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Intravesical Oxybutynin in Patients With Posterior Rhizotomies and Sacral Anterior Root Stimulators

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This report investigates the use of intravesical oxybutynin in spinal injury patients, who have had dorsal rhizotomies to abolish reflex detrusor activity and void with S2, S3, and S4 stimulation, done with the Brindley anterior root stimulator.

Six male patients (age range 27 to 56, mean 36 years) who have had Brindley anterior root stimulators implanted were included in this study. Video urodynamic assessment was done and 10 mg of oxybutynin hydrochloride was instilled through the urethral catheter. This was left in the bladder for 60 minutes and video urodynamics were repeated. Voiding, both pre and post oxybutynin, was achieved with sacral root stimulation.

Peak detrusor pressure (Pves) during voiding in the 6 patients before oxybutynin instillation was 89, 154, 90, 60, 56, and 80 (mean 88.2) cm of water. Post oxybutynin the pressures were 83, 163, 95, 40, 30, and 68 (mean 79.8) cm of water. The peak flow rate (Qmax) pre oxybutynin was 32, 24, 20, 20, 12, and 28 (mean 22.7) ml per second and this changed to 28, 31, 18, 24, 10, and 32 (mean 23.8) ml per second. This shows no difference in the detrusor pressure ($P = 0.2$) and flow rate ($P = 0.54$) pre and post oxybutynin instillation into the bladder.

Effectiveness of oxybutynin is attributed to a combination of M3 receptor antagonism in the smooth muscle and direct spasmolytic, local anaesthetic and calcium channel blocking action. Its therapeutic benefit is limited by the anti cholinergic side effects (40–80%) and recent studies have shown the intravesical route to be effective and better tolerated. However in this study it has been ineffective in abolishing any detrusor contractions generated by S2, S3, and S4 stimulation.

Key words: intravesical oxybutynin, posterior rhizotomy, sacral anterior root stimulator, detrusor contraction

INTRODUCTION

The management of patients with neurogenic bladder dysfunction has improved in the last two decades with the proper application of intermittent catheterisation and pharmacotherapy. Drugs available for the treatment of the overactive detrusor have been recently reviewed [Andersson, 1988; Andersson and Mattiasson, 1988]. These include anticholinergics (propantheline), calcium channel blocking drugs, and those

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with a mixed action (oxybutynin). Drugs acting on alpha and beta adenoceptors (phenoxybenzamine, terbutaline), prostaglandin synthetase inhibitors (indomethacin), and bromocriptine and baclofen have also been used for detrusor overactivity.

Oxybutynin is a tertiary amine [Majewski et al., 1965] and its effectiveness is attributed to a combination of M3 selective receptor subtype antagonism [Noronha-Blob and Kachur, 1991; Nilvebrant and Sparf, 1986] and antispasmodic [Anderson and Fredericks, 1977; Fredericks et al., 1977], local anaesthetic and calcium channel blocking action [Tonini et al., 1987; Lish et al., 1965]. Oral oxybutynin has a well-documented therapeutic effect in bladder hyperreflexia. Subjective responses of 60 to 75% and objective improvement in 39 to 76% have been reported [Thuroff et al., 1991; Moisey et al., 1980; Diokno and Lapides, 1972; Brooks and Braf, 1980]. The high incidence of anticholinergic side effects (40–80%) often results in dose reduction or discontinuation [Moisey et al., 1980; Cardozo et al., 1987]. Recent studies have shown the intravesical route to be effective and better tolerated [Brendler et al., 1989; Greenfield and Fera, 1991; Massad et al., 1992].

This study was undertaken to assess the efficacy of intravesical oxybutynin when given in spinal injury patients. These patients have had dorsal rhizotomies to abolish reflex detrusor activity and void with stimulation of the anterior roots of S2, S3, and S4 using the Brindley sacral root stimulator. Voiding in these patients is controlled and the parameters for electrical stimulation are adjusted to give optimal detrusor contraction and near complete emptying.

PATIENTS AND METHODS

Six adult male patients, age ranging from 27 to 56 (mean 36) years, with traumatic spinal cord transection in whom sensory deafferentation had been done by dividing the dorsal roots and who had the Brindley sacral root stimulator implanted, formed the study group. None of these patients had any reflex detrusor activity and they all voided by electrical stimulation of one or more of the anterior roots of S2, S3, and S4.

All patients had attended for routine video urodynamic testing of their sacral stimulator and only those patients who had good subjective and objective response on stimulation with adequate detrusor pressure rise and complete emptying with good flow rate were included in the study. Residual urinary volume in all patients was less than 50 ml. Initial video urodynamic were done. This involved bladder emptying with a bilumen catheter, filling the bladder with dilute Urografin (Sp. gravity 1,009 g/l) to a volume of 250 ml. There was no detrusor pressure change on filling and after the bladder had been filled, the patients were asked to void using their stimulators. Detrusor pressure rise after stimulation and the flow rate and residue were assessed. Through the urethral catheter (left in place) was instilled 10 mg of oxybutynin chloride (provided in a pre-prepared solution of 30 ml on a named patient basis for the purpose of this study). This was left in the bladder for 60 minutes and video urodynamics were repeated using the same parameters. The bladder was not emptied prior to post oxybutynin testing, 200 ml of contrast being filled over the residue.

RESULTS

Video urodynamics done on each patient before oxybutynin instillation show stimulated maximum detrusor pressure as 56, 60, 80, 89, 90, and 154 cm of water,

respectively. After oxybutynin had been allowed to stay in the bladder for 60 minutes, the maximum detrusor pressure on electrical stimulation was 30, 40, 68, 83, 95, and 163 cm of water in the 6 patients. This shows there has been no difference in the peak detrusor pressure after oxybutynin instillation. The mean pressure pre oxybutynin was 88.2 and post oxybutynin was 79.8 cm of water ($P = 0.2$) (Fig. 1). In the 6 patients the peak flow rate (Qmax) on detrusor stimulation was 12, 20, 20, 24, 28, and 32 ml per second (mean 22.7 ml/sec) and this changed after the oxybutynin had been instilled and remained in the bladder for 1 hour to 10 ,18, 24, 28, 31, and 32 ml per second (mean 23.8 ml/sec), respectively. Statistical testing on twin t-test did not show this difference as significant ($P = 0.54$) (Fig. 2). The residual volume was assessed subjectively on the X-ray screen and in no patient was it greater than 50 ml, both before and after oxybutynin instillation. None of the patients showed any increase in the urinary residue after oxybutynin.

DISCUSSION

Studies showing the effectiveness of intravesical instillation for suppressing bladder contractility are limited. The agents used include emeporium bromide (80% efficacy) [Obrink and Bunne, 1978], lignocaine (95% increase in capacity, 80% cystometrographic improvement) [Higson et al., 1979], and oxybutynin (subjective improvement 100%, objective improvement 91% [Brendler et al., 1989]; 80 and 90% improvement in patients with neurogenic bladder dysfunction and hyperreflexia [Greenfield and Fera, 1991; Madersbacher and Jilg, 1991]). In all these series the absence of systemic side effects would suggest that the efficacy of intravesical oxybutynin is due to a profound local effect and systemic absorption is minimal if any. However, recent work by Massad et al. [1992] where plasma concentration of oxybutynin was measured with oral and intravesical administration, showed a much higher plasma concentration after intravesical instillation. Plasma concentration peaked after 1 hour (mean after oral administration was 4.46 ng/ml and after intravesical administration was 18.5 ng/ml) and then dropped rapidly both after oral and intravesical administration. Douchamps and colleagues [1988] in a similar study of the pharmokinetics of oral oxybutynin in adult volunteers showed peak concentrations at about 1 hour with subsequent rapid decline. In our study oxybutynin was allowed to remain in the bladder for 1 hour to allow it to have maximal effect.

Patients with sacral root stimulators are an ideal group to study the effect of drugs in reducing bladder contractability. All the patients in our study group have had the posterior roots of S2, S3, and S4 divided and this sensory deafferentation abolishes any reflex detrusor activity. Voiding in these patients is electrically controlled by stimulation of the motor roots of one or more of S2, S3, and S4. The parameters of stimulation have been adjusted to allow adequate detrusor contraction and to facilitate bladder emptying. In none of our 6 patients did intravesical oxybutynin produce any effect by reducing artificially produced detrusor contraction or any reduction in the peak flow rate or any increase in the residual volume.

The mechanism of action of oxybutynin is not completely clear and a combination of muscarinic antagonism, antispasmodic, local anaesthetic, and calcium channel blocking action is suggested. As after oral administration the amount secreted in the urine is negligible, Douchamps et al. [1988] postulate that a predominant local effect is unlikely. It has, however, been suggested that the local detrusor action after

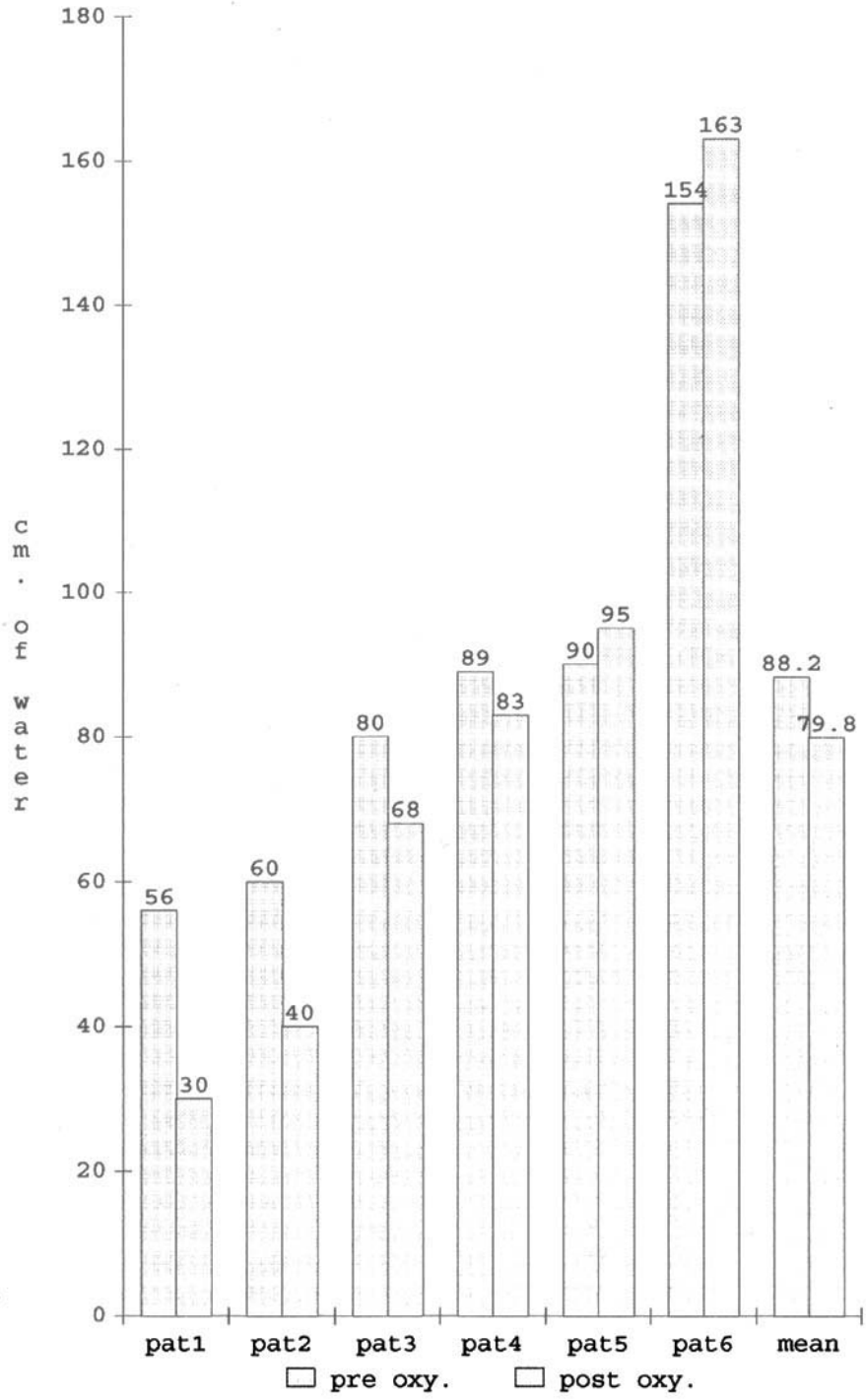

Fig. 1. Detrusor pressure. Maximum detrusor pressure on electrical stimulation is shown for each of the 6 patients by the numbers at the top of each bar. post oxy. (righthand bars), after oxybutynin instillation; pre oxy. (lefthand bars), before oxybutynin instillation.

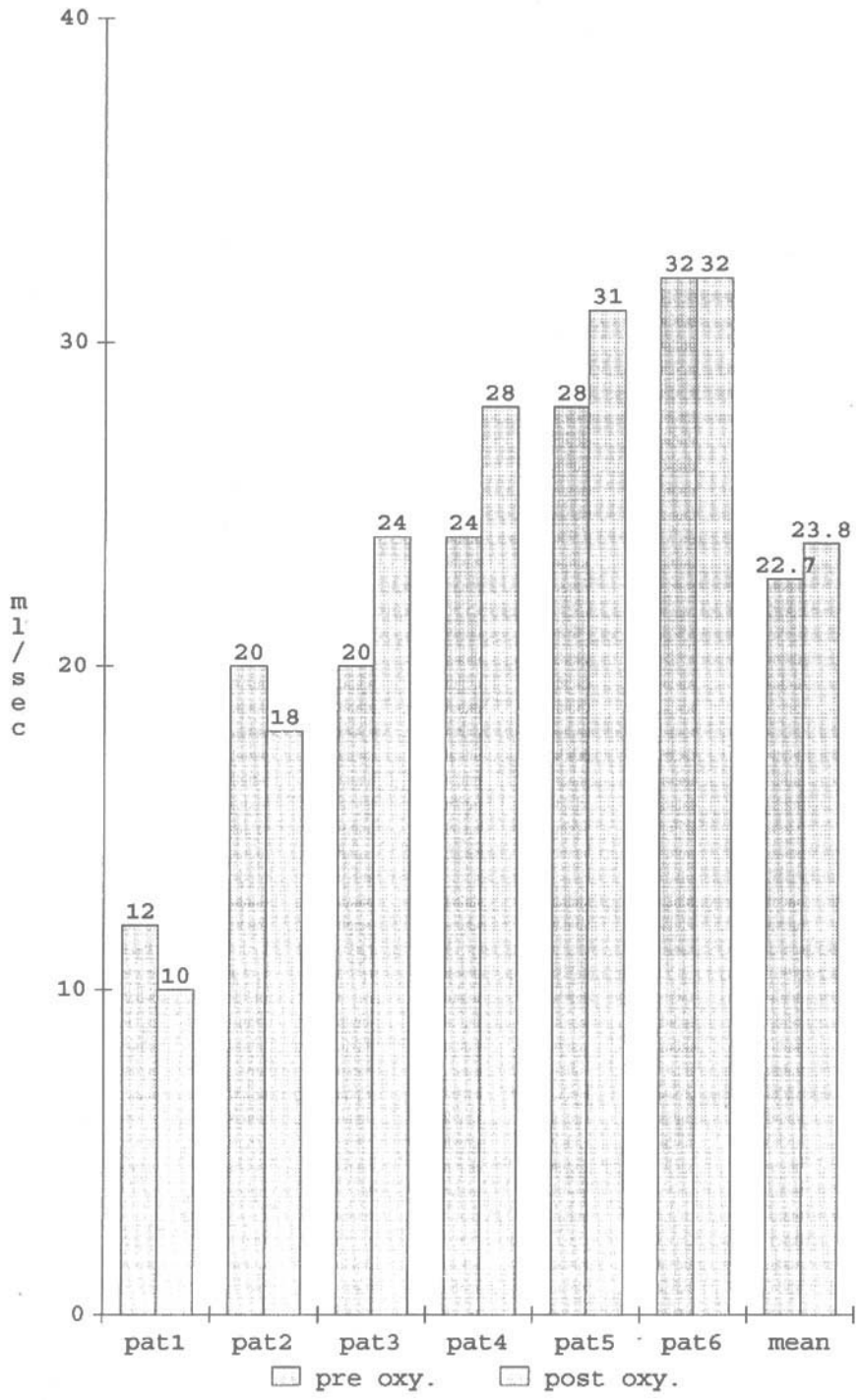

Fig. 2. Peak flow rate. Peak flow rate on detrusor stimulation is shown for each of the 6 patients by the numbers at the top of each bar. pre oxy., lefthand bars; post oxy., righthand bars.

intravesical administration is significant, as in an "in vitro" rabbit bladder study, oxybutynin suppressed pressure generated responses to bethanechol and electrical field stimulation [Kato et al., 1989]. The lack of side effects with bladder instillation despite high plasma concentrations would suggest a metabolite, after oral administration is responsible for the side effects. Perhaps this is also responsible in part for the efficacy of oxybutynin.

The patients in this study group, in an attempt to abolish hyperreflexic detrusor contractions, had their dorsal (sensory) roots divided; this was the one difference between them and patients in series where intravesical oxybutynin has been effective. Also in other series where topically instilled oxybutynin has been effective, the detrusor contractions have been both spontaneous and undesirable, unlike in patients in the present series when the detrusor contractions have been electrically induced to facilitate bladder emptying. Does oxybutynin in part act through a pathway requiring an intact sacral arc?

REFERENCES

Anderson GF, Fredericks CM (1977): Characterisation of the oxybutynin antagonism of drug induced spasm in detrusor. Pharmacology 15:31–39.

Andersson KE (1988): Current concepts in the treatment of disorders of micturition. Drugs 35:477–494.

Andersson KE, Mattiasson A (1988): Drug treatment of the overactive detrusor. Drugs Today 24:337–348.

Brendler CB, Radebaugh LC, Mohler JL (1989): Topical oxybutynin chloride for relaxation of dysfunctional bladders. J Urol 141:1350–1352.

Brooks ME, Braf ZF (1980): Oxybutynin chloride (ditrophan) clinical uses and limitations. Paraplegia 18:64–68.

Cardozo LD, Cooper D, Versi E (1987): Oxybutynin chloride in the management of idiopathic detrusor instability. Neurourol Urodyn 6:256–262.

Diokno AC, Lapides J (1972): Oxybutynin: A new drug with analgesic and anticholinergic properties. J Urol 108:307–309.

Douchamps J, Derenne F, Stockis A, Gangji D, Juvent M, Herchuelz A (1988): The pharmacokinetics of oxybutynin in a man. Eur J Clin Pharmacol 35:515–520.

Fredericks CM, Green RL, Anderson GF (1977): Comparative in vitro effects of imipramine, oxybutynin and flavoxate on rabbit detrusor. Urology 12:487–491.

Greenfield SP, Fera M (1991): The use of intravesical oxybutynin chloride in children with neurogenic bladder. J Urol 146:532–534.

Higson RH, Smith JC, Hills W (1979): Intravesical lignocaine and detrusor instability. Br J Urol 51: 500–503.

Kato K, Kitada S, Chun A, Wein AJ, Levin RM (1989): In vitro intravesical instillation of anticholinergic, antispasmodic and calcium blocking agents (rabbit whole bladder model). J Urol 141:1471–1475.

Lish PM, Labudde JA, Peters EL, Robbins SI (1965): Oxybutynin: A musclotropic antispasmodic drug with moderate anticholinergic action. Arch Int Pharmacodyn 156:467–488.

Madersbacher H, Jilg G (1991): Control of detrusor hyperreflexia by the intravesical instillation of oxybutynin hydrochloride. Paraplegia 29:84–90.

Majewski RF, Campbell KN, Dykstra S, Covinton R, Simms JC (1965): Anticholinergic agents. Esters of 4-Dialkyl (or 4-Polymethylene-) amino-2-butynols. J Med Chem 8:719–720.

Massad CA, Kogan BA, Trigo-Rocha FE (1992): The pharmacokinetics of intravesical and oral oxybutynin chloride. J Urol 148:595–597.

Moisey CU, Stephenson TP, Brendler CB (1980): The urodynamic and subjective results of treatment of detrusor instability with oxybutynin chloride. Br J Urol 52:472–475.

Nilvebrant L, Sparf B (1986): Diclomine, benzhexol and oxybutynin distinguish between subclasses of muscarinic binding sites. Eur J Pharmacol 123:133–143.

Noronha-Blob L, Kachur JF (1991): Enantiomers of oxybutynin: In vitro pharmacological characteristics

at M1, M2 and M3 muscarinic receptors and in vivo effect on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs. J Pharmacol Exp Ther 256:562–567.

Obrink A, Bunne G (1978): Treatment of urgency by instillation of emepronium bromide in the urinary bladder. Scand J Urol Nephrol 12:215–218.

Thuroff JW, Bunke B, Ebner A, Faber P, DeGeeter P, Hannappel J, Heidler H, Madersbacher H, Melchair H, Schafer W, Schwenzee T, Stockle M (1991): Randomised, double blind, multicentric trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: Oxybutynin versus propantheline versus placebo. J Urol 145:813–817.

Tonini M, Rizzi CA, Perucca E, De Ponti F, De Angelo L, Del Vecchio A, Crema A (1987): Depressant action of oxybutynin on contractility of intestinal and urinary tract smooth muscle. J Pharm Pharmacol 39:103–107.