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The Effect of Intravesical Oxybutynin on the Ice Water Test and on Electrical Perception Thresholds in Patients With Neurogenic Detrusor Overactivity

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Aims: The C-fiber-mediated bladder-cooling reflex and the determination of the current perception thresholds (CPTs) permit to investigate afferent LUT pathways. They have both been proposed to detect and differentiate neurologic bladder dysfunction. This study evaluates, prospectively, the effect of oxybutynin, an antimuscarinic with direct antispasmodic effect on smooth muscle, on repeated ice water test (IWT) and CPTs in patients with a known incomplete neurogenic bladder. **Methods:** Patients with a known incomplete lesion of the bladder innervation, detrusor overactivity during cystometric bladder filling and a continuous positive response to repeated IWT were included. After the initial tests, 30 mg intravesical oxybutynin (1 mg/ml) was instilled and left in the bladder for 15 min. Afterwards CPTs and IWT were re-assessed. **Results:** After the drug application, the bladder-cooling reflex could not be initiated, even after three instillations, in 16/17 patients. The bladder CPT increased from 29.7 ± 11.3 to 39.1 ± 15.7 mA after oxybutynin ($P = 0.001$). No difference was found in CPT of the left forearm ($P = 0.208$). **Conclusions:** Intravesical oxybutynin blocks the bladder-cooling reflex and increases but does not block CPT sensation in the bladder in most patients with incomplete neurogenic lesion and detrusor overactivity. These results help explain the clinical effect of intravesical oxybutynin in neurogenic patients. They also indicate that a pharmacological local influence on C-fiber-related activity can give different clinical effects. *Neurourol. Urodynam. 29:391–394, 2010.* © 2009 Wiley-Liss, Inc.

Key words: afferent; bladder; ice water test; oxybutynin; sensory; anticholinergic

INTRODUCTION

The bladder-cooling reflex is a reflex contraction evoked by intravesical instillation of cold water. It is present in newborns and disappears in infants between the age of four and six, due to an increasing inhibitory control by higher brain centers.[1] Experience learns that if this control is disturbed as with a neurologic lesion, the cooling reflex reappears, rendering the ice water test (IWT) positive again. However, several studies provide indirect arguments that a bladder-cooling reflex can also be elicited if there is a predominance of ascending excitatory over descending inhibitory pulses, rather than merely if there is a lack of descending inhibitory control.[2,3] A hyper-excitability of C-fibers could thus be put forward as the primum movens.

Originally the "IWT" was used as a clinical correlate for the bladder-cooling reflex. The presence or absence of the reflex was accepted as test to differentiate between a lower or upper motor neuron lesion in neurogenic bladder. The determination of bladder current perception threshold (CPT) is an estimate for the electrically stimulated afferent sensitivity of the bladder. Although it is still unknown which pathways are responsible for the perception of electrical stimulation, the height of the CPT in the bladder has been directly correlated to the outcome of the IWT in neurologic patients.[4]

If the hypothesis holds that a cold-induced bladder reflex contraction can result from an imbalance between excitatory and inhibitory pulses, one would expect that repeated exposure to cold stimulation enhances the reflex contraction, and that drugs suppressing afferent activity of cold-sensitive fibers would abolish the reflex. This study addresses these considerations. It also compares the influence of intravesical oxybutinin on bladder CPT.

MATERIALS AND METHODS

After approval by the local ethics committee, patients with a neurogenic bladder due to an incomplete spinal cord injury, multiple sclerosis, or a cerebro-vascular accident, who presented at the Urologic Department for evaluation, were considered eligible for inclusion. In all patients a conventional cystometry, an IWT and a determination of the CPT in the bladder and on the forearm were done.

The cystometry was conducted with body warm saline at a filling rate of 30 ml/min in accordance to the recommendations for good urodynamic practices.[5] Bladder filling was ended arbitrarily when the detrusor pressure exceeded 30 cm of water (due to detrusor overactivity or poor bladder compliance) or when a bladder volume of 500 ml was reached, whatever occurred first. The bladder was then emptied. The urodynamic catheter was left in place and IWT was performed three times.[4] Rapid instillation (5 sec) of 60 ml cold water (4°C) was done during measurement of detrusor pressure. The IWT

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was considered positive if cold water instillation elicited a reflex bladder contraction of >15 cm water.

Finally, the CPT was determined on the left arm using surface electrodes, and inside the bladder using a transurethrally inserted 8 F pacing catheter. Constant current at 2.5 Hz (pulse duration 1 msec, pulse interval 400 msec) was used. The bladder was filled with 50 ml saline containing contrast medium and the stimulation electrodes were visualized by radioscopy to ensure a stable and correct positioning and reproducible measurements. We used the "method of limits." The subject is asked to indicate the onset of sensation when a stimulus of increasing intensity is administrated. This threshold is averaged with the value at which a stimulus disappears when the intensity is progressively decreased.[6] Generally, the "method of limits" gives higher absolute values, but is sensitive in detecting neuropathy. A mean of three measurements was used as CPT value. If electrical stimulation at 80 mA was not felt inside the bladder, the electrical sensation was considered absent.

Study Protocol

Criteria to be fulfilled for inclusion in the study were: presence of neurogenic detrusor overactivity with a detrusor pressure exceeding 30 cm water during cystometry; presence of a positive IWT for all three consecutive evaluations and preservation of electrical sensation in the bladder (CPT < 80 mA). Patients already on anticholinergic medication or who presented with signs of a urinary tract infection on dipstick were excluded from participation.

For the patients who fulfilled the criteria, the empty bladder was instilled with 30 ml oxybutynin in saline solution at a concentration of 1 mg/ml. The catheter was clamped and the solution was kept inside the bladder for 15 min, after which it was drained. Then the IWT was again assessed three times inside the bladder as described above and the CPT again measured on the neurologic normal arm with the same surface electrodes. A single dose of 3 mg fosfomycin was given orally as prophylaxis.

Parameters are described as mean ± standard deviation. Computerized statistical analysis was done by using non-parametric tests (with SPSS© 16.0). The Wilcoxon matched pairs test was used. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Between August 2006 and October 2007, 17 patients fulfilled all criteria and were, after their agreement to participate, prospectively included in the protocol. They were 12 men and 5 women with a mean age of 43 ± 19 years. Ten patients had a neurogenic bladder due to an incomplete spinal cord injury, five due to a cerebro-vascular accident and two due to multiple sclerosis. The patient data are presented in Table I. As required for inclusion, all three IWT were positive in all patients, with a significant increase in contraction amplitude between the first and the second IWT (59.9 ± 38.6 to 92.9 ± 62.9 cmH_2O, $P = 0.002$), but without a difference between the second and third IWT (92.9 ± 62.9 to 84.0 ± 56.7 cmH_2O, $P = 0.39$). No difference was found in the duration of the evoked detrusor contraction between the consecutive IWT's (47 ± 26 sec duration, $P > 0.05$). A typical trace of the IWT is shown in Figure 1. The mean CPT on the arm and inside the bladder, respectively, was 1.8 ± 0.2 and 32.9 ± 14.8 mA.

After intravesical instillation and wash out of oxybutynin, the IWT was three times negative in all patients, except in one (patient 2). In this patient, the IWT remained positive after instillation for all three consecutive tests (mean amplitude of detrusor contraction 58 cmH_2O, mean duration 28 sec as before instillation).

After instillation, the CPT on the arm was not different from the pre-instillation threshold (1.8 ± 0.2 mA, $P = 0.2$). But the bladder CPT was significantly higher after instillation than before (39.1 ± 15.7 mA, $P = 0.001$). Electrical stimulation was not felt in three patients at 80 mA, although the sensation was present before instillation, (patient 4, 8, and 10 in Table I).

DISCUSSION

The bladder-cooling reflex is a sacral spinal reflex which is present in newborns and normally disappears between the age of four to six through maturation of the higher brain centers with the development of a strong descending

TABLE I. Results of the Patient Data

	1 Diagnosis	2 Age	3 Sex	4 CPT arm	5 CPT bladder	6 CPT arm post	7 CPT bladder post	8 IWT ampl	9 IWT duration
1	SCI	27	M	1.5	52	1.5	63	126	50
2	CVA	39	M	1.7	17	1.7	19.6	41	24
3	CVA	74	M	2.2	26.2	2.3	34	43	27
4	SCI	28	M	1.7	71	1.7	No sensation	133	44
5	CVA	38	F	1.5	43	1.5	58	17	22
6	SCI	27	M	1.8	36	1.8	49	116	37
7	MS	30	M	1.7	20.2	1.7	29	89	65
8	SCI	31	M	1.6	57	1.7	No sensation	135	77
9	MS	49	F	1.8	22	1.8	31	34	26
10	SCI	47	F	1.5	39	1.4	No sensation	45	73
11	SCI	41	M	1.7	22	1.8	26.5	143	110
12	SCI	16	M	1.9	21.8	1.9	25.6	96	36
13	SCI	71	M	1.9	22.8	2	28.9	60	85
14	CVA	34	M	2	26.3	2.1	36	36	35
15	SCI	28	F	1.9	35	1.9	59	154	35
16	SCI	73	M	1.9	23	1.9	25	47	16
17	CVA	78	F	2	49	2	63	28	43

SCI: spinal cord injury; CVA: cerebrovascular accident; MS: multiple sclerosis; M: male; F: female; CPT: current perception threshold; IWT: ice water test. The CPT values of the arm and bladder before and after instillation. Data are expressed in mA. The IWT values are measured before instillation and amplitude is expressed in cmH20, duration is expressed in seconds.

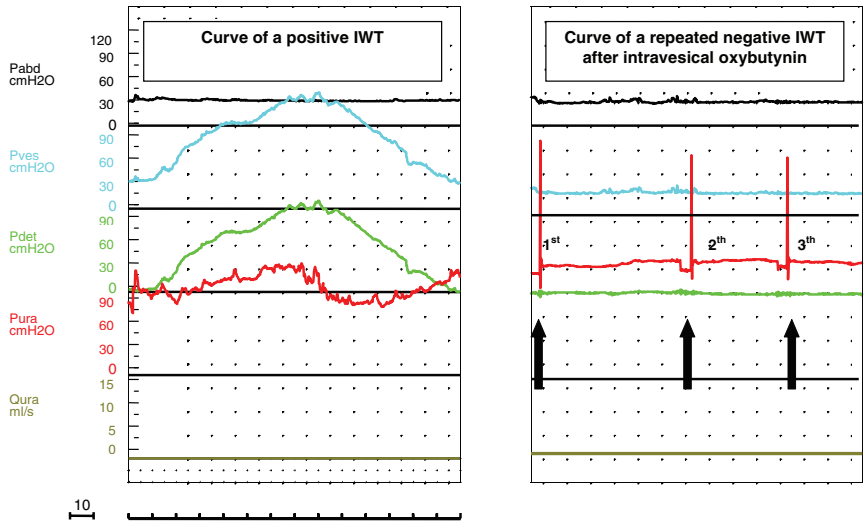

Fig. 1. Influence of oxybutynin on IWT in the same patient. Pabd, abdominal pressure; Pves, vesical pressure; Pdet, detrusor pressure, Pura, urethral pressure; Qura, flow rate is expressed milliliter per second.

inhibitory control. However, when the suprasacral pathways are damaged or interrupted, the cooling reflex may reappear and the interruption of the descending inhibitory pathways is believed to be responsible for this.[7]

In adults the bladder-cooling reflex is absent.[8] In patients with stress incontinence, ice water instillation did not elicit a cooling reflex, even after repeated instillations.[9] However, in patients with detrusor overactivity due to outflow obstruction, the IWT can be positive, even without any suspicion of neurogenic impairment.[9,10] These data show that the IWT can be positive in patients without interruption of the descending inhibitory pathways, if the responsible afferent pathways are in a state of hyperexcitability and if they are adequately stimulated. Strong stimulation, as with repeated instillation of icy water, can lead to a predominance of excitatory over inhibitory pulses, and elicit a positive bladder-cooling reflex.

Data from animal experiments show that the afferent limb of the bladder-cooling reflex is C-fiber mediated and originates from cold or cool receptors.[11,12] In man with neurogenic detrusor overactivity, the conversion from a positive towards a negative IWT has been reported following intravesical capsaicin or resiniferatoxin instillation also suggesting the involvement of C-fiber pathways.[13,14] Cool receptors from the TRP-family have also been described in the human bladder, and they appear to be localized in the urothelium but not in the muscle coat.[15] This makes them susceptible to intravesical modulation.

Oxybutynin is a mixed antimuscarinic drug with a local anesthetic, antispasmodic, and antimuscarinic action. Given intravesical, it exerts its effect through blocking C-afferent fibers.[7,8] Oxybutynin has also been shown to lower increased afferent stimulation in the bladder in patients with interstitial cystitis.[16] Intravesical oxybutynin converted the IWT in all but one of our patients from positive to negative. Such effect of local anesthetics has been demonstrated before, but only in 0–56% of the patients, depending on the drug used.[17] Therefore, the pronounced effect in our study cannot be attributed to the local anesthetic effect alone. More selective antimuscarinics also reduce C-fiber afferent activity, suggesting M3 receptors on the C-fiber endings.[10,18] The bladder-cooling reflex originates from cold-sensitive C fibers, leading to efferent discharge and subsequently activation of mechanosensitive afferent fibers.[19] From clinical experience it is known that patients are able to void after intravesical oxybutynin, showing only a minor involvement of efferent fibers for the observed effect. Because of the known selective action of intravesical oxybutynin on C fibers, the conversion of the IWT would seem due to action on the cold-sensitive C fibers. The possible relationship between C fibers in the urothelium/suburothelium and the response to intravesical pharmacotherapy has been demonstrated in spinal cord injured patients before.[20]

Square wave pulses have been used successfully for several decades to evaluate the integrity of the urinary tract's afferent nervous pathways.[21,22] Determination of CPT by square wave pulses is a sensitive and reproducible method to diagnose hyposensitivity in the lower urinary tract. However, C-fiber hyperexcitability is thought to be responsible for lower urinary tract dysfunction in many disorders, and currently no convincing data exist that correlate hyperexcitability to decreased bladder CPT's. However, both increase and decrease of bladder sensitivity have been correlated to changes in bladder CPT's.[9,23] In this study we observed a significant increase in bladder CPT after the use of oxybutynin, suggesting a decrease in sensitivity of at least a part of the afferent nervous pathways. In rats, intravesical oxybutynin decreases afferent activity in C fibers, which can be attributed to its local anesthetic effect and/or to its antimuscarinic effect.[7] Yokoyama et al.[24] showed an increase in bladder CPT at 5 Hz in patients with idiopathic overactive bladder who demonstrated a decrease in bladder hyperexcitability following instillation of the C-fiber neurotoxin resiniferatoxin. With tolterodine, an increase in bladder CPT using square wave pulses at 2.5 Hz was demonstrated.[9] As tolterodine inhibits C-fiber afferent activity in rats, it can be assumed that the increase in CPT's following antimuscarinic treatment is through a decrease of C-fiber afferent activity.[10] Intravesical oxybutinin increases bladder CPT but did not change arm CPT showing absence of a generalized anesthetic effect.

The question remains why IWT became negative while CPT sensation remained still present. One explanation can be that oxybutynin lowered the excitability of afferents of the

bladder-cooling reflex in such a way that icy water gave insufficient stimulus to evoke an efferent response, while still conducting sensory information to the brain. Another explanation could be that bladder-cooling reflex and CPT relate to different C fibers influenced by oxybutynin in a different level. More studies are needed to further develop this.

CONCLUSIONS

In a selected group of patients with neurogenic bladder, intravesical oxybutynin was able to abolish the bladder-cooling reflex and increase but not block the sensory thresholds for constant current electrical stimulation. It remains open if afferent receptors for cold and for electrical stimulation are different or if oxybutynin lowers afferent activity under the threshold for bladder-cooling reflex but not for electrical stimulation. A generalized anesthetic affect was not shown as demonstrated by unchanged arm thresholds.

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