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Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia

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Objective To compare trospium chloride (TCl), a quaternary ammonium derivative with atropine-like effects and predominantly antispasmodic activity, with oxybutynin (Oxy) in terms of efficacy and adverse effects.

Patients and methods In a randomized, double-blind, multicentre trial, 95 patients with spinal cord injuries and detrusor hyper-reflexia were studied. Treatment consisted of three doses per day over a 2 week period, with either Oxy (5 mg three times daily) or with TCl (20 mg twice daily) with an additional placebo at midday. The results were evaluated with regard to changes in objective (urodynamic) data and subjective symptoms as well as the incidence/severity of adverse effects.

Results With both drugs there was a significant increase in maximum bladder capacity, a significant decrease in maximum voiding detrusor pressure and a significant increase in compliance and residual urine; there were no statistically significant differences between the treatment groups. The percentage of patients who reported severe dryness of the mouth was considerably lower (4%) in those receiving TCl 2×20 mg/day than in those receiving Oxy (23%) 3×5 mg/day. Withdrawal from treatment was also less frequent in those receiving TCl (6%) than in those receiving Oxy (16%).

Conclusion Trospium chloride and oxybutynin, judged in terms of objective urodynamic parameters, are of substantially equal value as parasympathetic antagonists. However, assessment of tolerance in terms of adverse drug effects showed that TCl had certain advantages.

Keywords Bladder hyper-reflexia, therapy of detrusor hyper-reflexia, trospium chloride, oxybutynin hydrochloride

Introduction

Detrusor hyper-reflexia is a common problem in patients with suprasacral spinal cord lesions. It is usually combined with detrusor striated sphincter dyssynergia (DSD), which may cause increased detrusor hyper-reflexia and low compliance. Untreated detrusor hyper-reflexia and DSD may destroy the kidneys.

The combination of clean intermittent self-catheterization (CIC) and pharmacological relaxation of the detrusor is an established method of treating an unbalanced reflex bladder with reflex urinary incontinence. However, side-effects of the drugs used may limit their effects.

Trospium chloride (TCl)* is an antiparasympathetic quaternary ammonium derivative with atropine-like effects as well as effects on ganglia and smooth muscle [1]. Its antispasmodic activity is predominant. TCl has hydrophilic properties and does not pass the blood–brain barrier in significant amounts [1,2]. In the 1980s it was used in low daily dosages of up to 15 mg for the treatment of the unstable bladder, with promising results [3,4].

The efficacy and tolerance of high dose treatment with trospium chloride (20 mg twice daily *p.o.*) was demonstrated in a multicentre pilot study [5] and the results have been confirmed by Stöhrer *et al.* [6].

The tertiary amine oxybutynin (Oxy) is effective in the treatment of detrusor hyper-reflexia and is regarded as the therapeutic standard. The comparative pharmacological properties of both drugs are summarized in Table 1.

The aim of this study was to compare trospium chloride with oxybutynin hydrochloride to determine the efficacy and tolerance in a multicentre double-blind comparative clinical trial.

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*The oral application of trospium chloride 20 mg *b.d.* (Spasmolyt, Madaus, Germany), is licensed in Germany and under consideration for licensing in several European countries.

Table 1 Pharmacological characteristics of trospium chloride and oxybutynine

	Trospium chloride	*Oxybutynine*
Chemistry	Quaternary ammonium compound	Tertiary amine
Liquor penetration	No	Yes
Dosage	20 mg twice daily	2.5–5 mg two or three times daily
Galenics	Sugar-coated tablets	Tablets
Half-life time	5–15 h	2–3 h
Maximum serum level	4–6 h p.a.	1 h p.a.
Elimination	Kidney (unchanged)	Kidney
Metabolites	No	Yes

Patients and methods

Participants in the study were suffering from detrusor hyper-reflexia as defined by the International Continence Society [7]. Exclusion criteria were acute urinary tract infection, glaucoma, known allergy to atropine, Oxy or TCl, tachycardia, renal, hepatic and/or cardiovascular insufficiency, intake of other anticholinergic drugs, body weight over 90 kg or age below 18 years. Ninety-five spinal injury patients were enrolled in the trial. A total of 88 patients for whom urodynamic findings before and after treatment were available were included in the evaluation of efficacy: 52 were treated with TCl 20 mg twice daily and 43 with Oxy 5 mg three times daily. Both groups were comparable for sex distribution, age, body weight, maximum cystometric bladder capacity, maximum detrusor pressure, bladder compliance and residual urine (Table 2).

The study design comprised a week without drugs and then 2 weeks' treatment either with Oxy (5 mg three times daily) or TCl (20 mg twice daily). To maintain double-blind conditions the TCl group received a placebo at midday (double dummy technique) [8]. The evaluation before and after the treatment period comprised a urodynamic investigation with collection of data on maximum cystometric bladder capacity, maximum voiding detrusor pressure, compliance and residual urine, clinical symptomatology and adverse effects. Before the trial began patients were evaluated for any symptoms which might be regarded as adverse effects.

Results

The primary indices of efficacy were maximum bladder capacity and maximum voiding detrusor pressure during micturition. Maximum bladder capacity in the TCl group increased significantly ($P<0.001$) by 96.6 mL (group mean before treatment 215.2 mL; after treatment 311.9 mL). In the Oxy group there was an increase from 187.8 mL to 350.9 mL, amounting to an average of 163.0 mL ($P<0.001$). However, the difference between the two treatment groups ($P=0.057$) was not statistically significant at the 5% level (Fig. 1).

Maximum detrusor pressure during micturition was

Table 2 Demographic and urodynamic data

Variable	*Trospium chloride (n = 52)*	*Oxybutynine (n = 43)*
Sex (n)		
Male	28 (54%)	19 (44%)
Female	24 (46%)	24 (55%)
Age (years) (mean, range)	32.8 (16–56)	31.3 (18–54)
Body-weight (kg) (mean, range)	69.1 (47–91)	62.1 (42–87)
Maximum cystometric bladder capacity (mL) (mean, range)	215.5 (20–650)	185.1 (20–450)
Maximum voiding detrusor pressure (cmH_2O) (mean, range)	82.1 (25–150)	82.1 (31–175)
Compliance (mL/cmH_2O) (mean, range)	74.6 (2–480)	59.5 (3–375)
Residual urine (mL) (mean, range)	49.2 (0–520)	48.1 (0–360)

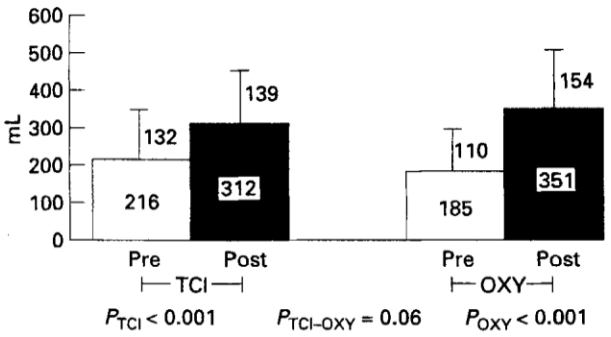

Fig. 1. Trospium chloride vs oxybutynine. Maximal cystometric bladder capacity (arithmetic mean and SD).

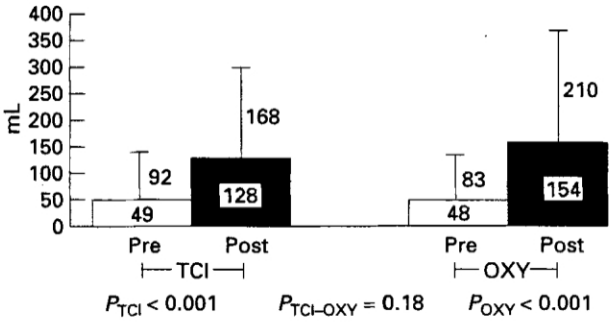

Fig. 3. Trospium chloride vs oxybutynine. Residual urine (arithmetic mean and SD).

comparable in both groups at the onset (TCl: x = 81.8 cm H_2O, Oxy:x = 79.9 cmH_2O). In the TCl group it fell by an average of 35.4 cmH_2O and in the Oxy group by 38 cm H_2O. This primary target variable thus showed statistically significant differences within each treatment group ($P < 0.001$). Comparison of the two groups showed a slight trend towards greater pressure reduction in the Oxy group (Fig. 2), but this was not statistically significant ($P = 0.63$).

Bladder compliance showed an increase from an average of 74.62 mL/cm to 92.75 mL/cm H_2O in the TCl group, i.e. 16.96 mL/cm H_2O ($P < 0.001$). A comparable improvement was seen in the Oxy group, where the mean initial reading of 59.49 mL/cm H_2O increased by 22.56 mL/cm H_2O to 78.24 mL/cm H_2O. As P was 0.43, there were no clinically relevant differences in terms of bladder compliance between the two treatment groups.

Residual urine increased significantly in both groups: in the TCl group from an average of 49.22–128.32 mL (increase of 76.45 mL), and in the Oxy group from an average of 48.14–154.36 mL (increase of 114.08 mL). This secondary target index seemed to show a trend towards a more pronounced increase in residual urine in the Oxy group, though this was not statistically significant ($P = 0.19$) (Fig. 3).

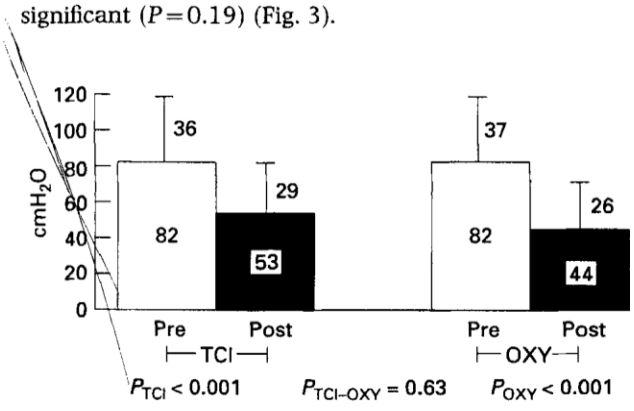

Fig. 2. Trospium chloride vs oxybutynine. Maximal voiding detrusor pressure (arithmetic mean and SD).

The frequency of hyper-reflexive waves tended to decrease in both groups as treatment progressed, but there were no statistically significant differences between the two drugs ($P = 0.16$).

As regards 'vital signs' — heart rate, systolic and diastolic blood pressure — there were no conspicuous changes in either group.

Analysis of tolerance was carried out on all 95 patients. Subjective assessment of tolerance was based on the following target indices:

Twenty 'wellbeing items' were the subject of direct questioning by the investigator before and at the end of the trial. Questions were asked about the following items in particular: dryness of mouth, blurred/double vision, palpitation, constipation, difficulty in swallowing. Severity was graded on the following scale: not present (0), slight (1), definite (2), severe (3). The overall rate of side-effects was almost comparable in both groups. Typical antiparasympathetic side-effects — dryness of the mouth and constipation — were encountered in both groups. In the TCl group, 26 patients (54%) and in the Oxy group 22 patients (56%) complained of dryness of the mouth. However, the severity grading showed marked differences. For instance, dryness of the mouth deteriorated to 'severe' in 4% in the TCl group, while the corresponding figure in the Oxy group was 23% (Fig. 4).

Withdrawal from the trial occurred more frequently in patients taking Oxy ($n = 7$, 16%) than in those taking TCl ($n = 3$, 6%). Furthermore, the Oxy patients withdrew earlier (after an average of 7.1 days) than the TCl patients (after an average of 14.3 days).

To provide objective assessment of the tolerance and side-effects of the two drugs the following factors were checked before and after treatment: serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum alkaline phosphatase, urea, creatinine, leucocytes, erythrocytes, platelets, haemoglobin and packed cell volume. In neither group was there any tendency to change.

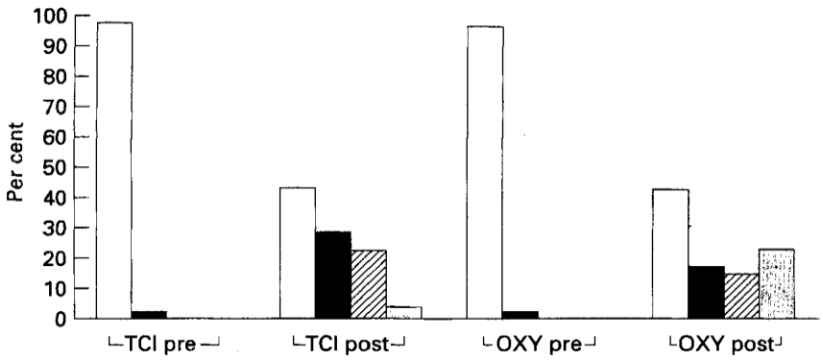

Fig. 4. Trospium chloride vs oxybutynine. Adverse effect — dryness of the mouth. □, None, ■, Mild. ▨, Marked. ▩, Severe.

Discussion

The increase in maximum bladder capacity together with the decrease in maximum detrusor pressure during micturition with both agents demonstrated statistically significant and clinically relevant changes and provided objective evidence of relaxation of the detrusor muscle. Furthermore, it can be assumed that TCl and Oxy are equal in their effects on detrusor hyperactivity. The inclusion criterion — only patients with detrusor hyperreflexia following spinal cord injury — excludes the possibility of placebo effects which might mask the actual drug effect. The improvement in bladder function was paralleled by the expected increase in residual urine. This is because although there is a decrease in detrusor contractility, dyssynergia of the striated muscle sphincter persists more or less unchanged.

In addition to efficacy, tolerance is the second crucial parameter in the overall assessment of any drug. The 20 'well-being items' related to typical anticholinergic symptoms and signs were the subject of targeted questioning in both groups before and at the end of the treatment period. The high frequency of typical anticholinergic side-effects associated with both drugs (e.g. dryness of the mouth: TCl 54%, Oxy 54%) occurred because the patients were specifically asked by the investigator whether they had dryness of the mouth or other symptoms [12]. Studies in which side-effects were recorded only when they were reported spontaneously by patients show a substantially lower rate [5,6,13,14]. The most frequent side-effect in this trial was dryness of the mouth; deterioration in the severity grading occurred more frequently during treatment with Oxy.

Analysis of premature withdrawals from the trial (total 11%) shows certain differences in favour of TCl. There were three withdrawals during treatment with TCl (6%) in contrast to seven during treatment with Oxy (16%). The lower incidence of withdrawals is related to the broad therapeutic range of TCl: Breuel reported that even single oral doses of 360 mg (factor 18 of a single therapeutic dose) were tolerated with only minor complaints [15]. Although several reasons were given by all 10 patients who terminated the trial prematurely, it seems likely that in most cases typical anticholinergic drug effects were the crucial factors and at least contributed to premature withdrawal.

One critical comment which must be made is that the less favourable results for tolerance of Oxy could be attributed to the fixed dose of 5 mg three times daily [10]. This dose conformed to the manufacturer's recommendations when the trial was being planned.

In patients who cannot tolerate oral administration of these drugs, alternative routes might be associated with better compliance. Intravesical instillation of Oxy has proved effective without causing the usual side-effects, especially in patients who could not tolerate the drug orally [16,17]: the intravesical application of anticholinergic drugs is logical, especially for patients already on CIC, as the drug could easily be instilled regularly at the end of catheterization without additional instrumentation. However, no solution of these drugs ready for instillation, preferably in a disposable package and with a suitable attachment to the catheter, is currently available.

The results of this trial demonstrate that TCl has certain advantages over Oxy in terms of the severity of adverse drug reactions, underlined by the fact that patients receiving TCl withdrew from treatment less frequently than those receiving Oxy.

Assessment of the efficacy and tolerance of trospium chloride in comparison with the internationally accepted standard drug — oxybutynin — demonstrates that the former is of equal value. The risk-benefit ratio of the beneficial effects versus the more severe anticholinergic side-effects supports the use of trospium chloride. Patients prone to dry mouth, e.g. the elderly, may therefore benefit from trospium chloride.

Conclusions

The clinical efficacy and tolerance of trospium chloride and oxybutynin for the treatment of detrusor hyperreflexia were compared in a controlled, double-blind, multicentre study. Of 95 patients with spinal cord injuries enrolled in the trial, 88 were suitable for statistical evaluation of efficacy. With both drugs there was a significant increase in maximum bladder capacity, a significant decrease in maximum voiding detrusor pressure and a significant increase in compliance and residual urine. Maximum bladder capacity showed statistically significant increases ($P<0.001$) during the 2-week period of treatment with both drugs. There were no statistically significant differences between the treatment groups with regard to these parameters. Where tolerance is concerned, the percentage of patients who reported severe dryness of the mouth was considerably lower in those receiving trospium chloride (4%) 2×20 mL/day than in those receiving oxybutynin (23%) 3×5 mg/day. Withdrawal from treatment was also less frequent in those receiving trospium chloride (6%) than in those receiving oxybutynin (16%).

This study shows that when objective urodynamic parameters are used to assess the clinical efficacy of trospium chloride and oxybutynin, both drugs are of substantially equal value as parasympathetic antagonists. However, assessment of their tolerance in terms of adverse drug effects shows that trospium chloride has certain advantages.

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