This further led to the use of gabapentin for the treatment of OAB and nocturia. Carbone et al. [9] reported significant modification of urodynamic indexes, particularly for DO, while the symptomatic score evaluation and voiding diary data demonstrated a considerable lowering of the irritative symptoms. Furthermore, they did not record significant adverse effects and no patient stopped the drug treatment. It was inferred that the DO may be controlled by modulating the afferent input from the bladder and the excitability of the sacral reflex center, and this was suggested as a novel method to treat OAB patients [13]. Similarly, Yoshimura and Chancellor [8] documented that 14 out of 31 (45%) patients with refractory OAB reported subjective improvement in terms of frequency of micturition ($p = 0.01$) and nocturia ($p = 0.03$). In this study, it was interesting to see that gabapentin was able to help in certain cases of nocturia, which had tended to be a refractory symptom for oral antimuscarinic agents [8].

These data provide a reasonable justification that modulation of the afferent input via unmyelinated C-fibers from the bladder and the excitability of the sacral reflex center may control DO. Data on gabapentin and its use in pediatric urological disorders are sparse. In the present study, the authors used gabapentin in children with refractory OAB and the results were encouraging. Generally, the drug is well tolerated and lacks systemic antimuscarinic adverse effects. Only 1 patient complained of additional adverse effects or exaggeration of the effects of the anticholinergics they were previously receiving. Most of the patients experienced mild and some moderate adverse reactions, but all continued with the medicine. Serious side effects were noted in 1 patient only in whom the drug had to be stopped.

This is the first study highlighting the use of gabapentin in children in a prospective manner. The limitations are that the study is non-randomized, lacks a placebo arm, and has a relatively short follow-up.

In conclusion, with good tolerability, clinical safety and efficacy, gabapentin appears to be a viable alternative to treat refractory LUTS in children. Prospective, randomized and placebo-controlled studies with long-term follow-up are needed to further evaluate the effectiveness of this drug.

Conflict of Interest

None

Funding

None

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