Intravesical capsaicin for treatment of detrusor hyperreflexia

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Abstract

An intravesical instillation of 100 ml 1 or 2 mmol/l capsaicin has been used to treat detrusor hyperreflexia giving rise to intractable urinary incontinence in 12 patients with spinal cord disease and two other patients with detrusor overactivity of non-spinal origin. Nine patients, all of whom had spinal cord disease, showed some improvement in bladder function. The benefit was only shortlived and partial in four, but the remaining five achieved complete continence while performing intermittent self catheterisation. Urodynamic studies in these nine patients showed an increase in mean (SD) bladder capacity from 106 (57) to 302 (212) ml and a fall in the maximum detrusor pressure from 54 (20) to 36 (10) cm of water. There were no short term ill effects from the instillation and the improvement in bladder function lasted for between three weeks to six months, when in some patients it was repeated. The improvement in bladder behaviour shown in this study can be interpreted as showing that capsaicin sensitive afferents play an important part in the pathogenesis of detrusor hyperreflexia in spinal humans. Intravesical capsaicin seems a promising means of treating intractable detrusor hyperreflexia and studies with this substance may shed new light on other disorders of detrusor activity that cause incontinence.

(*J Neurol Neurosurg Psychiatry* 1994;57:169-173)

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Received 11 March 1993
and in revised form
17 May 1993.
Accepted 21 May 1993

Incontinence of neurological origin is most often due to detrusor hyperreflexia. Current treatment relies on partially blocking the efferent parasympathetic innervation to the detrusor with anticholinergic drugs. These often have troublesome side effects, however, and may be insufficiently effective to restore continence in patients with severe hyperreflexia. Although there are other treatments, which aim to block the afferent arc of the reflex that causes detrusor contractions, sacral root rhizotomy is best limited to patients with a complete suprasacral spinal cord lesion and the various attendant complications of injection of phenol in the subtrigonal region of the bladder make that procedure, which has only transient benefit, unsuitable for repeated use. A non-surgical therapy which could selectively destroy those

afferent nerves that give rise to abnormal reflex detrusor contractions would have significant advantages over other means now available to treat neurogenic incontinence, especially if it were easy to administer and repeat and had a prolonged action.

Detrusor hyperreflexia can result either from loss of the normal inhibitory input from higher centres on to the pontine micturition centre or after a spinal lesion from interruption of the spinobulbospinal pathways that normally control physiological bladder behaviour. Animal models of chronic spinal cord disease have shown that after disruption of the connections between the pons and the sacral spinal cord a new segmental sacral reflex arc becomes functional.¹ The afferent neurones of this emergent reflex in the cat are mostly unmyelinated C fibres whereas in the neurologically intact animal afferent neurones from the bladder are small myelinated Aδ fibres.² Little is known of the neurological mechanism of bladder reflexes in spinally injured humans.¹ Disconnection of the sacral cord from the pons results in detrusor areflexia that lasts for about six weeks before volume determined bladder reflex emptying becomes established. A speculative hypothesis is that this change in detrusor behaviour results from synaptic reorganisation and possibly new nerve growth forming the neurological basis of an emerging reflex arc.

Pharmacological experiments show that in many species there is a large group of fibres innervating the bladder that are capsaicin sensitive.³⁻⁶ These are mostly unmyelinated fibres in the cat¹ and rat.⁷ They are silent under physiological conditions but may be activated by bacterial or chemical irritants in the bladder⁸ giving rise to symptoms of cystitis. It is probably these same fibres that emerge active and serve as the afferent arc for detrusor hyperreflexia in spinally injured animals.¹

Capsaicin activates a vanilloid receptor on the cell membrane of sensitive primary sensory neurones⁹ causing an increase in cation permeability and leading to membrane depolarisation. Activation of the vanilloid receptor produces a biphasic response. The immediate effect is stimulatory with transmission of sensory impulses from the periphery to the central nervous system sensed as a painful irritation and a peripheral release from the receptor terminals of neuropeptides including substance P and CGRP. After exposure to high concentrations of capsaicin, afferent C fibres may show long lasting functional

changes, with many unmyelinated fibres having morphological evidence of structural damage. The degree of neurotoxicity that follows exposure to systemic treatment with capsaicin depends on the age of the animal: high doses given subcutaneously to newborn rats result in a 50% or greater reduction in unmyelinated fibres¹⁰ whereas when given to adult animals there is not so much fibre loss.¹¹ Applied topically to peripheral nerve, capsaicin has an extensive selective neurotoxic effect on unmyelinated fibres irrespective of the animal's age and causes axonal loss of unmyelinated fibres^{12,13} and depletion of neuropeptides.¹⁴ Little is known about the long term neurotoxic effects of capsaicin when it is applied directly to nerve terminals.

Capsaicin has been enjoyed as a constituent of the human diet for thousands of years and no long term side effects have been recognised from ingestion of large quantities of it. Capsaicin applied directly to the eyes, nose, mouth, and throat is intensely painful—a property of the substance now being exploited by riot control police.¹⁵ Low doses of capsaicin have been injected intravenously into human volunteers to study its effect on respiratory and cardiovascular reflexes¹⁶ and it is now being used to examine the cough reflex in patients with various types of lung disease.¹⁷ Skin ointments containing capsaicin are being used to treat postherpetic neuralgia¹⁸ and painful diabetic neuropathy. Its potential application in the treatment of other painful disorders has recently been reviewed.¹⁹ The use of capsaicin in the human bladder has so far been limited to treatment of painful bladder disorders, with concentrations of 0.1–10 μm .²⁰

Systemic administration of capsaicin to neonatal rats results in urinary retention and loss of those bladder afferents immunoreactive for substance P.²¹ When capsaicin-sensitive afferents were shown to be present in the human bladder²⁰ the use of intravesical

capsaicin to lessen detrusor hyperreflexia in humans was suggested (CA Maggi, personal communication). The lessening of detrusor hyperreflexia in spinal cats after a subcutaneous injection of capsaicin¹ made bladder instillation with this substance the logical step when faced by patients with neurogenic incontinence resistant to currently available medical treatments and unsuitable for surgery.

The early results of this study were the subject of a preliminary report.²²

Patients

All patients gave informed consent after a clear explanation that capsaicin was being obtained as a chemical, not a medicine and had no certification for use in humans. A medicine exemption certification was obtained for the use of capsaicin for intravesical administration from the Medicines Advisory Committee and the project was approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery and Institute of Neurology.

The table gives details of patients. Twelve patients had spinal cord disease: eight had multiple sclerosis with varying degrees of disability, one had tropical spastic paraparesis with moderate lower limb paraparesis but could walk with sticks, one had had an arteriovenous fistula of the spinal cord and was confined to a wheel chair, one had had an episode of transverse myelitis three years earlier, and one patient had congenital spina bifida. All patients with multiple sclerosis and the one with tropical spastic paraparesis had urodynamically verified hyperreflexia with phasic detrusor contractions and incontinence induced at a mean volume of 106 (57) ml. The remaining three patients (2, 4 and 5) had a steady rise in detrusor pressure on filling with poor compliance calculated at 3.7, 2.6, and 1.3 ml/cm water, respectively.

Table Clinical details of 14 patients treated with intravesical capsaicin showing the clinical extent of their incontinence and cystometric findings before and after treatment

Patient no	Age (y)	Diagnosis	Disability	Extent of clinical incontinence		Capacity (ml)		Detrusor pressure at capacity (cm H ₂ O)	
				Before treatment	After treatment	Before	After	Before	After
1	68	Neurologically normal	Walking normally	Pads	No improvement	20	20	65	60
2	27	Vegetative state	Bed bound	Bypassing and extruding catheter	No extrusion for 3 weeks	N/P	N/P		
3	22	Spina bifida	Chair bound	Pads	No improvement	130	100	35	60
4	57	Cord AV malformation	Chair bound	Indwelling catheter	No improvement	220	220	85	80
5	14	Transverse myelitis	Walking abnormally	Pads	Mostly dry	80	70	60	50
6	37	Multiple sclerosis	Chair bound	Indwelling catheter	No improvement	100	300	40	30
7	38	Multiple sclerosis	Bed bound	Bypassing and extruding catheter	Less bypassing for 8 weeks	30	30	30	30
8	57	Multiple sclerosis	Bed bound	Bypassing and extruding catheter	No bypassing for 8 weeks	140	N/P	70	
9	67	Multiple sclerosis	Bed bound	Bypassing catheter	No improvement	150	N/P	95	
10	54	Tropical spastic paraparesis	Walking with sticks	Pads	Continent with ISC	195	400	50	32
11	40	Multiple sclerosis	Walking with sticks	Pads	Continent with ISC	130	250	95	45
12	45	Multiple sclerosis	Walking with sticks	Urosheath and bag	Continent with ISC	110	560	60	30
13	57	Multiple sclerosis	Walking with sticks	Urosheath and bag	Continent with ISC	150	260	45	20
14	56	Multiple sclerosis	Walking with frame	Indwelling catheter	Continent with ISC	50	550	40	28

ISC = intermittent self catheterisation; N/P = not performed.

Intravesical capsaicin was also used in two other patients, one of whom was in a persistent vegetative state with an indwelling catheter after severe cerebral anoxia. The other was the only patient in this series who was neurologically normal and the cause of her disabling incontinence due to involuntary detrusor contractions is unknown.

The table shows the clinical extent of incontinence in all patients before capsaicin instillation and the results of urodynamic studies.

Methods

Preliminary studies in one of the patients (14) carried out in 1990 showed that low concentrations of capsaicin (0.1–10 $\mu\text{mol/l}$) had no effect on improving bladder capacity or lessening hyperreflexia. From May 1991 onwards, 100 ml of either 1 mmol/l (0.3 g/l) or 2 mmol/l solution of capsaicin dissolved in 30% alcohol in saline were used. This was introduced into the bladder with a balloon catheter to minimise the risk of leakage into the urethra. The instillation was left in the bladder for 30 minutes.

For the first five patients the instillation procedure was carried out in the operating theatre with full cardiovascular monitoring and in the presence of an anaesthetist to give analgesia or sedation if required. All patients, except one who had lost bladder sensation, reported immediate suprapubic burning that persisted with severe intensity for between 5–10 minutes, but no patient requested analgesia. When it became clear that the instillation was adequately tolerated in alert subjects, subsequent patients were treated in the uro-neurology laboratory with an anaesthetist available. No medical intervention was ever required either for management of pain or cardiovascular support.

Two bed-bound patients with multiple sclerosis and catheter-induced urethral incompetence had a bladder neck suspension procedure carried out under general anaesthetic at the same time as the instillation to prevent leakage of the capsaicin into the urethra.

Blood was taken for measurement of alcohol concentrations over the period of the instillation and up to four hours later.

All except one patient had standard medium fill (50 ml/minute) subtraction cystometry studies before and after the instillation. Whenever possible cystometry was carried out immediately before the capsaicin instillation and intravesical pressure measurements were continued during the instillation. Urodynamic studies were repeated four to eight weeks after the capsaicin instillation in 11 patients but not in those who were bed-bound (patients 2, 8 and 9).

Results

IMMEDIATE EFFECTS AND SHORT TERM RESULTS (FIRST 14 DAYS)

When the procedure was carried out in the operating theatre the patients were connected

to a Po_2 oximeter and ECG monitor. No significant alteration in cardiovascular state occurred during or after the procedure. Although most patients reported immediate suprapubic pain, lasting with intensity for 5–10 minutes and then diminishing, none reported symptoms that could have been related to systemic effects of capsaicin. The rise in blood alcohol after the instillation never exceeded 3 mmol/l, indicating that there was little diffusion of the alcohol through the bladder wall. Patients who had had the procedure once and were returning for repeated treatments denied undue apprehension of discomfort and it seemed that subsequent treatments were less uncomfortable than the first. Patients were well enough to go home immediately afterwards.

When urodynamic studies were performed during the instillation a sharp rise in detrusor pressure was immediately seen, often followed by a series of phasic contractions. A full report of aspects of this phenomenon will be the subject of a separate paper.

All patients reported an initial deterioration of their symptoms with either worsening incontinence or catheter bypassing for a period that varied between 24 hours to 14 days followed then by clinical improvement or a return to their previous state. Patients who had the instillation carried out more than once seemed to have the same pattern of response on each occasion.

LONG TERM RESULTS (TWO WEEKS TO SIX MONTHS)

The table summarises the urodynamic changes and clinical response after intravesical capsaicin. An improvement in some aspect of bladder behaviour was seen in nine of the 14 patients. In five the improvement was highly satisfactory so that these patients who had formerly required the long term use of a continence appliance or pads, became continent between intermittent self catheterisations. The bladder capacity in these five patients increased from 127 to 404 ml (fig 1). Hyperreflexic contractions were reduced with a fall in detrusor pressure from 58 to 31 mm H_2O and lessening of the degree of urgency. In another four patients the improvement was less impressive both in terms of degree and duration. Two of these patients had procedures for bladder neck suspension carried out at the time of capsaicin instillation because they had such severe dilatation of the urethra after catheter extrusions that leakage of capsaicin into the urethra during the instillation procedure would otherwise have been inevitable. It is possible that the surgical procedure alone improved continence although one patient continued to be incontinent for two weeks after the procedure and only then stopped leaking around the catheter for the next eight weeks before the problem returned. An improvement in clinical continence was achieved in one other patient (5) in whom medium fill (50 ml/min) cystometry showed no change although filling at a slow rate (10 ml/min) after the treatment showed a

Figure 1 Changes in bladder capacity in the 11 patients in whom data were available, before and after capsaicin instillation.

greatly improved capacity.

The remaining four patients showed neither clinical nor urodynamic evidence of improvement after capsaicin instillation. This group included the patient who was neurologically normal and one with severe multiple sclerosis who was incontinent with severe flexor leg spasms. Also in the non-responding group were two patients (3 and 4) whose urodynamic studies had shown poor compliance rather than phasic detrusor hyperreflexia.

DURATION OF ACTION AND REPEATED INSTILLATIONS

Figure 2 shows the timing of the intravesical instillations in each patient. Three patients have had the instillation repeated at intervals of between four and nine months when they have felt a return of their urinary urgency and reduction in their postmicturition residuals as assessed by intermittent self catheterisation. Urodynamic studies carried out at this stage show that there had been a reduction in blad-

Figure 2 Time in months since capsaicin instillation. Patient numbers as used in the table are given on the ordinate. Each square indicates an episode of intravesical capsaicin. A line indicates the duration of improved bladder function.

der capacity and return of hyperreflexia, but never so severe as before the first capsaicin instillation. The instillation has not been repeated in those who showed neither clinical nor urodynamic change.

Discussion

This is the first human study to show that capsaicin-sensitive afferents are important in the pathophysiological mechanisms which cause the detrusor hyperreflexia that follows a spinal lesion. Although clinical continence was achieved in only five out of the 14 patients treated with intravesical capsaicin, there was evidence of either short-lived clinical improvement in four others and urodynamic evidence of an increased capacity in one further patient. Those who did not respond included two patients with low bladder compliance rather than phasic detrusor contractions, a patient with severe flexor leg spasms, and the patient who was neurologically normal. The pathogenesis of low bladder compliance is unknown but these findings suggest that it is different from that which causes phasic detrusor hyperreflexia. It is not surprising that the neurologically normal patient did not respond and the failure of response of the patient with extreme disability and multiple sclerosis may lie in the severity of the abnormality in that case.

A complete block of the emergent reflex that drives volume-determined detrusor contractions would result in an areflexic bladder, as occurs in neonatal rats treated with capsaicin.²¹ The bladder would then require to be emptied by intermittent self catheterisation; a technique already practised by many patients with spinal cord disease. This state was not reached in any of the patients in the series described here although conditions approaching it were achieved in the five patients with the best responses. The severity of urinary incontinence of a spinally compromised patient depends on a combination of factors that include a reduction in bladder capacity and the magnitude of hyperreflexic detrusor contractions. In patient 6 there was an increase in bladder capacity but persisting clinical continence was not achieved as she was still incontinent with low pressure rises.

The duration of benefit after intravesical capsaicin is variable and ranged from months to weeks (fig 2). There is a clear suggestion that the effectiveness of intravesical capsaicin in improving continence is related to the patient's overall neurological state, best illustrated by the fact that clinical continence was achieved only in those whose neurological disability was less severe and who were still able to walk (patients 1-5, table). The benefit in those with the most severe neurological deficit was short lived and difficulties with mobility and transport in such patients made repeated treatments, with the expectation of only temporary relief of symptoms, impractical in a pilot study. This aspect of the relation between responsiveness and neurological deficit deserves further study because if it

were possible to measure the neural depletion responsible for symptomatic improvement, and in the severely disabled this was only partial, a treatment regimen with either higher concentrations or more frequent instillations would be rational.

Topical capsaicin applied to the skin results in a reduction of the flare response and raising of heat pain thresholds lasting several weeks.²³ The prolonged effect seen in some of these patients implies that there has been a degree of axonal loss. The rich plexus of suburothelial nerves in the bladder of humans are thought to be sensory²⁴ and substance P and other neuropeptides known to occur in association with sensory nerves have been identified in the human bladder.²⁵ It is proposed that in the circumstances of the instillation procedure described here, high concentrations of capsaicin reached the nerve terminals themselves. Future studies will include an immunocytochemical examination of the suburothelial sensory nerves before and after topical application of capsaicin to assess the extent of substance P depletion and to test whether clinical response can be correlated to measurable neuronal loss.

Little is known about the effect of alcohol in the human bladder. Two patients have been reported in whom undiluted Bonney's blue (a 1:1 mixture of brilliant green and crystal violet dissolved in 90% ethanol) was mistakenly instilled intravesically, resulting in chemical cystitis and in the long term, a reduced bladder capacity.²⁶ The possibility that the changes in bladder behaviour reported here might be due to the 30% alcohol in saline solution has not been eliminated. A study is in progress to examine this with patients who have been shown to respond to capsaicin, waiting until the benefit of the last capsaicin instillation has worn off and then instilling the solution of alcohol in saline alone. A blinded study will not be possible because the pungent effects of capsaicin are so obvious to both the administrator and recipient.

The promising results of intravesical capsaicin treatment reported here were predicted from the extensive animal studies that have shown the presence of capsaicin-sensitive afferents in the bladder of many species^{4,5} and the work of de Groat and colleagues¹ who have shown the change in nature of the afferent limb of the reflex arc for detrusor hyperreflexia in chronic spinal animals. Its use in other conditions where unwanted detrusor contractions cause incontinence, such as detrusor instability in the elderly, might shed light on the neurobiology of such disorders. This study suggests a new method of treatment for patients with intractable neurogenic incontinence and confirms that capsaicin sensory afferents exist in the human bladder and are functionally significant in detrusor hyperreflexia secondary to spinal disease.

We thank consultants of the National Hospital for Neurology and Neurosurgery, Queen Square for referring patients and the Joint Ethics Committee of the Hospital and Institute of Neurology for their advice. The assistance given by the Department of Anaesthesia and the Pharmacy of the National Hospital is gratefully acknowledged. Discussions with Dr Chet de Groat, Dr Bruce Lynn, and Dr Carlo Maggi have been invaluable. Equipment used for urodynamic studies was purchased by a grant from the Multiple Sclerosis Society of Great Britain and Northern Ireland.

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