The effects of capsaicin on the neurogenic hyperreflexic detrusor. A double blind placebo controlled study in patients with spinal cord disease. Preliminary results

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Purpose: Several recent open studies have provided encouraging results as to the efficacy of intravesical installations of capsaicin for neurogenic hyperreflexivity. The present trial was performed to verify these results under controlled conditions. Intravesical installation of capsaicin represents a new therapeutic hope for the treatment of the neurogenic hyperreflexic bladder.

Method: This randomized, double-blind study compared the results of the intravesical installation of 30 mg capsaicin in 100 ml of 30% alcohol (experimental group) with those of installing 100 ml 30% alcohol alone (control group). On day 0 and day 30, urodynamic and biopsy examinations were performed in all subjects of each group.

Patients: All the subjects included in the study had a functionally disabling form of neurogenic hyperreflexic bladder resistant to the usual therapies. Cystoscopy and retrograde cystography were performed to exclude any patient who presented with a tumor-like lesion or had vesicoureteral reflux.

Results: Twelve paraplegic or tetraplegic subjects, seven women and five men whose average age was 46, were included. Eight had multiple sclerosis, and four had sustained a traumatic spinal cord injury. The patients were randomly separated into two groups of six. Initially, there was no clinical or urodynamic differences in these groups. Installation immediately triggered side effects and during the first 7 days (suprapubic burning sensation, sensory urgency, hot flushes, autonomic hyperreflexia, hematuria) in five of the six subjects in both groups. Bladder biopsy revealed no significant deterioration. On day 30, there was improvement in all of the experimental-group of patients with significant regression of leakage ($P=0.002$) and of sensory urgency ($P=0.01$). Only one control subject had amelioration. Urodynamic examination showed a rise in bladder capacity from 172.5 to 312.3 ml in the experimental group, significantly greater ($P=0.03$) than the rise from 129 to 175.3 ml observed in the control group.

Conclusion: This trial fully confirms the efficacy of intravesical installations of capsaicin, an efficacy obtained at the cost of nonnegligible side effects. An intermediate-term follow-up of this treatment will be necessary before considering more widespread use of this agent.

Keywords: capsaicin; detrusor hyperactivity; neuropathic bladder; multiple sclerosis; paraplegia

Introduction

Studies on spinal cord injured animals^{1,2} and preliminary studies on a small population of spinal cord injured patients³ suggest that capsaicin-sensitive, C-fiber bladder afferents are involved in pathological conditions associated with a neurogenic hyperreflexic bladder. Open trials indicate substantial therapeutic potential for intravesical capsaicin treatment of a neurogenic hyperreflexic detrusor,^{4–9} but controlled trials have not

yet been published.⁷ We report the results of a double-blind, placebo-controlled study performed to delineate clinical and cystometric effects of intravesical capsaicin treatment, and to provide further data concerning its potential short-term side effects.

Methods

Patients

We included in this protocol patients showing severe neuropathic incontinence resistant to currently avail-

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able medical treatments. All of these patients had spinal cord disease, considerable detrusor hyperreflexia. Patients showing progression of neurological symptoms during the previous 6 months were excluded from our study. Those with urinary tract infection and lithiasis were ruled out or were treated before the capsaicin installation. If there was malignancy or ureteral reflux, after cystographic and cystoscopic examinations, patients were excluded.

Twelve patients (seven females, five males) meeting these criteria were included (see Table 1). They ranged in age from 38 to 66 years (mean=45.9 years). All patients had spastic paraplegia or tetraplegia. Eight had multiple sclerosis and the other four had either a traumatic spinal cord injury. Among the latter, one had T4 complete paraplegia (ASIA Impairment scale (AIS) grade A), one T10 complete paraplegia (AIS grade A), one C7 complete tetraplegia (AIS grade A), and one C7 incomplete tetraplegia (AIS grade C).

Procedures

The ethics committee of Bordeaux University Hospital approved the protocol. All patients gave personal informed consent to participate in the trial and were randomly assigned to either the trial or control (placebo) groups. Synthetic capsaicin was prepared by the Pharmacy School of the University of Bordeaux.

Twenty minutes after an intravesical installation of 40 ml lidocain (2%) solution, the patients randomly received installation of capsaicin (100 ml of 1 mmol/l [0.3 g/l] solution in 30% alcohol) or placebo (solution of 30% alcohol) during 30 min. All installations were carried out at the hospital as outpatients, and they returned home 1 h after installation.

The subjects were questioned about the clinical effects, especially with regard to incontinence and side

effects. Along with these clinical aspects, cystometric parameters volume of the first urge to void, bladder capacity (leak point pressure), and pressure of the detrusor at maximum capacity, were determined at Day 0 (D0) before installation, and 30 days after the installation (D30). Gas cystometric studies (50 ml/min) were performed with a Urolynx 2000 apparatus (Dantec Inc.). All of patients underwent a rigid cystoscopic examination 3 weeks before the installation, and at D30. A biopsy specimen was obtained from the dome and trigone of the bladder.

The Mann-Whitney nonparametric test was used to compare the two groups at D0 and D30.

Results

Initially the two groups presented no significant difference in their general characteristics (Table 1), mode of voiding (Table 2), or urodynamic parameters (Table 3).

The installation induced frequent, but well tolerated side effects (no patient came out of the study) with no significant difference between the two groups (Table 4). Among the side effects occurring during or immediately after the installation were a suprapubic burning sensation (in spite of local anesthesia with lidocain), sensory urgency and/or a hot flush in five of six cases in the capsaicin group, and in four of the six control subjects. Only one subject (capsaicin group) developed moderate hyperreflexia, rapidly regressing after treatment with calcium channel blockers. These immediate symptoms are to be distinguished from delayed side effects arising from 12 h to 6 days after installation: suprapubic pain sensation (SPP) or increasing incontinence (II) or macroscopic haematuria (MH) in five of the six patients in the capsaicin group and in all of the controls. One patient who had

Table 1 General characteristics of patients

	Patients	Sex, age at inclusion	Primary disease	Duration of illness (years)	Neurological examination	Mode of voiding
Experimental Group Capsaicin	1—	M48	MS	15	incomplete tetraplegia	IC+VV
	2—	M38	SCI	5	complete paraplegia	IC+RV
	3—	F55	MS	17	incomplete paraplegia	RV
	4—	F46	MS	25	incomplete paraplegia	VV
	5—	F45	MS	27	incomplete paraplegia	VV
	6—	M66	SCI	5	complete paraplegia	IC+RV
mean		49.6		15		
Control group Placebo	7—	F42	MS	24	incomplete paraplegia	IC+VV
	8—	M42	SCI	17	complete tetraplegia	RV
	9—	F40	MS	12	incomplete paraplegia	VV
	10—	F37	SCI	7	incomplete tetraplegia	IC+RV
	11—	M46	MS	9	incomplete paraplegia	IC+VV
	12—	F46	MS	13	incomplete paraplegia	VV
mean		42.1		13.6		

MS: multiple sclerosis, SCI: spinal cord injury, RV: reflex voiding, VV: voluntary voiding, IC: intermittent catheterization

Table 2 Clinical results

Patients		Voiding(N:24H)		Leakages(N/24H)		Patient satisfaction on D30
		D0	D30	D0	D30	
Experimental group	1.2	7	6	4	2	Yes
	2.3	6	5	3	0	Yes
Capsaicin	3.6	5	5	3	0	Yes
	4.8	12	5	5	0	Yes
	5.10	8	5	5	0	Yes
	6.12	6	5	2	0	Yes
Mean(SD)		7.3(2.5)	5.1(0.4)	3.6(1.2)	0.3(0.8)	
Control group	7.1	16	7	8	4	Yes
	8.4	12	12	6	6	No
Placebo	9.5	12	12	3	3	No
	10.7	6	6	6	6	No
	11.9	5	5	5	5	No
	12.11	14	14	6	3	No
Mean(SD)		10.8(4.4)	9.3(3.7)	5.1(1.9)	4.5(1.3)	
Significance		P=0.22	P=0.016	P=0.13	P=0.002	

Voiding: self catheterization or voluntary micturition; Leakages: non-voluntary micturition

Table 3 Urodynamic Results

Patients	First urge of void		Bladder capacity		Presson of detrusor at maximum capacity	
	D0	D30	D0	D30	D0	D30
1.2	80	102	188	243	90	50
2.3	121	107	300	319	50	20
3.6	96	180	109	420	73	47
4.8	51	140	206	340	40	42
5.10	92	159	103	389	70	51
6.12	84	141	129	163	82	80
	87.3(22.8)	138.1(29.9)	172.5(75.3)	312.3(95.2)	67.5(19)	48.3(19.2)
7.1	40	105	70	200	27	36
8.4	60	103	75	211	72	80
9.12	68	63	146	165	55	42
10.7	95	85	116	102	61	65
11.9	200	201	206	277	59	65
12.14	106	88	161	97	82	80
	94.8(56.7)	107.5(48.2)	129(52.5)	175.3(69)	59.3(18.6)	61.3(18.6)
	$P=0.87(NS)$	$P=0.10(NS)$	$P=0.37(NS)$	$P=0.037(S)$	$P=0.4(NS)$	$P=0.4(NS)$

autonomic hyperreflexia was noted in the control group, and another who had symptomatic lower urinary tract infection in the capsaicin group. Urinary retention was not observed in patients who voided voluntarily.

The cystoscopies and biopsies performed before and after installation showed only non specific aspecific alterations of the vesical mucosa, with no difference between the two groups (the detailed histopathology results will be published separately).

On D30, among the clinical results (Table 2) there appeared to be a significant improvement in the frequency of voiding in the capsaicin group in which the average number of daily catheterizations was

reduced from 7.3 to 5.1, compared to a smaller reduction in the control group, from 10.8 to 9.3 ($P=0.016$). Similarly, the number of daily incidents of leakage fell from 3.6 to 0.3 in the capsaicin group compared to the decrease from 5.1 to 4.5 in the controls ($P=0.002$). The mode of voiding remained unchanged in all of the patients. These results concur well with the subjective judgment of the patients who were all satisfied in the capsaicin group, compared to only one satisfied patient amongst the controls.

Urodynamically (Table 3), the first urge to void was noted at an average volume of 87.3 ml before and 138.1 ml after the installation of capsaicin compared to 94.8 and 107 ml, respectively, in the control group

(NS: $P=0.1$). Similarly, the detrusor pressure at maximum bladder capacity was not significantly lowered in the experimental group (from 67.5 to 48.3 cm water) compared to the control group (from 59.3 to 61.3) ($P=0.4$). Bladder capacity significantly improved in the capsaicin group, rising from 172.5 ml on the average on D0 to 312.3 ml on D30, whereas it rose from 129 ml to 175.3 ml in the controls ($P=0.037$). In this limited study, there did not appear to be any differences between the patients with traumatic spinal injury in comparison with those with multiple sclerosis.

Discussion

This is the fourth report concerning the use of intravesical installation of capsaicin for the neurogenic hyperreflexic bladder, and the first conducted according to the recommendations of Nitti,⁷ i.e. double blinded *versus* placebo. Indeed, although previous works⁴⁻⁷ have produced very encouraging results, none permitted, from a strictly methodological point of view, affirmation of the efficacy of capsaicin.

In view of the complexity of the protocol, our trial included only 12 patients, but the two groups were quite homogeneous, initially presenting no differences in general, clinical and urodynamical characteristics. The other four series^{4,6,8,9} included 41, seven, 12 and three patients, respectively. The installation protocol used in our study was strictly that described by Fowler.⁵

We obtained detailed data on side effects (Table 4) which were present in almost every patient at the time of the installation (suprapubic burning sensation, sensory urgency, hot flush and, more rarely, autonomic hyperreflexia) as well as within the following 6 days (suprapubic burning sensation, exacerbation of

incontinence, macroscopic hematuria). These effects were also reported by the previous authors, who considered them to be clinically tolerable, as did we. As previously stated, none of our subjects at any point requested to drop out of the study.

One of the principal findings of our study was, as had not been anticipated, the absence of more severe or more frequent secondary effects clinically or histologically documented in the capsaicin group in comparison with the control group. This suggests that the solvent of the installed solution, 30% alcohol would be just as deleterious to the bladder mucosa as is capsaicin. Further work is called for in order to improve the quality of the solvent. Igawa,¹⁰ recently observed the absence of autonomic hyperreflexia in two patients having undergone vesical installation with 10% ethanol alone, whereas it occurred when capsaicin was installed using that solvent. Unfortunately, he made no mention of the other side effects. It is also noteworthy, from a purely methodological standpoint, that the presence of identical side effects in our two groups preserved the double-blind nature of the study consequently reinforcing the reliability of the results.

In terms of clinical efficacy, we found a very marked improvement in leakage and voiding frequency associated with the general satisfaction of the subjects treated with capsaicin. The mode of voiding did not change, but the feeling of greater security in these patients allowed most of them to return to social activities that had previously been limited by their incontinence: shopping, restaurants, movies, the beach, etc. In contrast, in the control group (except for patient 1) the clinical condition remained unchanged without any lasting aggravation. We noticed slight improvement in four of six patients in the control group which could be due to the placebo effect itself or

Table 4 Adverse effect

	<i>Patients</i>	<i>D0</i>	<i>D1 to D7</i>	<i>After D7</i>
Experimental Group	1.2	SPP,FI	SPP,II,	UTI
Capsaicin	2.3	AD,FI	MH	none
	3.5	none	none	none
	4.8	SPP,II	SPP,II,UTI	none
	5.10	SPP,2II	SPP,II	none
	6.12	FI	SPP,II,MH	none
Summary		SPP:3,II:2,FI:3,none:1	SPP:4,II:4,MH:2,UTI:1	UTI:1,none:5
Control Group	7.1	SPP,FI	SPP,II,MH	none
Placebo	8.4	none	MH	none
	9.5	II	none	UTI
	10.7	SPP	SPP,II,UTI	none
	11.9	none	SPP,MH	none
	12.11	II	II	
Summary		SPP:2,II,FI:1,none:2	SPP:3,II:3,MH:3,UTI:1,none:1	UTI:1,none:5

SPP: suprapubic pain, FI: flush, II: incontinence increasing, MH: macroscopic haematuria, UTI: urinary tract infection, AD: autonomic dyreflexia

to a positive anticipatory attitude of the examiner. This is why a double blind placebo study was necessary. These good results are perfectly compatible with the findings of the open studies: nine out of 12 patients satisfied in Fowler's study,⁵ six of seven for Geirsson,⁶ 34 of 41 for de Ridder.⁹ In our study, there were no differences in efficacy between the spinal cord traumatic injury subjects and those with multiple sclerosis, which corresponds to Geirsson's results in seven spinal injury patients.

The urodynamic data confirmed the clinical impression and provided interesting complementary information. The principal improvement concerned the peak bladder capacity which increased by 140 ml on the average in the capsaicin group compared to only 46 ml in the controls ($r=0.037$). This latter increase could be attributed to a placebo effect, to a possible action of the solvent itself, or to a positive anticipatory effect of the examining physician, but which of these is or are responsible remains uncertain.

These values lie in the range of the results reported in the open studies which found average gains of 50 ml for de Ridder,⁹ 104 ml for Geirsson,⁶ and 201 ml for Fowler.⁵ An improvement of 140 ml in the bladder capacity should, for a mean hourly diuresis of 50 to 100 ml, result in an increase in the intervoiding period of 1.5 to 3 h. This corresponds quite closely with the reduction in voiding frequency found in our trial.

The bladder capacity corresponding to the initial urge to void tended to be improved in our capsaicin group, but the difference with controls was not statistically significant. This may have been due to methodological problems—too few subjects, impossibility of analyzing the urge to void in patients with a complete spinal cord injury. Another possibility that might explain this lack of statistical improvement in initial urge could be the destruction by capsaicin of the nonmyelinated fibers carrying this signal toward the centers of perception. Upscaling of our study with a greater number of subjects might provide answers to this question which was not directly addressed in the previous reports.

The maximal filling bladder pressure, which reflects the vesical contractility was decreased in average of 19 cm water, but it did not reach significance. Significance could probably be reached with a greater number of patients. This decrease could explain the decrease of sensation of emergency voiding as well as the leakage. Our data are again comparable to previous studies: Geirsson:⁶ 7 cm water; Fowler:⁵ 12 cm; de Ridder:⁹ 15 cm. This was probably due to the persistence of a certain number of nonmyelinated fibers which resisted the installation as was suggested by Chandiramani.⁸ Another hypothesis to explain the maintenance of bladder activity could be the existence of other neurourological pathways responding to other stimulations.

In summary, urodynamically the situation corresponded to one with slightly attenuated bladder contraction and, above all, more delayed volume evoked contraction. This would explain the absence of any urinary retention and the conservation of the mode of voiding.

Conclusions

This initial double-blind, placebo-controlled trial confirmed the efficacy of capsaicin for neurogenic hyperreflexic bladder, finding clinical and urodynamic results similar to those of the preliminary open studies with tolerable side effects. However, numerous questions remain to be addressed, in particular concerning the long-term maintenance of effects and tolerance.

We are currently extending our double-blind study, progressively increasing the number of subjects. In parallel, we are carrying out an open medium-term follow-up of patients periodically receiving installations.

Acknowledgements

This study was funded in part by a grant from the Ligue Française Contre la Sclérose en Plaques. We wish to thank CJ Fowler for her help in designing this study.

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