Urodynamic assessment during intravesical infusion of capsaicin for the treatment of refractory detrusor hyperreflexia

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Purpose: Parameters to predict outcome and the urodynamic effects during infusion of capsaicin, seem not to have been assessed in patients with chronic cord injury. We monitored bladder activity urodynamically during infusion of high dosage of capsaicin.

Material and methods: Thirty patients, 18 women and 12 men (average age 29 years, range 20–59 years), suffering from chronic spinal myelopathy, who presented a refractory detrusor hyperreflexia, were studied. They received saline solution containing 10^{-3} M capsaicin at a flow rate of 2 ml min^{-1} for 15 min (total volume 30 c.c.). The detrusor activity was monitored by a real-time cystometrogram during infusion and 15 min after the end of the infusion itself. New filling cystometrograms were recorded after 30 days and after 6 months.

Results: We obtained a clinical and significant urodynamic improvement in 15 of the 30 patients (50%), confirming that intravesical capsaicin may represent a therapeutic option for a selected group of patients suffering from refractory detrusor hyperreflexia due to chronic spinal upper motor neuron lesion. Best results were observed in patients who showed, during the infusion of capsaicin, early uninhibited bladder contractions which disappeared within 10–12 min from the beginning of the infusion (desensitisation). The patients of this group presented a significant increase of mean cystomanometric capacity after 6 months (from 190.7 to 396.7 ml). No significant clinical or urodynamic improvement was observed in the group of patients in whom uninhibited activity of detrusor was recorded for all the time of infusion.

Conclusion: Our results support the idea of a major complexity of spinal reflex in paraplegic patients and may offer a clue to explain the failure of therapy with capsaicin. The present results support a new approach in the treatment of detrusor hyperreflexia. The ideal dosage and treatment interval are not at present established and further studies are needed to explain substantial differences in the outcome according to different urodynamic responses.

Keywords: capsaicin; sensory neurons; spinal cord; paraplegia

Introduction

Capsaicin, the active ingredient in hot red peppers, has been considered a new strategy for the treatment of neurogenic incontinence in humans.^{1,2} Its mechanism of action is based on the interference with A δ thinly myelinated fibres and sensory unmyelinated C fibres which mediate the afferent limb of micturition reflex in chronic spinal animals. The clinical outcome of intravesical capsaicin, in patients suffering from refractory detrusor hyperreflexia, has been recently reviewed by a dual-centre study with a long term follow-up.³ De Ridder reported that the effectiveness of the treatment persisted at least 3–5 years. Such results have not been confirmed by other American studies, perhaps because of different drug concentration, vehicle, duration and frequency of treatment.⁴

Up to now, urologists have not obtained parameters to predict outcome; the urodynamic effects, during the infusion of capsaicin, seem not to have been assessed in patients with a chronic cord injury. In adult spinal rats intravesical capsaicin, as recorded by filling cystometrogram, triggers phasic detrusor contractions, decrease of bladder capacity and leakage of urine.⁵ For these reasons we monitored bladder activity urodynamically during infusion of large dosage of capsaicin, providing a relationship between the behaviour of detrusor and outcome. Furthermore, the data collected allow us to offer a new insight into the pathophysiology of detrusor hyperreflexia in patients suffering from chronic spinal pathology.

Materials and methods

The study involved 30 patients: 18 women and 12 men (average age 29 years, range 20–59 years) suffering

from chronic spinal myelopathy (Table 1). All presented a detrusor hyperreflexia refractory to oral and/or intravesical oxibutynin chloride; seven had undergone sacral neuromodulation, and 13 intravesical electrostimulation. None reported clinical changes: all the subjects had problems with a high voiding pressure and/or severe hyperreflexia associated with frequent urine leakage. They were invited to undergo intravesical infusion of high dosage of capsaicin and all the patients gave their consent. The study was approved by a Local Ethical Committee because of the non-medicine status of capsaicin in Italy.

The clinical history, including current urological symptoms and associated medical disorders, was recorded. All the subjects underwent physical and neurological examination. Haematological and biochemical screenings, urinary ultrasonography, classical microbiological examination and urine analysis were also performed. A simple voiding pattern (frequency–nocturia–incontinence) was recorded throughout the period of the study.

The patients underwent urodynamic assessment by water filling cystometrogram before the study began. All the tests were performed by the same physicians

(M Laggeri and M Spinelli). Filling cystometrogram was performed with saline solution at a flow rate of 20 ml min^{-1} by a double lumen 10 Ch. catheter (one lumen was used to fill the bladder and one lumen was connected to a pressure transducer to measure intravesical pressure), and a balloon catheter placed in the rectum to record abdominal pressure. After the standard cystometrogram, the bladder was filled with saline solution containing 10^{-3} M capsaicin at a flow rate of 2 ml min^{-1} for 15 min (total volume 30 c.c.). Ethanol 10% was used as vehicle. The terminology used conformed to standards recommended by the International Continence Society.⁶ Abnormal cystometrogams were identified as unstable detrusor (hyperreflexia) when an uninhibited detrusor contraction, with an increase in intravesical pressure greater than $15 \text{ cmH}_2\text{O}$, was recorded. The detrusor activity was monitored by a real-time cystometrogram during the time of infusion and for 15 min after the end of the infusion itself without emptying the bladder. A new filling cystometrogram was recorded after 30 days. After 6 months a new urodynamic assessment was performed in patients of Group 1.

Statistical analysis

Values represent the mean $\pm$ the s.d. The experiment was analyzed by the analysis of variance (ANOVA) for repeated measures otherwise termed Split Plot. *Post-hoc* comparisons were performed by Tukey Kramer procedure. A $P < 0.05$ was accepted as significant.

Results

At filling cystometrogram performed before the study began, all the patients presented a neurogenic overactive bladder (detrusor hyperreflexia) with reduced compliance, bladder capacity and urine leakage. The mean bladder capacity was $184 \pm 71.6 \text{ ml}$ and the mean maximum bladder pressure was $65.4 \pm 22.3 \text{ cmH}_2\text{O}$.

On the basis of urodynamic assessment performed during infusion and for 15 min after, we divided our patients into three groups according to the behaviour of the detrusor.

Group 1

In 11 patients (10 were suffering from post-traumatic lesion and one from ischemic lesion) early uninhibited bladder contractions, starting within 3 min from the beginning of the infusion, were recorded. In this group no leakage of urine was observed. The amplitude of detrusor pressure significantly decreased within 10–12 min and at the end of the recording no bladder activity was present. Here we concluded that the patients underwent desensitisation of sensory-efferent innervation. Ten patients (90.9%) reported a significant improvement of their symptoms (urgency and frequency) with significant increase of bladder capacity after 30 days ($403.7 \pm 65.9 \text{ ml}$). A significant decrease

Table 1 Clinical data of patients

1. No Patients: 30
18 women
12 men
2. Pathology
Post-Traumatic: 18
• Complete lesion: 14
• Partial lesion: 4
• Level:
C ₇ : 1
D _{3–4} : 2
D _{4–5} : 1
D ₆ : 1
D ₁₀ : 1
D _{10–11} : 6
D ₁₂ : 4
D _{12–L₁} : 2
Myelitis: 7
• Complete lesion: 3
• Partial lesion: 4
• Level:
D _{6–7} : 3
D ₇ : 3
D ₉ : 1
Ischemic: 2
• Complete lesion: 2
• Level:
D ₅ : 1
D _{6–7} : 1
Herniation of the nucleus pulposus: 2
• Partial lesion: 2
• Level:
D ₁₂ : 1
D _{12–L₁} : 1
Aeroembolism: 1

of incontinence was also observed: seven patients remained dry and three reported occasionally incontinence. The patient who reported the failure of treatment underwent neuromodulation.

Group 2

In 14 patients (six were suffering from post-traumatic lesion, five from myelitis, two herniation of nucleus pulposus and one from aeroembolism) early uninhibited detrusor contractions were recorded. They remained of the same amplitude and were associated with urine leakage. In this group the infusion was stopped many times in order to wait for the disappearance of contractions. At the end of a contraction we again filled the bladder but uninhibited activity persisted. In 11 patients (78.6%) capsaicin failed to produce significant urodynamic and clinical improvement after 30 days: the mean bladder capacity remained low 204.7 ± 78.9 ml. Four of them underwent bladder augmentation, three received botulinus toxin, two intravesical oxibutinin and two sacral neuromodulation.

Group 3

In five patients (two were suffering from post-traumatic lesion, two from myelitis and one from ischemic lesion) no bladder activity was recorded for the entire period of infusion. Two of them (40%) reported a significant improvement of symptom (urgency, frequency and incontinence) and urodynamic assessment revealed a significant increase in bladder capacity. The other three underwent sacral neuromodulation. All data are summarised in Table 2.

In total we obtained a clinical improvement in 15 of the 30 (50%) patients included in our study. The total cystomanometric capacity remained significantly increased after 6 months in patients of Group 1 (396.7 ± 48 ml). Many patients of Group 2 and 3 received, after the first end-point, a new therapy and for this reason they did not undergo follow-up after 6 months.

During the intravesical instillation of capsaicin no severe symptomatic autonomic dysreflexia was recorded. Three patients, who presented an incomplete spinal lesion, reported a burning sensation at suprapubic level during the infusion. In these cases it was not necessary to interrupt the infusion. No other significant side-effect was recorded.

Table 2 Bladder capacity of the three different groups before and 30 days after capsaicin treatment

Bladder capacity (ml)	Group 1	Group 2	Group 3
Pre-capsaicin	190.7	178.1	201.4
30 days after capsaicin	403.5**	204.7	265.7

** $P < 0.01$

Discussion

Our results confirm that intravesical capsaicin may represent a possible treatment for a selected group of patients suffering from refractory detrusor hyperreflexia due to chronic spinal lesions. However, we did not confirm the good results obtained by other studies,³ but this datum may be due to different drug concentration, vehicle, duration and frequency of treatment. Fowler *et al.* reported an improvement of clinical and urodynamical parameters also in patients suffering from Multiple Sclerosis (MS) and neurogenic urinary incontinence.¹ These patients are not good candidates for the study and estimation of clinical and urodynamic results after intravesical administration of large dosage of capsaicin. MS is a disorder of unknown aetiology that is defined by its clinical characteristics and by typical central nervous system white matter lesions. Patients recover clinically to some extent from individual bouts of demyelination that produce the classical remitting and exacerbating course of the disorder particularly in the early phases. For these reasons we ruled out patients suffering from MS.

We found no previous paper which studied the detrusor response to capsaicin during the infusion as strategy for predicting treatment outcome. Chardimani *et al.* used intravesical lignocaine, before starting the infusion of capsaicin, to reduce the discomfort of patients with conserved suprapubic sensation and abolish phasic detrusor contraction.⁷ They did not report or use the behaviour of the detrusor, observed during the time of infusion, to predict success or failure of the therapy and to support functional differences in the neurological mechanisms which regulate the bladder hyperreflexia in chronic spinal injured men. In our work we recorded different responses of the bladder muscle during the infusion of capsaicin as shown at a real time monitorisation. We used this observation to predict the outcome and to suggest a complex physiopathology of the reflexes which regulate the lower urinary tract function after a spinal lesion.

In normal conditions the voiding reflex is mediated by the spino-bulbo-spinal micturition reflex pathway which is also present in decerebrate animals but not in acute or chronic spinal animals. Kuru,⁸ and later de Groat⁹ reported, by electrophysiological studies, that detrusor contraction is activated by a long latency supraspinal reflex pathway which passes through a regulatory centre in the rostral brainstem: the pontine micturition centre. This pathway functions as an 'on-off switch' activated by a critical level of afferent activity, conducted by unmyelinated A δ fibres, arising from tension receptors of the bladder (ascending limb) and modulated by inhibitory and excitatory influence from areas of the brain rostral to the pons. The pontine micturition centre regulates bladder capacity and coordinates the activity of the external urethral sphincter by a descending limb projecting to autonomic and somatic sphincter motoneurons of the lumbosacral spinal cord.¹⁰

Bladder activity is also mediated by a spinal micturition reflex pathway.¹¹ This reflex arc is weak or absent in adult animals with intact nervous systems but may become prominent in animals following a spinal cord injury above the lumbosacral segment. In animals, as in humans, transection of the spinal cord rostral to the lumbosacral segment produces acutely an areflexic bladder and complete urinary retention. The bladder activity slowly recovers over the course of weeks or months and the detrusor becomes hyperreflexic. Experimental studies have shown that the reflex pathways which modulate micturition in chronic spinal animals are markedly different from that of the normal animal. In chronic spinal animals the afferent limb of the micturition reflex consists of unmyelinated C fibres⁹ whereas in the intact cord it consists of myelinated A δ fibres.¹² Capsaicin does not block the A δ fibres evoked bladder reflex when it is injected systemically in normal cats but blocks C fibre evoked long latency reflex in spinal animal models. These observations have justified the clinical use of capsaicin to treat detrusor hyperreflexia due to a spinal cord lesion.

In our study 50% of patients presented a long lasting reduction of bladder hyperactivity and reported an improvement of symptoms. These patients belong mostly to Group 1 (66.6%). It seems possible, on the basis of these observations, to use the urodynamic behaviour, at the time of infusion of capsaicin, to predict the success or failure of the treatment. We did not consider correlation between bladder compliance and detrusor hyperreflexia because, as reported by McGuire (personal communication at XXII annual meeting of SIUD (Società Italiana di Urodinamica)), the pathogenesis of detrusor hyperreflexia is different from that of poor bladder compliance.

We suggest that unmyelinated C fibre-evoked bladder reflexes, which occur in paraplegic patients, may be complex and depend on multiple factors. First, unmyelinated C fibres are a morphological entity but they are not functionally equivalent.¹³ These neurons can respond to different stimuli (mechanical, thermal and chemical) either exclusively or in combination or, in some viscera, appear to be unresponsive to any of these stimuli. Secondly, in paraplegic patients there may be changes in the synthesis/release of sensory neuropeptides and alterations in afferent input from peripheral organs.¹⁴ VIP immunoreactivity, which is a marker of unmyelinated C fibres, is distributed over a wider area of the dorsal horn in paraplegic animals and the effects of intrathecal administration of VIP on bladder function are changed: in normal cats VIP inhibits bladder reflexes, whereas in paraplegic cats small doses of VIP facilitate reflexes. Thirdly the mechanism which rules the spinal reflexes seems to be affected by the peripheral organs.¹² Experimentally, a partial urethral ligation, that mimics a urinary obstruction, increases bladder activity inducing bladder hypertrophy. This is accompanied by the increase

of Nerve Growth Factor in the bladder and expansion of afferent fibres in the spinal cord.¹⁵ We speculate that detrusor sphincter dyssynergia or an outlet obstruction in paraplegic men could alter reflex mechanisms. Fourthly, the synthesis/release of trophic factors (NGF and Semaphorin) by the peripheral organs may have an impact on spinal reflex. NGF which is a survival factor for both sympathetic and sensory neurons during prenatal life, regulates, in the adult, the function of sensory neurons and it is essential for the function of the complex 'vanilloid receptor/aspecific cation channels'. Semaphorine on the other hand inhibits the development of sensory innervation *in vivo* and should have an important role in pathological conditions such as paraplegia.¹⁶

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