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Original Article

Gabapentin Treatment of Neurogenic Overactive Bladder

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Abstract

Objective:
Detrusor overactivity is a well-recognized and distressing medical condition affecting both men and women, with a significant prevalence in the population and with a higher incidence rate in people older than 70 years. This pathological condition is characterized by irritative symptoms: urinary urgency, with or without incontinence, and urinary frequency, often seriously compromising the quality of life of the people who have it. The complaint of these symptoms is defined by the International Continence Society (www.continet. org) as "overactive bladder." Many neurological patients experience irritative symptoms of the lower urinary tract related to their disease, and this condition drastically limits their social life. Various drugs have been introduced in therapy protocols to treat neurogenic detrusor overactivity; however, in many cases, the outcomes of these treatments have proven to be unsatisfactory. This fact is probably related to the incomplete understanding of the pathophysiological aspects of detrusor overactivity. Recent studies suggest the possible role in the detrusor overactivity pathogenesis of bladder receptors, afferent pathways, and spinal cord interneurons; consequently, the modulation of bladder receptor and/or spinal cord center activity has been proposed as a possible approach to control involuntary detrusor contractions, using drugs capable of acting on bladder afferent pathways.
The aim of this study was to evaluate the efficacy of gabapentin, an anticonvulsive agent used by neurologists in the treatment of epilepsy and neurogenic pain, in the treatment of detrusor overactivity of neurogenic origin.

Methods:
Sixteen patients affected by neurogenic overactive bladder were enrolled in the study. The clinical outcomes were assessed by symptomatic score evaluations, voiding diary, and urodynamic test before and after 31 days of gabapentin treatment.

Results:
The preliminary results showed significant modifications of urodynamic indexes, particularly of the detrusor overactivity, whereas the symptomatic score evaluation and the voiding diary data demonstrated a significant lowering of the irritative symptoms. Furthermore, we did not record significant adverse effects and no patient interrupted the drug treatment.

Conclusions:
These data support the rationale that detrusor overactivity may be controlled by modulating the afferent input from the bladder and the excitability of the sacral reflex center and suggest a novel method to treat overactive bladder patients.

Key Words: gabapentin, neurogenic detrusor overactivity, treatment of neurogenic overactive bladder

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The overactive bladder is a well-recognized, chronic, and distressing medical condition characterized by urinary urgency and frequency, with or without incontinence.[1] In the United States, overactive bladder affects at least 17 million individuals, whereas European studies show a 17% prevalence in people older than 40 years.[2–5] In fact, the incidence of overactive bladder among individuals 20 to 60 years old has been estimated at 10%.[6] This condition is most common in the elderly, with a prevalence of 50% in asymptomatic men older than 70 years and 30% in co-aged women.[7] In the symptomatic elderly, it increases to 80% in women and 90% in men older than 75 years.[8] Furthermore, overactive bladder is present in patients with neurogenic disorders showing urological symptoms (urgency,

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frequency, with or without urinary incontinence) and is often the consequence of detrusor overactivity, an alteration of bladder function characterized by involuntary detrusor contractions during the filling phase. Symptoms secondary to detrusor overactivity may be responsible for discomfort, shame, and loss of self confidence; and in neurogenic patients, who already often present limited autonomy, this urinary distress can determine a complete social withdrawal.[3,4] Many of these patients need continuous and fairly expensive home care. In many countries, especially the United States, urinary distress in neurogenic patients is responsible for 40% to 60% of all nursing-home admissions, with very high costs for public health care and financing policies.[5]

Whereas overactive bladder diagnosis is based on symptoms evaluation, the diagnosis of detrusor overactivity is possible only through the urodynamic test. This is an instrumental diagnostic tool that allows the evaluation of the bladder function during the filling (cystometry) and the voiding phase (pressure/flow study). It is performed by the simultaneous recording of bladder and abdominal pressures by using electronic transducers connected to bladder and rectal catheters. In neurogenic patients, a contextual pelvic electromyography is recommended. The neurogenic detrusor overactivity presents some specific urodynamic features: it occurs at low bladder filling, it is recurrent during the cystometry, the test/retest provides similar outcomes, and it is often associated with urinary leakage.

Today, various drugs are used in the treatment of overactive bladder; the antimuscarinics are recommended, although they may be the cause of various adverse effects. In the past years, the most frequently prescribed drug has been oxybutinin, an antimuscarinic and antispasmodic drug, whereas most recently (in 1997, the first use in healthy human volunteers), tolterodine has been used. This is a uroselective, potent, competitive muscarinic receptor antagonist particularly developed for the treatment of overactive bladder, which has demonstrated a better tolerability profile and a higher efficacy. Today, other antimuscarinics are available. Of recent introduction is darifenacin, an antagonist at muscarinic cholinergic M1, M3, and M5 receptors, which has been shown to be significantly superior to placebo in reducing the numbers of micturitions, incontinence, and urgency episodes; reducing urge severity; and increasing the warning time and volume per micturition.[9] Similar results in treating symptoms secondary to detrusor hyperactivity are reported by using solifenacin, another antagonist at muscarinic cholinergic M1, M2, and M3 receptors.[10] Trospium chloride, a quaternary amine, has also been shown to be effective in relieving overactive bladder symptoms.[11] All these drugs have a good safety profile; but they also present, in a considerable amount of patients, unsatisfactory outcomes or adverse effects (dry mouth, constipation, and headache) that induce therapy withdrawal. The changeable outcomes obtained by antimuscarinics could be related to the different pathogenetic mechanisms that determine detrusor overactivity. These data underline the need for an effective, long-term and adverse effect–free treatment.

Recent physiological and pharmacological studies[12,13] have suggested that bladder receptors, afferent pathways, and spinal cord interneurons may be involved in the pathophysiology of detrusor overactivity. Basing on this hypothesis, different pathogenetic mechanisms for detrusor overactivity have been considered, prompting various authors to develop new models in treating overactive bladder. The afferent pathways hyperactivation, mediated by C and Aδ fibers, and the consequent increase in the afferent input to the spinal cord, where the sacral reflex controlling detrusor activity is located, are considered possible causes of detrusor overactivity.[13–15] Consequently, the modulation of bladder receptor and/or of the spinal cord reflex centers has been proposed as a possible approach to control involuntary

detrusor contractions (IDCs). Various drugs used by neurologists to treat epilepsy, neurogenic pain, and spasticity may control the excitability of the nervous fibers acting on the calcium and sodium channels or may modulate the activity of spinal reflex centers because of their GABAergic activity. Some of these may have urological applications.

The aim of this study was to evaluate the efficacy of treating overactive neurogenic bladder using gabapentin. This drug is an anticonvulsive agent widely used by neurologists to treat epilepsy and neurogenic pain. It is a gamma aminobutyric acid analog that does not interact with gamma aminobutyric acid receptors.

Gabapentin has different mechanisms of action. The most important is probably related to its high affinity to the alpha-2-delta subunit Ca^{++} channels that are capable of reducing the calcium current type L,[16–19] present in both Aδ and C fibers. Particularly, gabapentin reduces activation of C and Aδ fibers, which strongly depends on the Ca^{++} channel mediating presynaptic transmitter release responsible for detrusor contraction after submucosal receptor stimulation.[20] In addition, gabapentin modifies afferent input from the periphery, acting on a wide dynamic range of interneurons of the dorsal horn of the spinal cord (responsible for "gate control" of the afferent inputs with a prevalent

TABLE 1. Age, Neurogenic Diagnosis, and Clinical Features of the Patients in the Study

Patient	Age, year	Pathology	Year of Diagnosis	Exordium Voiding Symptoms	Clinical Features
1	73	MIE	1994	2000	Hyperreflexia, paraplegia
2	69	MIE	2000	2000	Hyperreflexia, paraplegia
3	75	MIE	1998	2000	Hyperreflexia, paraplegia
4	70	MIE	2001	2002	Hyperreflexia, paraplegia
5	76	MIE	1998	1999	Hyperreflexia, paraplegia
6	69	PD	1990	2000	Rigidity, tremor
7	66	PD	1992	1999	Rigidity, tremor
8	59	PD	1998	2002	Rigidity, tremor
9	47	MSA	2001	2001	Extrapyramidal, pyramidal signs
10	55	MSA	2001	2001	Extrapyramidal, cerebellar signs
11	56	SM	1999	2002	Hyperreflexia, paraparesis
12	48	SM	1992	2002	Hyperreflexia, paraparesis
13	45	IM	2000	2000	Hyperreflexia, paraplegia
14	72	IM	1998	1998	Hyperreflexia, paraplegia
15	56	IM	1995	1995	Hyperreflexia, paraparesis
16	51	FS	Surgery: 1993	1993	Hyperreflexia, ataxic gait

MIE indicates multiple infarction encephalopathy; PD, patients with Parkinson disease; MSA, multisystemic atrophy; SM, multiple sclerosis; IM, postinfectious myelitis; FS, frontal syndrome.

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modulator function), and decreases the glutamate release modulated by substance P facilitatory effect.[21] Indeed, gabapentin produces an increase in *N*-methyl-D-asparate transmission, which increases activity in spinal excitatory and inhibitory neurons, the latter resulting in reduced nociceptive neurotransmission.[22]

In the treatment of epilepsy, neurologists recommend a starting dose of 900 mg daily of gabapentin and subsequent titration upward to 1800 to 2400 mg daily. However, on the low side, 900 mg daily may be administered. Dosing should begin with 300 mg daily and increased by an additional 300 mg every 1 to 3 days. The drug is usually well tolerated; but it may cause dizziness, gastroenteric upset, somnolence, fatigue, and ataxia. Alcohol can augment these adverse effects.

MATERIAL AND METHODS

Patient Selection and Assessment

Sixteen patients, 15 men and 1 woman, 45 to 76 years old (median, 61.6 ± 10.7 years) were enrolled in the trial. Five patients had multiple infarction encephalopathy, 3 patients had Parkinson disease, 2 patients had multisystemic atrophy, 2 patients had multiple sclerosis without any clinical or radiological evidence of spinal cord involvement, 3 patients had postinfectious myelitis, and 1 patient was affected by frontal syndrome after the surgical removal of a meningioma (Table 1). Despite the heterogeneity of patient population, we felt confident that the lack of neuropathological homogeneity would not have altered our findings because all diseases share bladder dysfunction at the urodynamic evaluation.

After an informed consent was obtained, the patients were submitted to the following diagnostic work-up: history; general and neurological physical examination; voiding diary; International Prostate Symptom Score (IPSS; a voiding, self-administered questionnaire that allows the classification of severity of lower urinary tract symptoms; Table 2); urinalysis and urine culture; renal, vesical, and prostatic ultrasonography; uroflowmetry; cystometry; and pressure-flow study (urodynamic test) repeated twice in the same session (45 minutes apart) with simultaneous concentric needle electromyography of the pelvic floor. Room temperature saline solution was used for water cystometry at a filling rate of 30 mL/min.

During the cystometry, the following parameters were considered for further statistical analysis: bladder volume at the first desire to void, bladder volume at first IDC, IDC maximum amplitude, and cystometric capacity. During the pressure/flow study, the maximum flow, the detrusorial pressure at maximum flow (Pdet/Qmax), and the electromyographical behavior of the perineal muscles were considered.

All patients were evaluated at the baseline level and after 31 days of treatment with gabapentin by means of IPSS, voiding diary, flowmetry, cystometry, and pressure/flow study (in duplicate) with simultaneous electromyography of the perineal floor. Gabapentin dosage began with 300 mg orally once daily for the first 3 days, increased by an additional 300 mg for 3 days (300 mg twice daily), up to a maximum of 900 mg/d (300 mg 3 times daily), and reevaluated.

Statistical Analysis

Unless otherwise indicated, all data are expressed as means ± standard deviation. Statistical analysis was carried out by means of Student *t* test. *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

The results are summarized in Table 3, Table 4, and Figure 1.

All 16 recruited patients who entered the study completed the treatment period. None of them reported severe adverse events. Minor adverse events (dizziness and somnolence) were reported by 2 (12.5%) of 16 patients; consequently, none dropped out

TABLE 2. The IPSS Questionnaire

	Not At All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always	Your Score
Incomplete emptying							
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency							
Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
Intermittency							
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency							
Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream							
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining							
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times or More	Your score
Nocturia							
Over the past month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS score							

Total score: 0 to 7, mildly symptomatic; 8 to 19, moderately symptomatic; 20 to 35, severely symptomatic.

of the trial. After 31 days of therapy, all the patients reported a significant decrease in the previously referred symptoms, particularly regarding urinary urgency, frequency, and urgency incontinence, as confirmed by the voiding diaries data (Table 3) and by the IPSS score evaluation (IPSS score before drug 14.8 vs after drug 8.8; $P = 0.023$; Table 4).

The urodynamic evaluation demonstrated during the filling phase a significant delay

TABLE 3. Data of Voiding Diaries Before and After Gabapentin Treatment

	Before Treatment	After Treatment
Micturitions per day	7 (± 4)	5 (± 1.2)
Urgency episodes per day	13 (± 3)	8 (± 0.7)
Incontinence episodes per day	3 (± 2)	1 (± 0.3)
Pad use per day	2 (± 0.76)	1 (± 0.5)

Comparison between the data of voiding diaries before and after gabapentin treatment shows an improvement in daily micturition frequency and a reduction in urinary urgency and urinary incontinence episodes. Consequently, a lower pad use has been reported by the patients.

of the first desire to void (before drug 121.25 ± 25.9 mL vs after drug 140.19 ± 35.2 mL; P = 0.021) and of the maximum cystometric capacity (before drug 342 ± 99 mL vs after drug 430 ± 98 mL; P = 0.05); 4 of 16 patients showed, at the control, a complete absence of the IDCs previously discovered, whereas the others presented a delay of the first IDCs' volume (before drug 217.2 ± 120 mL vs after drug 318.7 ± 70.5 mL; P = 0.05) and a reduction in their medium amplitude (before drug 49 ± 16 cm H_2O vs after drug 42.4 ± 17 cm H_2O; P = not statistically significant). During the pressure/flow study, a decrease in the Pdet/Qmax, without significant modifications of the maximum flow indexes, was observed (before drug 47.74 ± 20 cm H_2O vs after drug 36 ± 12 cm H_2O; P = 0.05). Uncontrolled urinary leakage was not found in 6 of 8 patients who presented it before the treatment. Dyssynergia disappeared in 2 of 6 patients.

DISCUSSION

The most important finding in this study was a significant improvement of voiding diary and urodynamic parameters in patients with neurogenic overactive bladder who were submitted to gabapentin treatment. The results underline the efficacy of this treatment in decreasing detrusor overactivity and in improving cystometric capacity. Furthermore, the IPSS score confirms these satisfying results.

Research-based evidence suggests 2 main theories to explain the detrusor overactivity pathogenesis: (1) myogenic theories and (2) neurogenic theories. The myogenic theories indicate some changed properties of the smooth bladder muscle, confirmed

TABLE 4. IPSS Score and Urodynamic Evaluation Before and After Gabapentin Treatment

	Before Treatment	After Treatment	*P<
IPSS	14.8	8.8	0.023
No. patients with IDC	16 of 16	12 of 16	—
No. patients with urinary leakage	8 of 16	2 of 16	0.05
Volume at first desire to void (mL)	121.25 ± 25.9	140.19 ± 35.2	0.021
Volume at first IDC (mL)*	217.2 ± 120	318.7 ± 70.5	0.05
Maximum IDC amplitude (cm H_2O)†	49 ± 16	42.4 ± 17	NS
Cystometric capacity (mL)	342 ± 99	430 ± 98	0.05
Pdet/Qmax (cm H_2O)	47.74 ± 20	36 ± 12	0.05
No. patients with dyssynergia	6 of 16	4 of 16	NS

*Student t test.
†Mean values in 11 patients with IDCs after gabapentin treatment.
NS indicates not significant.

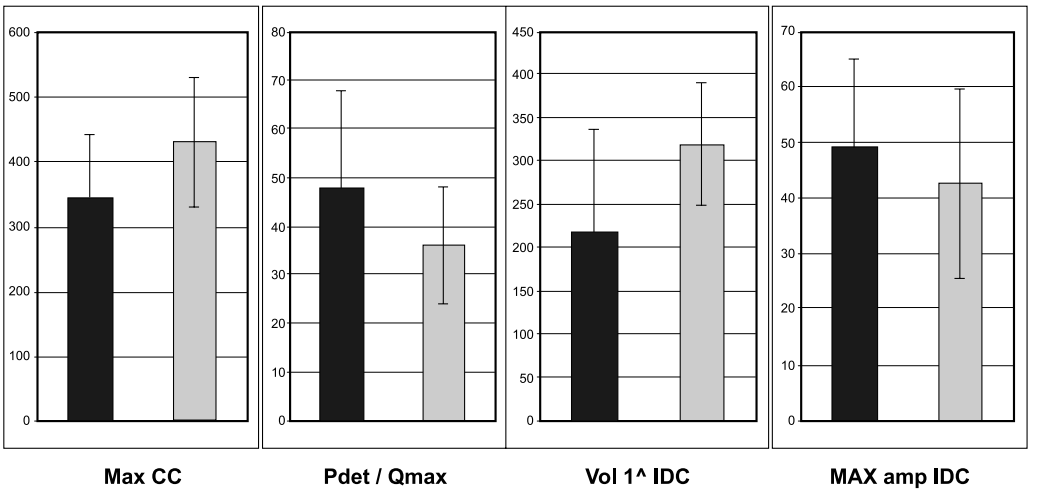

FIGURE 1. Max CC indicates cystometric capacity (in milliliters); Pdet/Qmax, detrusorial pressure at maximum flow during pressure/flow study (in centimeters of water); Vol 1 IDC, bladder volume at evidence of first involuntary detrusor contraction (in milliliters) during the cystometry; Max amp IDC, maximum amplitude of the involuntary detrusor contraction (in centimeters of water).

by electron-microscopic findings, as the main cause of detrusor overactivity.[22,23] The neurogenic theories are based on evidence showing alterations in the neurophysiological control of the urinary storage and voiding phase. Recent electrophysiological experiments carried out on animals proved that the stimulation of anterior and lateral hypothalamic regions induces bladder contractions, whereas the stimulation of posterior and medial parts of the same region causes bladder activity inhibition.[24–30] Furthermore, positron emission tomographic studies carried out on humans showed physiological changes of blood perfusion of the right dorsolateral prefrontal cortex and of the anterior cingulate gyrus during bladder voiding.[31] Similar studies indicated that these regions are underperfused in patients with detrusor overactivity.

Several hypotheses may explain how gabapentin decreases detrusor hyperactivity. One of these may be represented by the inhibition of the micturition reflex through higher brain centers that regulate bladder capacity and coordinate bladder and external urethral sphincter activity.[24–26] Indeed, gabapentin may act at a supraspinal level, modifying the descending inhibitory pathways as shown in previous studies carried out on patients with spasticity associated with the upper motor neuron syndrome.[32–34]

Gabapentin could activate posterior and medial hypothalamic regions, which determine inhibition of bladder activity. Although there is a lack of evidence, gabapentin may inhibit anterior and lateral hypothalamic regions, which induce bladder contraction[24–28] modulating the afferent sensitive input in hypothalamic nuclei. Another possible action is in the right dorsolateral prefrontal cortex and in the anterior cingulate gyrus. Indeed, patients reported a significant lowering of urgency, frequency, and urge incontinence.

We exclude a supraspinal action because patients reported a decrease in voiding reflex and a delay of the first desire to void. A supraspinal action would have determined only a decrease in voiding reflex without modifying the first desire to void, hence the afferent input from the bladder and the excitability of the sacral reflex center. Furthermore, the exclusion of a supraspinal action is further supported by the evidence of a similar effectiveness on bladder function despite neuropathological heterogeneity in the patient population.[35–37]

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The more plausible hypothesis is that gabapentin might control detrusor overactivity, reducing afferent signaling of the C and Aδ fibers. Indeed, bladder distension during the filling phase activates receptors located at the submucosal and detrusor level[9,20]; and it causes firing of C and Aδ fibers responsible for filling sensation. Previous articles reported that gabapentin has been shown to be efficacious in the treatment of neuropathic pain because it reduces the activation of C and Aδ fibers. In a study carried out on rats with peripheral inflammation, Stanfa et al[38] found that gabapentin was able to inhibit the responses of dorsal-horn neurons evoked by C fiber stimulation. Hence, when the activation of C and Aδ fibers is reduced, the first desire to void would appear at a higher bladder filling volume.

A further suggested hypothesis is that gabapentin might modulate the excitability of the sacral reflex center, at the S3-S4 level,[16–18] where sensitive inputs are integrated. In agreement with this hypothesis, Bayer et al[39] demonstrated that gabapentin reduces glutamatergic and glicinergic synaptic transmission in the spinal cord.

However, because the reduced bladder filling sensation parallels the decrease in voiding reflex activation, the more putative mechanism for gabapentin-induced changes would be a decrease in the afferent firing set up by bladder filling. If gabapentin acted only at the spinal level, perception of bladder filling and voiding reflex could vary independently. Consistent with the hypothesis that gabapentin can modulate afferent fiber activation, our patients reported a delay in the first desire to void at a higher bladder filling volume.

Recent studies raise the hypothesis that detrusor overactivity depends on hyperexcitability of the spinal reflex center mediated by the afferent pathways, and it has also been postulated that the modulation of the receptors and reflex center activity can cause the bladder hyperactivity reduction.[40]

In conclusion, we suggest that gabapentin activates inhibitory spinal interneurons inducing a decrease in detrusor hyperactivation during urodynamic test, a significant delay of the first desire to void during the filling phase, and an increase in the maximum cystometric capacity. Hence, gabapentin might directly modulate the gain of the spinal sacral reflex, reducing the activation of C and Aδ fibers mediating presynaptic transmitter release. These data suggest that gabapentin could be a novel treatment for patients with overactive bladder.

Further investigations are needed, including a double-blind randomized study on a larger patient series involving non-neurogenic overactive bladder patients and an evaluation of the viscerosomatic reflexes in patients receiving gabapentin, to establish the impact of such treatment on micturition pathophysiology.

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