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Intravesical instillation of oxybutynin hydrochloride therapy for patients with a neuropathic bladder

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Intravesical oxybutynin hydrochloride was administered to 17 patients with a neuropathic bladder (myelomeningocele in 15 and spinal cord tumour in two) and urinary incontinence refractory to intermittent catheterisation. Therapy consisted of instillation of a 10 ml solution containing 5 mg oxybutynin hydrochloride twice daily. The cystometric bladder capacity before and after 1 hour of intravesical oxybutynin hydrochloride was 132 ± 45 ml and 193 ± 71 ml (mean $\pm$ 1 standard deviation, $p < 0.01$) in all 17 patients. In 13 patients with low compliant bladders, the mean bladder compliance before and after 1 hour of instillation was 4.2 ± 2.4 ml/cmH_2O and 8.5 ± 6.4 ml/cmH_2O respectively ($p < 0.01$). The period of the intravesical oxybutynin hydrochloride treatment ranged from 2 to 16 months (mean 11.1 months). The improvement rate of 'moderately improved' and better response was 76.5% in all 17 patients. One patient complained of slight lower abdominal pain, which receded as treatment continued. Since the pH value of the solution appeared to be so low as to irritate the vesical mucosa, the value was adjusted to 5.85. No local or systemic side effects were observed thereafter. These encouraging results suggest that intravesical instillation of oxybutynin hydrochloride is an attractive alternative in patients with a neuropathic bladder, who are either unresponsive to or have intolerable side effects from oral medications.

Keywords: urinary catheterisation; intravesical administration; neuropathic bladder; oxybutynin hydrochloride.

Introduction

The urinary complications of patients with a neuropathic bladder consist of incontinence, inability to empty the bladder, urinary infection, and deterioration of the upper urinary tract. In 1972, Lapides and associates[1] reported the successful treatment of neuropathic bladders with clean intermittent catheterisation (CIC) and since then CIC has become widely accepted as the main therapeutic management for patients with such bladders. Adequate bladder emptying can be achieved by CIC, but urinary incontinence may persist in the presence of detrusor hyperreflexia and/or low compliance bladder. Management of patients with urinary incontinence secondary to a neuropathic bladder includes treatment with anticholinergic and antispasmodic agents, such as oxybutynin hydrochloride. Unfortunately, many patients do not respond to oral medications or have side effects that cause discontinuation of the treatment.

Intravesical administration of drugs with known effects on bladder relaxation may offer an attractive therapeutic alternative. Recently, several investigators have reported the positive effects on urodynamic parameters and improved symptomatology in patients after intravesical instillation of oxybutynin hydrochloride.[2–6] However, there have been few reports on long term clinical effects concerned with intravesical instillation of bladder relaxants. Herein, we investigated long term clinical effects of intravesical instillation of oxybutynin hydrochloride.

Materials and methods

Subjects consisted of 17 patients (nine males and eight females) with neurogenic vesical dysfunction, ranging from 4 to 45 years old (mean age, 12.3 years). The aetiology of the neuropathic bladder was meningomyelocele in 15 patients and spinal cord tumour in two. The patients were classified into two groups: 13 patients in group 1 had low compliant bladders (≤ 10 ml/cmH_2O) with detrusor areflexia, whereas four patients in group 2 had uninhibited detrusor contraction (detrusor hyperreflexia). All patients in this study rely on CIC and continue to suffer from severe incontinence. For these patients, oral medications are not effective.

At first, we used a solution of oxybutynin hydrochloride tablets which were crushed and dissolved in sterile saline (5 mg/10 ml). But the pH of the solution was 4.55 and the acidity might cause an irritating reaction in the vesical mucosa. So, we prepared the oxybutynin hydrocloride solution as follows. Tablets (500 mg as oxybutynin hydrochloride) were crushed, and extracted with 0.1 N HC1 800 ml, then filtered through a 0.45 μm membrane filter to exclude the insoluble excipients of the tablet. The solution was neutralised with 1 N NaOH 80 ml to pH 6.0, and a 1 M phosphate buffer of 50 ml was added. Finally, the total amount of a 1000 ml solution was filtered through a 0.22 μm membrane filter for sterilisation and dispensed into 100 tubes (5 mg/10 ml). The pH of the solution was 5.85, and oxybutynin hydrochloride was stable for 3 months at room temperature protected from light.

Urodynamics

Cystometry was performed with the patient in the supine position. A single lumen catheter (8–12 Fr) was introduced via the urethra for carbon dioxide filling and pressure recording. Rectal pressure was considered representative of abdominal pressure and registered with a rectal balloon catheter. Detrusor pressure (Pdet) was estimated by subtracting abdominal pressure from intravesical pressure. Carbon dioxide filling rates ranged from 50 to 100 ml per minute. The cystometry was performed in all patients prior to the instillation of oxybutynin hydrochloride. The solution of oxybutynin hydrochloride was instilled into the bladder through the catheter which was used for cystometry, and the catheter was clamped. An hour later, the solution and stored urine were evacuated, and cystometry was repeated. Cystometry was performed in 13 patients after continuing the instillation therapy for a month. A statistical analysis of the change of cystometric bladder capacity and bladder compliance was done with the Student's *t* test.

Clinical effects

The patients were asked about the clinical effects especially with regard to continence/incontinence and to general side effects. They were instructed to instill the solution via a catheter used for CIC. The solution was left in the bladder until the next catheterisation. Instillation was done twice a day. Seven patients who had already been prescribed oral oxybutynin hydrochloride continued taking the same dosage during the study of instillation. Clinical improvement was classified into four grades of 'markedly improved', 'moderately improved', 'slightly improved' and 'poor', evaluated from the condition of the incontinence.

Results

Cystometric findings

Cystometric bladder capacity increased in 14 patients whereas it had not changed in three. Mean bladder capacity before and after an hour of instillation was 132 ± 45 ml and 193 ± 71 ml ($p < 0.01$) in all 17 patients (Fig 1). In 13 patients, reexamined after 1 month of instillation therapy, the mean bladder volume was 208 ± 55 ml. Compliance of the bladder after the instillation was measured at the same point of the bladder volume as before the instillation. In 13 patients with low compliant bladders, the mean bladder compliance before and after 1 hour of instillation was 4.2 ± 2.4 ml/cmH_2O and 8.5 ± 6.4 ml/cmH_2O ($p < 0.01$, Fig 2). In 10 patients, reexamined after 1 month

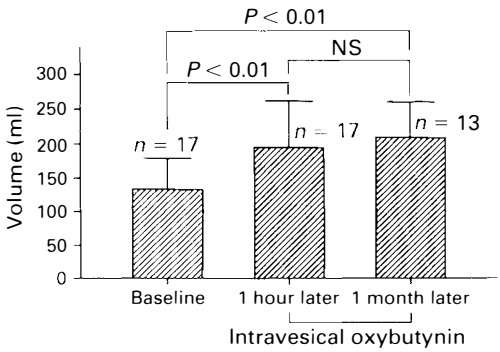

Figure 1 Bladder capacity in 17 patients before and after the use of intravesical oxybutynin hydrochloride. Bladder capacity significantly increases after instillation.

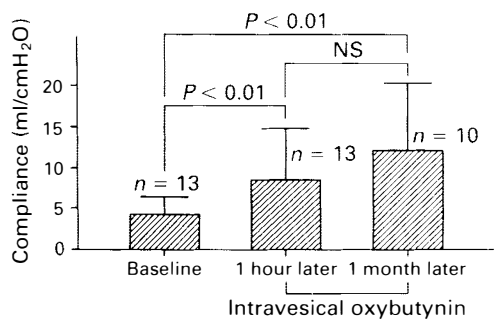

Figure 2 Bladder compliance (ml/cmH_2O) in 13 patients (group 1) before and after the use of intravesical oxybutynin hydrochloride. Bladder compliance significantly improved after instillation.

of instillation therapy, the mean bladder compliance was 12.1 ± 8.1 ml/cmH_2O. The cystometric curves before and after instillation in two patients (group 1 and group 2) are depicted in Figures 3 and 4.

Clinical symptomatology

The period of the bladder instillation therapy ranged from 2 to 16 months (mean 11.1 months). The overall clinical effect of this therapy in all 17 patients is depicted in Figure 5: 'markedly improved' in six, 'moderately improved' in seven, 'slightly improved' in two, and 'poor' in two. In group 1 (low bladder compliance) four were 'markedly improved', five were 'moderately improved', two were 'slightly improved' and two were 'poor'. In group 2 (detrusor

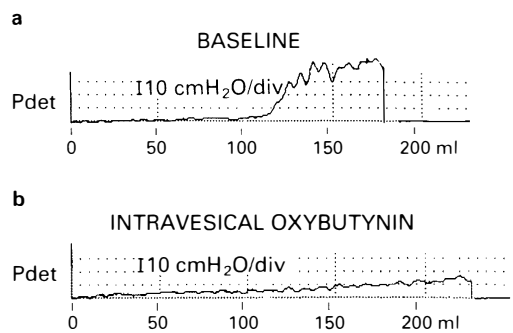

Figure 4 Cystometrograms (a) before and (b) after intravesical oxybutynin hydrochloride in a 15 year old boy with a spinal cord tumour.

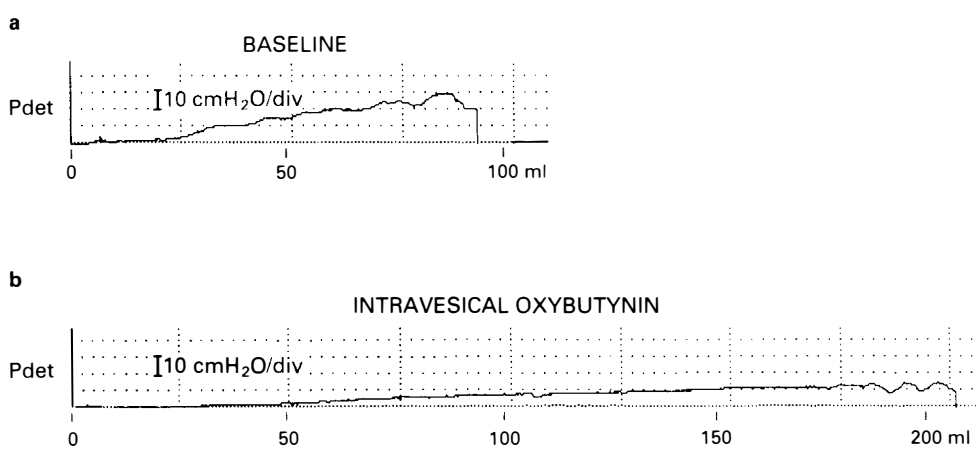

Figure 3 Cystometrograms (a) before and (b) after intravesical oxybutynin hydrochloride in a 7 year old boy with meningomyelocele.

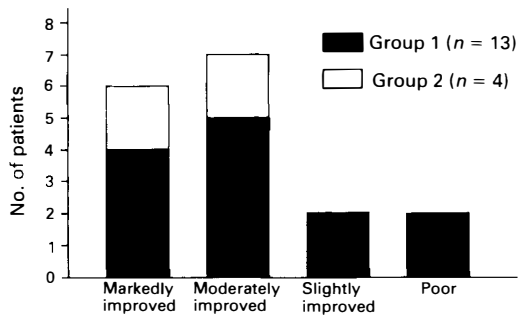

Figure 5 The overall clinical effect of intravesical oxybutynin hydrochloride in 17 patients.

hyperreflexia) two were 'markedly improved', and two were 'moderately improved'. Two patients whose effects were 'poor' discontinued therapy after 2 and 7 months of the therapy, respectively. The remaining 15 patients continue intravesical instillation of oxybutynin hydrochloride twice a day at present.

No significant adverse effect appeared with this therapy. One patient complained of slight lower abdominal pain after instillation. Within 2 weeks this side effect gradually receded as instillation continued. After altering the pH value of the solution of 5.85, no local or systemic side effects were observed.

Discussion

Oxybutynin hydrochloride is a tertiary amine having a weak cholinergic blocking effect. It is a potent local anaesthetic and effective spasmolytic agent in a variety of smooth muscle tissues,[7] and has also been shown to improve the symptoms of frequency and of urinary incontinence in patients with a neuropathic bladder associated with an increase in functional bladder capacity.[8]

In an effort to maximise the beneficial effects of oxybutynin hydrochloride and reduce the side effects, Brendler *et al*[2] reported that intravesical oxybutynin hydrochloride was effective in patients with detrusor hyperreflexia who were unresponsive to or had intolerable side effects with oral medications. Madesbacher and Jilg[3] also reported improved continence after intravesical oxybutynin during a 6 hour period in nine of 10 spinal cord injury patients. Greenfield and Fera[4] reported improved continence and urodynamic parameters after intravesical oxybutynin in eight of 10 children with neurogenic bladder dysfunction. Massad *et al*[5] reported significant improvement in symptomatology (incontinence and urgency) after intravesical oxybutynin in all of eight children with urodynamic evidence of uninhibited detrusor activity and/or poor bladder compliance.

These investigators have used 5–7.5 mg crushed oxybutynin hydrochloride tablet dissolved in 10–30 ml of water or saline. At first, we also used 5 mg crushed tablet dissolved in 10 ml sterile saline. However, the solubility of oxybutynin hydrochloride from a crushed tablet to water was poor, and excipients of the tablet were not soluble. Moreover, the acidity of the solution might cause an irritating reaction in the vesical mucosa. Therefore, we prepared an original solution of oxybutynin hydrochloride.

This pilot study demonstrates that the favourable clinical effect of oxybutynin hydrochloride is unchanged and no side effects have been observed. The improvement rate of 'moderately improved' and a better response is 69.2% in group 1 (low bladder compliance) and 100% in group 2 (detrusor hyperreflexia). The urodynamic data correlate with the clinical findings. In patients with low compliance neuropathic bladder, the improvement rate is lower than in those with detrusor hyperreflexia. It is considered that intravesical oxybutynin may not be effective when low compliance of the bladder results from fibrosis of the tissue wall.

In a study of the pharmacokinetics of intravesical oxybutynin in children Massad *et al*[5] found that intravesical oxybutynin was rapidly absorbed, resulting in plasma concentrations markedly higher than after oral administration. As to the lack of systemic side effects despite high plasma concentrations, they thought that it was a hepatic metabolite of the oral oxybutynin that was responsible for the anticholinergic side effects. However, the mechanism of the

action of intravesical oxybutynin in relaxing bladder muscle is also unclear.

From our experience, intravesical instillation of oxybutynin hydrochloride is suitable for patients who are already on CIC but are still incontinent due to detrusor hyperreflexia and/or low bladder compliance. We have continued this therapy for 1 year or more in 11 out of 17 patients, and favourable clinical effects have not changed for a long time. It is hoped that a solution of oxybutynin hydrochloride in a disposable package with a suitable attachment to a catheter will be commercially available in the near future.

Acknowledgement

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