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Treatment of Overactive Bladder with Modified Intravesical Oxybutynin Chloride

Motoaki Saito,[1]* Fumie Tabuchi,[2] Kenji Otsubo,[2] and Ikuo Miyagawa[1]*

[1]Department of Urology, Tottori University Faculty of Medicine, Yonago, Japan
[2]Division of Pharmacy, Tottori University Hospital, Yonago, Japan

Intravesical oxybutynin chloride has been reported to be effective for overactive bladder, although sometimes the efficacy does not last long enough. To improve this deficiency, we report the effects of intravesical oxybutynin chloride with hydroxypropylcellulose (modified intravesical oxybutynin). Modified intravesical oxybutynin (5 mg/10 mL, twice a day) was administered to six overactive bladder patients for more than 1 year (two men and four women; average age, 56.5 years) who did not respond to oral anticholinergic agents and electric stimulation. Cystometography (CMG) was performed before, 2 hours, and 1 week after the start of modified intravesical oxybutynin. In addition, plasma levels of oxybutynin and its active metabolite, N-desethyl-oxybutynin (DEOB), were measured by high-performance liquid chromatography before, 1, 2, and 4 hours after the initial treatment of modified intravesical oxybutynin. CMG studies revealed that two of the six patients did not demonstrate uninhibited contractions 1 week after the treatment and that cystocapacity of before, 2 hours, and 1 week after the initial modified intravesical oxybutynin was 141.8 ± 15.3, 210.0 ± 35.5, and 305.0 ± 21.3 mL, respectively. Plasma levels of oxybutynin and DEOB before, 1, 2, and 4 hours after the first instillation of modified intravesical oxybutynin were oxybutynin; not detected, 8.8 ± 2.5, 6.8 ± 1.1, 3.0 ± 1.0 ng/ml, and DEOB; not detected, 4.2 ± 1.3, 6.4 ± 1.7, 5.1 ± 1.4 ng/ml, respectively. No side effects were observed in any of the patients. Modified intravesical oxybutynin is an effective and safe therapy option for overactive bladder patients who do not respond to other treatments such as oral anticholinergic agents and electric stimulation. *Neurourol. Urodynam. 19:683–688, 2000.*

Key words: intravesical oxybutynin chloride; overactive bladder; hydroxypropylcellulose

INTRODUCTION

Treatment with oral anticholinergic drugs, e.g., oxybutynin chloride and propiverine chloride, is effective for patients with detrusor instability and/or detrusor hyperreflexia. There is, however, a subset patients who do not respond to oral medication or who experience intolerable systemic side effects from these drugs [Massada et al., 1992; Mizunaga et al., 1996; Buyse et al., 1998]. These systemic side effects are

*Correspondence to: Motoaki Saito, M.D., Ph.D., Department of Urology, Tottori University Faculty of Medicine, 86 Nishimachi, Yonago, Tottori 683-0826, Japan. E-mail: saitomo@grape.med.tottori-u.ac.jp

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reported to be caused by the high plasma level of its active metabolite N-desethyl-oxybutynin (DEOB) [Massada et al., 1992; Buyse et al., 1998]. There is increasing evidence that intravesical oxybutynin chloride, which reduces the plasma level of DEOB compared to that with oral administration of oxybutynin chloride, is an effective therapy against overactive bladder [Greenfield and Fera, 1991; Madersbacher et al., 1991; Kasabin et al., 1994; Kaplinsky et al., 1996; Buyse et al., 1998]. However, the effect of intravesical oxybutynin chloride often does not last long enough. Recently, to improve this deficiency, the use of oxybutynin chloride solution containing hydroxypropylcellulose (HPC), a mucosal adhesion substance, was reported (modified intravesical oxybutynin) [Mizunaga et al., 1996; Chiba et al., 1997]. In this article, we report the effects, safety, and plasma levels of oxybutynin and DEOB in overactive bladder patients treated with modified intravesical oxybutynin.

PATIENTS AND METHODS

Patients

Modified intravesical oxybutynin chloride was administered to six overactive bladder patients (two men and four women) who had presented with urinary frequency and urge incontinence at the outpatient clinic of Tottori University Hospital from May 1998 to January 2000. These patients were carefully provided information about any risk and the possible side effects of this treatment before starting this study. Before modified intravesical oxybutynin treatment, all patients were treated with oral anticholinergic medication (oxybutynin chloride or propiverine chloride), which were not effective and had side effects, e.g., thirst and constipation. The patients were 14 to 74 years old. All patients had undergone urodynamic testing including cystometography (CMG), if possible, with electromyography of the external urethral sphincter, measurement of single voided volume and residual urine volume, and uroflowmetry to establish the diagnosis of neurogenic bladder. Before this new treatment, four patients (TS, HA, DY, and HH) had been performing clean, intermittent self-catheterization (CIC) because of detrusor-sphincter dyssynergia and an excessive volume of residual urine (>100 mL). The other two patients (TH and MI) started CIC to prepare for this new treatment.

Composition of the Oxybutynin Solution

The composition of the oxybutynin solution was oxybutynin chloride 5 mg, sodium chloride 58 mg, HPC 100 mg, sodium dihydrogenphosphate (anydrous) 52.6 mg, disodium hydrogenphosphate (anhydrous) 8.7 mg, and water 10 mL (pH. 5.85) according to Chiba et al. [1997].

Evaluation of the Treatment

This oxybutynin solution was instilled twice daily via the catheter used for bladder emptying at a dosage of 5 mg/10 mL. Before, 2 hours, and 1 week after the first instillation of oxybutynin, CMG was performed. Moreover, before, 1, 2, and 4 hours after the initial treatment of modified intravesical oxybutynin, plasma levels of oxybutynin and its active metabolite DEOB were measured by high-performance liquid chromatography (HPLC), using the Waters 2690 Alliance (Milford, MA,

TABLE I. Patient Information

Patient	Age	Gender	Disease/type of bladder dysfunction
ST	48	F	Adhesive arachnoiditis/detrusor hyperreflexia + DSD
TH	71	F	Unstable detrusor
HA	67	M	Behçet's disease/detrusor hyperreflexia + DSD
YD	14	F	Brain injury/detrusor hyperreflexia + DSD
MI	74	M	Herniated disk/detrusor hyperreflexia
HH	65	F	HAM/detrusor hyperreflexia + DSD

DSD, detrusor-sphincter dyssynergia; HAM, human adult T-cell leukemia virus-1 associated myelopathy.

U.S.A.) system. The remainder of the study was according to Buyse et al. [1998]. Four weeks after the beginning of this therapy, we asked the patients about their satisfaction with this therapy compared to previous therapy (excellent, good, fair, unchanged, and worse). Statistical analyses among groups were performed using analysis of variance and the multiple comparison Fisher's test. $P < 0.05$ was considered as the level of significance.

Chemicals and Drugs

Oxybutynin chloride and hydroxypropylcellulose were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). All other chemicals were of reagent grade.

RESULTS

Patient information is shown in Table I. In this study, six overactive bladder patients (two males and four females; average age, 56.5 years) were treated with modified intravesical oxybutynin treatment. The CMG data are shown in Table II. Before the treatment, all patients demonstrated uninhibited contractions (UICs), and bladder capacity was 141.8 ± 15.3 mL. Just 2 hours after the initial treatment, bladder capacity slightly increased to 210.0 ± 35.5 mL with UICs, and 1 week after the treatment, bladder capacity was significantly increased (305.0 ± 21.3 mL) compared to that before treatment. Furthermore, UICs were not detected in two patients (ST and YD) after 1 week. Plasma levels of oxybutynin and DEOB are shown in Table III. The peak level of plasma oxybutynin was detected at 1 hour and the plasma level of oxybutynin at 4 hours was significantly lower than that at 1 or 2 hours. On the other hand, the peak level of plasma DEOB was detected at 2 hours, which was not significantly different from that at 1 or 4 hours. Four weeks after the start of this therapy, the patients were asked to evaluate this therapy, and the results are shown in Table II. Four patients (ST, HA, YD, and HH) responded that the results with this therapy were excellent and the other two patients (TH and MI) as good. Although patient number is small, modified intravesical oxybutynin therapy was highly evaluated by these patients who did not response to oral anticholinergic medication. No side effects were observed in the patients in this study.

DISCUSSION

In this study, we investigated the effects of intravesical oxybutynin treatment on patients who did not respond to oral medication and who experienced intolerable systemic side effects from oral anticholinergic drugs. Although the number of patients

TABLE II. Bladder Capacity of the Patients Before and After Modified Intravesical Oxybutynin

Patient	Bladder capacity (mL)			UIC (1 wk)	Satisfaction
	Before	2 h	1 wk		
ST	90	158	347	(−)	Excellent
TH	143	155	215	(+)	Good
HA	106	143	333	(+)	Excellent
YD	152	278	341	(−)	Excellent
MI	180	170	270	(+)	Good
HH	180	356	325	(+)	Excellent
Avg.	141.8 ± 15.3	210.0 ± 35.5	305.0 ± 21.3[a]		

[a]Significantly different from before treatment. Satisfaction with this therapy was questioned 4 weeks after the start of this therapy. $P < 0.05$ was the level of significance.

in this study was small, a significant increase of bladder capacity was observed. Moreover, serum oxybutynin and serum DEOB were measured before, 1, 2, and 4 hours after the initial treatment of intravesical oxybutynin. Patient satisfaction with this therapy was also remarkable. Our data suggested that modified intravesical oxybutynin is one treatment option for the overactive bladder patient who does not respond to oral anticholinergic agents.

Brendler et al. [1989] first reported the treatment of intravesical oxybutynin chloride for neurogenic bladder. Since then, evidence of the efficacy of intravesical oxybutynin has been reported [Greenfield and Fera, 1991; Madersbacher and Jilg, 1991; Madersbacher and Knoll, 1995]. The mechanisms of action of intravesical oxybutynin, still unknown, may be the direct effect on the bladder muscle, topical anesthetic effect, and the indirect effect of absorbed oxybutynin and its metabolites. Weese et al. [1993] reported 42 cases of intravesical oxybutynin treatment, in which they reported nine patients with difficulty retaining the solution in the bladder. Kasabian et al. [1994] reported the side effects of this therapy (one patient experienced hot flashes, three patients thirst, one patient urinary tract infection, and two patients difficulty retaining the solution in the bladder) in a total of 19 neurogenic bladder patients. In this study, we attempted to reduce the side effects of intravesical oxybutynin and retaining the solution longer in the bladder. HPC is a well-known agent whose main effect is retaining drugs in the bladder.

TABLE III. Plasma Levels of Oxybutynin and DEOB[a]

Patient	Oxybutynin (ng/mL)				DEOB (ng/mL)			
	0	1 h	2 h	4 h	0	1 h	2 h	4 h
ST	ND	2.6	1.9	0.6	ND	1.1	1.2	1.1
TH	ND	6.8	7.0	1.6	ND	1.6	2.9	2.4
HA	ND	1.6	6.7	7.6	ND	4.4	5.9	3.9
YD	ND	11.3	8.1	2.3	ND	7.5	12.4	9.2
MI	ND	15.1	9.3	2.7	ND	2.4	6.0	4.4
HH	ND	15.2	8.0	3.3	ND	8.3	10.2	9.6
Avg.	ND	8.8 ± 2.5	6.8 ± 1.1	3.0 ± 1.0[b]	ND	4.2 ± 1.3	6.4 ± 1.7	5.1 ± 1.4

[a]At 1, 2, and 4 hours after the initial treatment of intravesical oxybutynin chloride, respectively.
[b]Significantly different from 1- and 2-h groups. $P < 0.05$ was the level of significance.
ND, not detected.

Indeed long-term retention of intravesical adriamycin and peplomycin was reported [Ueda et al., 1988; Yasumoto et al., 1988]. Yasumoto et al. [1988] reported that the half-life of peplomycin intravesical treatment with HPC was 10 times longer than without HPC, and they suggested HPC is effective in adhering chemicals to the bladder mucosa. Mizunaga et al. [1996] reported intravesical oxybutynin with HPC for six healthy volunteers and seven overactive bladder patients. They demonstrated that the concentration of plasma oxybutynin in intravesical oxybutynin treatment with HPC was significantly lower than that without HPC and that the effect of oxybutynin with HPC lasted longer than that without HPC, as measured by average flow rate in the healthy volunteers.

In this study, we demonstrated the plasma concentrations of oxybutynin and its active metabolite DEOB. In the first phase study of oral administration of oxybutynin in Japan, the C_{max} values and T_{max} values of 6 mg/body weight oral administration were 9.28 ± 1.01 ng/mL and 0.67 ± 0.11 hour, respectively [1986]. From previous studies and this study, plasma levels of oxybutynin plus HPC intravesically administered are similar to those of orally administered (6 mg/body weight). Furthermore, the levels of the serum oxybutynin in our study are lower than those in the study of Massada et al. [1992]. The plasma levels of DEOB in our study were shown to have no significant differences at 1, 2, and 4 hours after the initial administration. Massada et al. [1992] reported that the serum oxybutynin concentration after oral administration was significantly lower than that after intravesical administration and that the metabolite that may be generated after oral administration is responsible for the side effects. Buyse et al. [1998] reported that a significantly lower ratio of AUC (area under the plasma concentration time curve) of DEOB over oxybutynin may reduce systemic side effects. Our data suggest that modified intravesical oxybutynin may possibly reduce absorption of oxybutynin from the bladder mucosa and retain oxybutynin in the bladder longer and that modified intravesical oxybutynin may reduce systemic side effects compared to those of intravesical oxybutynin without HPC.

As this was a study using a small number of the patients and a preliminary report, our data provide the possibility of another treatment option for overactive bladder and/or detrusor hyperreflexia patients who do not respond to oral medication or who experience intolerable systemic side effects of anticholinergic drugs.

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