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Relaxation of Intestinal Bladders by Intravesical Oxybutynin Chloride

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Incontinence is a frequent complication of continent urinary diversions and neurogenic bladder augmentations constructed from intestinal segments. Oxybutynin chloride was delivered intravesically and orally to six beagles 9 months after bladders were replaced by tubularized ileum (in three dogs) or sigmorectum (in three dogs). Intravesical oxybutynin produced greater bladder relaxation by urodynamic criteria. Measured oxybutynin chloride concentrations suggested that high tissue levels were achieved at low systemic levels. In two human patients with ileocecal urinary diversions, intravesical oxybutynin chloride decreased bladder pressure and decreased the number and magnitude of superimposed contractions. Intravesical application of oxybutynin chloride may produce local drug levels unachievable by oral administration and may better treat incontinence in patients who intermittently catheterize intestinal bladders or intestinally augmented neurogenic bladders.

Key words: bladder augmentation, topical oxybutynin chloride, incontinence

INTRODUCTION

Incontinence is a frequent complication of continent urinary diversions and neurogenic bladder augmentations constructed from intestinal segments. Administration of oral dosages of pharmaceuticals sufficient to effect bladder relaxation is often prevented by the development of incapacitating anticholinergic side effects. Performance of chronic intermittent clean catheterization of intestinally replaced or augmented bladders provides a convenient mechanism of administration of bladder relaxants.

We compared the ability of oxybutynin chloride to relax segments of intestine by oral and intravesical routes of administration in dogs with ileal or colonic bladders. Intravesical administration produced higher tissue levels of oxybutynin chloride in an ileal bladder compared with intact ileum. Application of this agent to human patients was evaluated in two patients with intestinal bladders.

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Throughout this manuscript, the terms *bladder*, intra*vesical*, and *cysto*metrogram were applied to a urinary reservoir constructed from intestinal segments.

METHODS

Six Berkshire beagles (mean weight 12.1 kg, range 11.4–12.7 kg) underwent cystoprostatectomy under pentobarbital anesthesia. Sixteen-centimeter segments of intestine (ileum-3; sigmorectum-3) were used to fashion urinary bladder substitutes by a canine adaptation of the method of Camey [Lillien and Camey, 1984]. Nine months later, all animals had normal upper tracts by intravenous pyelography and normal urinary creatinine clearances. At the time of cystometrograms, all dogs were healthy, free of urinary tract infections, and voided with residual urine volumes of less than 30 ml. Each animal had cystometrograms performed as a baseline, 2 hours after the third oral 5 mg every-12-hours dose of oxybutynin chloride, and 30 minutes after a 20 minute instillation of 5 mg oxybutynin chloride dissolved in 30 ml normal saline. Cystometrograms after oxybutynin chloride administered orally and intravesically were separated by at least 48 hours to allow drug washout.

Animals were sedated with 1.5 mg/kg of intravenous acepromazine maleate. The bladder was drained via a #8 French pediatric feeding tube, and two #5 French pediatric feeding tubes were placed into the urinary bladder. Normal saline was infused through one urethral catheter at a continuous pressure of 30 cm of water. A three-channel cystometrogram machine (Lifetech Inc., Model 1152, Houston, Texas) allowed simultaneous monitoring of rectal pressure via rectal balloon catheter and intravesical pressure through the second urethral catheter. Subtraction of intra-abdominal (rectal) pressure from intravesical pressure yielded the true intravesical pressure, which was the subject of all analyses. All cystometrograms were reproduced in Figure 1 and described by six parameters. Bladder pressure was expressed as mean and standard deviation of individual bladder pressures at 1 second intervals over the course of bladder filling. Volume and pressure at bladder capacity were measured in milliliters and centimeters of water pressure, respectively. Bladder capacity was defined by the occurrence of continuous leakage about the urethral catheters. Number, mean pressure (cm water), and maximum pressure (cm water) of contractions greater than 2 cm water pressure were determined. Cystometrograms were compared by mean bladder pressure, volume at bladder capacity, and number and mean pressure of contractions. Standard deviation of bladder pressure, pressure at bladder capacity, and maximum contraction pressure gave redundant or unusable information. Baseline cystometrograms were compared with cystometrograms performed after intravesical and oral administration of oxybutynin chloride by paired Student's *t*-tests.

The mechanism for bladder relaxation produced by intravesically administered oxybutynin chloride was evaluated in an ileal-substituted animal. After general anesthesia was administered, specimens of peripheral venous blood were obtained by venipuncture, ileum by resection, ileal-substituted bladder by cystotomy, and mesenteric venous blood that drained the bladder substitute by cannulation. Oxybutynin chloride, 5 mg dissolved in 30 ml of normal saline, was instilled into the bladder through a urethral catheter and left indwelling for 20 minutes; specimens were obtained again. All blood samples were collected in glass syringes and 10 ml injected immediately into glass tubes containing 2,500 units of sodium heparin and mixed. Samples were immediately centrifuged at room temperature for 15 minutes at 2,500 rpm. The plasma was separated and transferred to glass culture tubes with Teflon-lined screw caps using a #4-0 silicate glass pipette. Tissue samples were washed in large volumes of normal saline and placed in glass containers with Teflon-lined screw

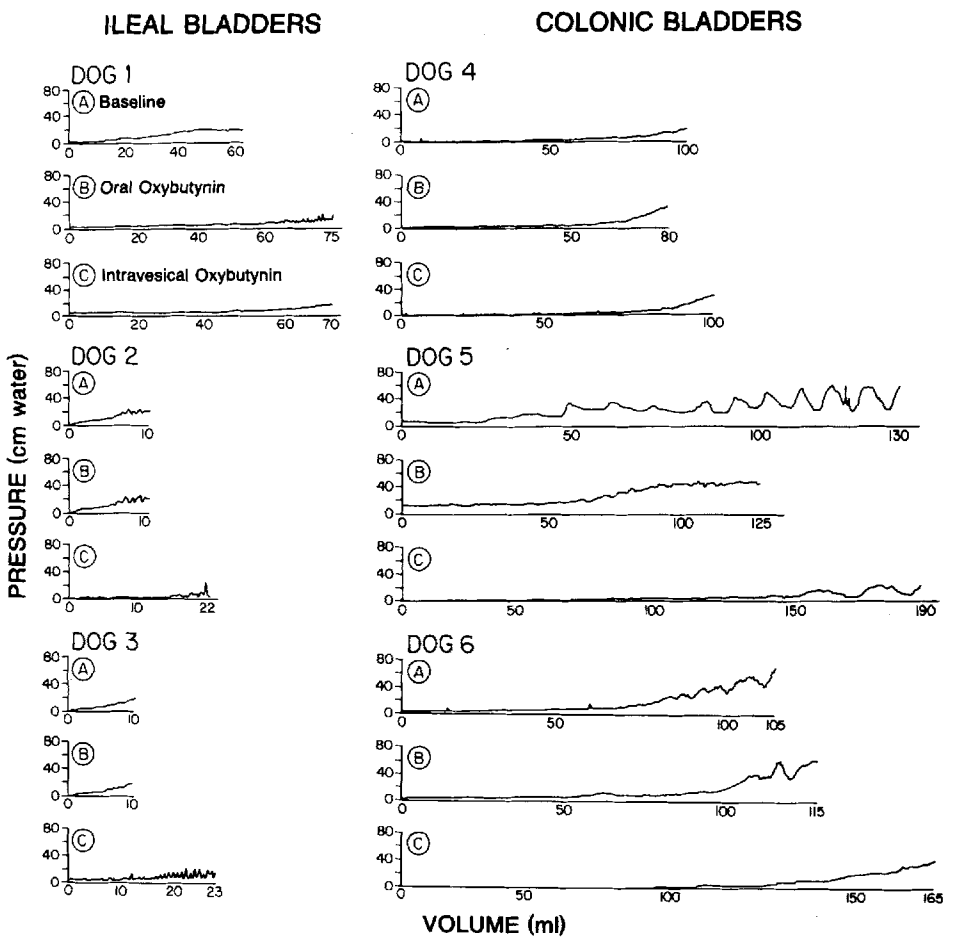

Fig. 1. Ileal and colonic bladder cystometrograms. Baseline cystometrogram (**A**), cystometrogram after oral oxybutynin chloride (**B**) and cystometrogram after intravesical oxybutynin chloride (**C**) in dogs 1–3 with ileal bladders and dogs 4–6 with colonic bladders.

caps. All specimens were stored at −18° C immediately after collection and transported on dry ice. After organic extraction of the oxybutynin chloride from plasma and pulverized and solubilized tissue, oxybutynin chloride concentrations (ng/ml plasma and ng/mg frozen weight tissue) were measured by combined gas chromatography/mass spectrometry using single-ion monitoring (analyses performed courtesy of Marion Laboratories, Inc., Kansas City, Missouri, by proprietary methodology). All specimens were analyzed in triplicate. Plasma and tissue concentrations were reported as mean ± standard error (SEM), and assay reproducibility was expressed as coefficient of variation (CV).

The potential application of intravesical oxybutynin chloride for bladder relaxation in human patients was evaluated in two patients. A 64-year-old white male underwent radical cystectomy for transitional cell carcinoma of the bladder. His urinary tract was reconstructed with an ileocecal continent urinary diversion as described by Rowland and associates [1985]. When the cecostomy tube was removed 3

TABLE I. Effect of Oxybutynin on Ileal and Colonic Bladders*

	Pressure	Bladder capacity	Number	Mean pressure
Ileal bladder				
Baseline	14 ± 1	27 ± 17	7 ± 4	14 ± 7
Oral oxybutynin	5 ± 1	32 ± 22	6 ± 4	4 ± 7
Intravesical oxybutynin	6 ± 2	38 ± 16	5 ± 5	2 ± 2
Colonic bladder				
Baseline	13 ± 5	112 ± 9	6 ± 3	13 ± 7
Oral oxybutynin	13 ± 3	108 ± 12	1 ± 1	7 ± 5
Intravesical oxybutynin	6 ± 1	152 ± 27	1 ± 1	4 ± 4

*All pressures (cm water) and volumes (ml) are mean ± standard error (n = 3).

weeks postoperatively, the patient had difficulty achieving sufficient continent intervals on intermittent catheterization. Ten weeks postoperatively, a cystometrogram was performed. Five milligrams of oxybutynin chloride in 60 ml of normal saline were instilled for 30 minutes and a cystometrogram repeated. A 47-year-old female underwent radical cystectomy for carcinoma in situ unresponsive to topical therapy with thiotepa and BCG. Her urinary tract was reconstructed as described by Rowland and associates [1985] except the reservoir was detubularized. In spite of oral oxybutynin chloride therapy at a dosage of 10 mg every 12 hours, the patient suffered embarrassing episodes of incontinence intermittently throughout the day and night and had severe abdominal cramping comparable to labor contractions. Cystometrograms were performed while the patients were on no medications, following 10 mg of oxybutynin chloride orally and following instillation of 10 mg of oxybutynin chloride in 50 ml of normal saline for 30 minutes. Cytometrograms from both patients were evaluated and compared as described for the animal studies. In addition, the patients' sensations of fullness and comfort were noted.

RESULTS

All cystometrograms performed in six dogs at baseline and after oral and intravesical oxybutynin chloride were reproduced in Figure 1 for visual inspection. In all six animals studied, bladder capacity increased after intravesical oxybutynin chloride compared with baseline and/or orally administered drug. In most cases, bladder pressure and frequency of contractions appeared reduced by intravesical drug administration.

Cystometrograms were analyzed more completely and objectively among the two groups of three dogs with bladder replacements by ileum or colon. When administered to three animals with ileal bladders, oxybutynin chloride reduced mean bladder pressure compared with baseline (14 cm water) when administered intravesically (6 cm water, $P < 0.05$) or orally (5 cm water, $P < 0.05$) (Table I and Fig. 1). Oxybutynin chloride by either route of administration increased bladder capacity and decreased contraction pressure when compared with baseline, but these changes were not statistically significant. In both cases, the change from baseline was more pronounced following intravesical administration; however, no significant differences in cystometrogram parameters occurred between the two routes of administration. The number of contractions was not affected. In three dogs with colonic bladders, intra-

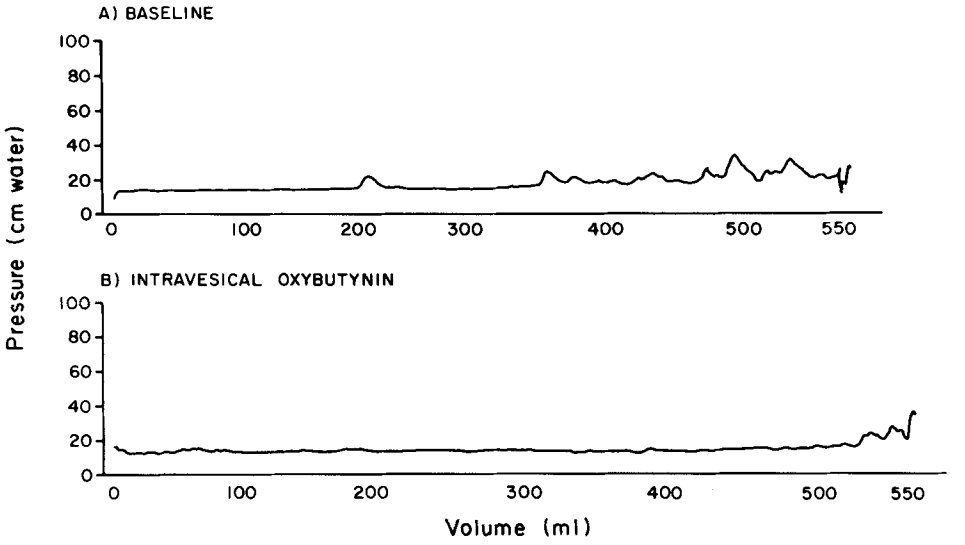

Fig. 2. Cystometrograms of a 64-year-old male with continent urinary diversion after radical cystectomy. **A:** Baseline. Intravesical pressure increased gradually with superimposed high amplitude, low-frequency contractions. They began in an isolated fashion at 200 ml of filling and became continuous and of increasing amplitude at 350 ml of filling. Leakage occurred at a bladder capacity of 550 ml. **B:** Cystometrogram after intravesical oxybutynin chloride. Intravesical pressure increased gradually; however, compared with baseline, contractions failed to develop until after 500 ml of bladder filling. Once they began, the contractions produced leakage at a bladder capacity of 550 ml, which was unchanged compared to baseline.

vesical oxybutynin chloride reduced the mean bladder pressure from 13 to 6 cm water and increased bladder capacity from 112 to 152 ml (Table I, Fig. 1), but differences were not statistically significant. When administered orally, oxybutynin had no effect on pressure or capacity.

Prior to administration of intravesical oxybutynin chloride, all plasma and tissue levels performed in triplicate were below the limits of quantitation (0.15 ng/ml plasma, 2.25 ng/g tissue). Immediately following a 20 minute intravesical instillation of oxybutynin chloride, systemic drug concentration was 9.12 ± SEM 0.39 ng/ml plasma (assay CV 4.2%). Simultaneously, venous effluent from the ileal bladder substitute contained 2,830 ± 138 ng/ml plasma of oxybutynin chloride (assay CV 4.9%). The difference ($P < 0.0001$) represented a 310-fold concentration of effluent oxybutynin chloride over circulating drug. Tissue levels of oxybutynin chloride from samples of ileal bladder (2,951 ± 1583 ng/mg) were 52 times those of simultaneously obtained intact ileum (57 ± 9 ng/ml) (assay CV 7.0%).

Intravesical oxybutynin chloride relaxed an ileal patched tubularized cecal continent urinary diversion in a 64-year-old male. The baseline cystometrogram (Fig. 2a) revealed a bladder with a mean pressure of 17 cm water and a capacity of 550 ml. Nine contractions began at 350 ml volume and mean contraction pressure was 7 cm water. Following administration of intravesical oxybutynin chloride (Fig. 2b), mean bladder pressure was reduced to 15 cm of water. The contractions were reduced to two and did not begin until 500 ml of bladder filling. Once they began, their mean pressure

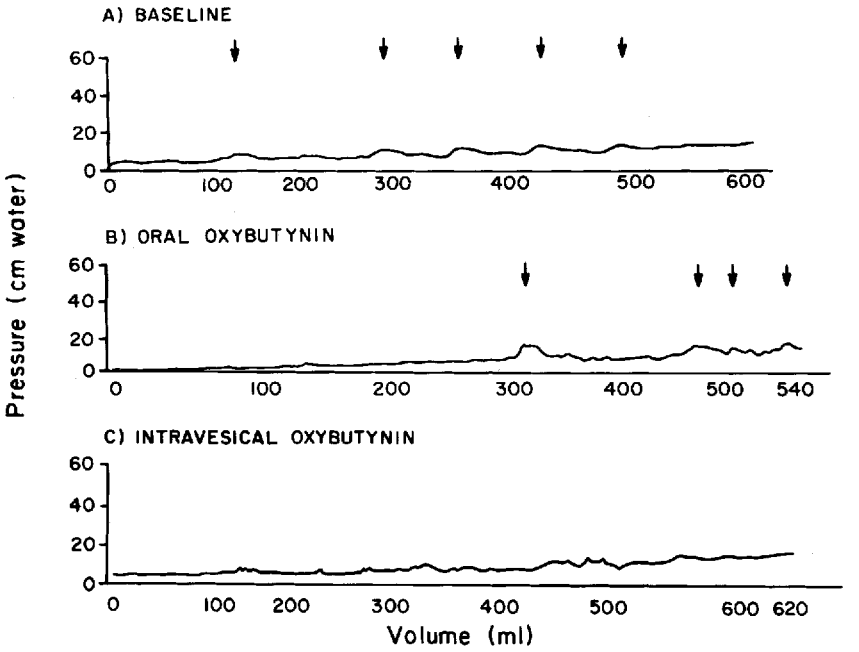

Fig. 3. Cystometrograms of a 39-year-old female with continent urinary diversion after radical cystectomy. **A:** Baseline. Intravesical pressure increased gradually until leakage occurred at a capacity of 600 ml. Five high-amplitude, low-frequency contractions began at a volume of 125 ml. Each contraction was associated with severe abdominal cramping (arrows) and a 10 ml jet of fluid. **B:** Cystometrogram after oral oxybutynin chloride. Intravesical pressures and bladder capacity were similar to baseline. Contractions did not begin until 300 ml of filling but were still associated with severe cramping and incontinence (arrows). **C:** Cystometrogram after intravesical oxybutynin chloride. Intravesical pressure and bladder capacity remained similar to cystometrograms performed as a baseline and after oral oxybutynin chloride. Contractions were eliminated and no cramping or incontinence occurred until bladder capacity was reached after 620 ml of filling.

was unchanged, and they produced leakage around the catheter at a capacity of 550 ml, which was not different from baseline. This patient had foregone his intermittent catheterization program and had a decompensated continent urinary diversion and thus experienced no increase in capacity with oxybutynin chloride instillation. The diminution of contractile activity was reflected in a mild reduction in the mean bladder pressure. The patient was returned to an intermittent catheterization program and was continent on catheterization every 6 hours without pharmacological manipulation.

A 47-year-old female with a detubularized ileocecal urinary continent diversion had an excellent symptomatic and objective response to intravesical oxybutynin chloride administration. Her baseline CMG (Fig. 3a) revealed mean bladder pressure of 8 cm water and capacity of 600 ml. Five contractions occurred with a mean amplitude of 4 cm water. After oral administration of oxybutynin chloride (Fig. 3b), mean pressure was unchanged at 9 cm of water pressure, bladder capacity was 540 ml, and three contractions occurred having a mean pressure of 4 cm water. After intravesical instillation of an identical dose of oxybutynin chloride (Fig. 3c), mean bladder pressure was reduced by 38%, to 5 cm water. Bladder capacity was 600 ml, and a single contraction of 3 cm water pressure occurred. More importantly, symptoms of severe

abdominal cramping, which corresponded to contractions observed in the baseline and after oral oxybutynin chloride cystometrograms, were eliminated. Six months postoperatively, the patient had achieved sufficient reservoir capacity and accommodation, no longer experienced abdominal cramping, and thus did not require bladder relaxant medication.

DISCUSSION

Over the past 10 years, a revolution has occurred in urinary tract reconstruction. In patients with neurogenic bladders incontinent upon intermittent catheterization, bladder augmentation has improved continence. After cystectomy for bladder cancer, bladder replacements have been constructed from tubularized or detubularized small or large bowel and combinations thereof. They were anastomosed to the abdominal wall and incorporated a continence mechanism that necessitated intermittent catheterization for emptying [Kock et al., 1982]. Alternatively, they were anastomosed to the urethra and depended upon the external sphincter or artificial sphincters [Light and Scott, 1984] for continence and Valsalva and gravity for emptying. Regardless of the method of reconstruction, the bowel maintained an inherent contractility that increased as fluid content increased. Tubularized segments of small or large bowel generated pressures in excess of 50 cm of water [Light and Englemann, 1985], which often overcame continence mechanisms. In spite of alterations in fluid intake, adjustments in intermittent catheterization frequency or timed voidings and pharmacological manipulation, many patients remained incontinent.

The bowel employed in urinary tract reconstruction provides a highly absorptive surface for many medications commonly given orally. In addition, intermittent catheterization provides an avenue for instillation of medications that may enable achievement of therapeutic effects at systemic drug levels far below those encountered with orally administered pharmaceuticals. The ideal agent for intestinal bladder substitute relaxation would achieve 100% saturation of its receptor within the tissue of the bowel after complete absorption of the medication from the lumen of the substitute. Extraction of the medication from the instilled fluid would be complete during passage through the mucosa, interstitial spaces, and vasculature of the bowel such that no drug reached the venous effluent from the bladder substitute and, hence, the systemic circulation, where side effects could result. If the perfect agent could not be uncovered, a commonly administered medication with known, mild side effects that is absorbed across intestinal mucosa and relaxes smooth muscle of intestinal segments would be acceptable.

Atropine completely abolishes the effects of acetylcholine on the gastrointestinal tract; however, gut motility persists, but at a greatly reduced level. This probably results from incomplete inhibition of the effects of vagal impulses as well as the presence of neurohumoral transmitters other than acetylcholine [Innes and Nickerson, 1975]. Doses of atropine that sufficiently decreased tone and peristaltic contractions of the bowel depressed salivary secretion and usually produced ocular and cardiac effects [Innes and Nickerson, 1975]. Many anticholinergic drugs with postganglionic atropine-like effects have been developed in an attempt to provide selective bladder relaxation. Propantheline (a quaternary ammonium compound) and oxybutynin chloride (a tertiary amine) are both widely employed for the treatment of detrusor instability. A clear advantage of one agent over the other has not been demonstrated

[Wein, 1982]. Comparisons of these and other anticholinergic agents are compromised by reliance upon symptomatic responses and the difficulty in quantification of cystometric evaluations. With both agents, achievement of optimal clinical or cystometric responses is often precluded by the development of systemic side effects. A means of topical administration by periodic intravesical instillation, placement of intravesical time-release pellets or other means should be investigated.

Intravesically administered oxybutynin chloride produced greater bladder relaxation when compared with cystometrograms performed as baseline studies or after oral administration of oxybutynin chloride in six dogs with bladders constructed from intestinal segments. Reduction in contractile activity in tubularized as well as detubularized continent urinary diversions was clearly demonstrated by cystometric study in two human patients. In addition, in a symptomatic patient, severe abdominal cramping disappeared with intravesical administration of oxybutynin chloride.

A possible mechanism for the value of intravesical administration was suggested by the concentration of oxybutynin chloride in the tissue of the ileal bladder substitute as compared with normal ileum. Extremely high smooth muscle concentrations of drug may have been established by absorption of oxybutynin chloride across the intestinal mucosa with diffusion through the interstitium and saturation of target sites. Complete muscosal confinement or absorption of oxybutynin chloride was excluded by the achievement of high drug concentrations in venous effluent from the bladder substitute as compared with systemic concentrations. However, the elevated tissue levels may have represented oxybutynin chloride located within the intravascular compartment of the bladder replacement. Increased tissue levels observed in conjunction with documented physiological effect favored a drug/effector relationship. Serum and tissue levels of oxybutynin chloride after oral administration were not studied. However, tissue levels of oxybutynin chloride in bladder replacements after oral administration should be similar to those of intact ileum after intravesical administration of equivalent amounts of drug. Systemic drug levels probably preclude achievement of tissue drug concentrations possible with topical administration, but no conclusions about the superiority of intravesical administration upon drug levels can be made based upon our study.

Patients with continent urinary diversions managed by intermittent catheterization who are incontinent may benefit from a trial of oxybutynin instillation [Brendler et al., 1989]. Patients with incontinence who depend upon natural, surgically created, or prosthetic continence mechanisms may be spared further operative procedures by bladder relaxation with intravesical oxybutynin chloride. Reconstruction of the urinary tract with detubularized segments of intestine appears to have diminished the incidence of incontinence due to elevated intraluminal pressures. However, as experience with this newer technique accrues, problems with incontinence may occur. Regardless of the method of bladder replacement, incontinence may occur in the immediate postoperative period. Pharmacological relaxation may allow further accommodation of new intestinal bladders to larger urinary volumes without incontinence producing contractions.

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