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A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence

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Objective To assess the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence in a randomized, double-blind placebo-controlled clinical trial.

Patients and methods In all, 366 patients (149 on propiverine, 145 oxybutynin and 72 placebo, ratio 2:2:1) with urgency and urge incontinence were recruited in 32 study centres. Propiverine (group 1, 15 mg three times daily), oxybutynin (group 2, 5 mg twice daily) or placebo (group 3) were administered for 4 weeks, using the double-dummy technique. The dosages were selected specifically to compare the tolerability profile of propiverine with the commonly used therapeutic dosage of oxybutynin. Tolerability was assessed by directly questioning the patients about adverse events at four visits (V-1 before and V0 after a 1-week 'washout' period, V1 after 1 week and V4 after 4 weeks of treatment) during a 5-week surveillance period, and by tolerability ratings of the physicians. Efficacy was assessed using urodynamics at V0 and V4, evaluating the cystometric bladder capacity at maximal and first desire to void, and postvoid residual urine, according to the criteria of the International Continence Society. Additionally, a voiding protocol, overall assessment of clinical symptomatology and efficacy ratings by the physicians were documented.

Results A remarkably high percentage of adverse events was reported in the washout period (VO: 13%, 16% and 18% in groups 1–3, respectively). At V4, the clinically most relevant symptom (dry mouth) occurred in 53% of patients in group 1, in 67% of group 2 and in 28% of group 3. Furthermore, dry mouth was less severe in group 1 than group 2. In contrast to groups 2 and 3, only patients in group 1 showed increasing tolerability during the treatment (from V1 to V4). These tolerability results were further supported by the overall tolerability assessment ('very good' or 'good' tolerability in 67% of group 1, in 59% of group 2 and in 83% of group 3). The urodynamic assessment of efficacy (comparing V0 and V4) showed a statistically significant increase in the mean (SD) maximal cystometric bladder capacity in group 1, being 222 (77) mL at V0 and 311 (125) mL at V4, an increase of 89 (108) mL, and in group 2, at 226 (75) mL and 322 (123) mL, an increase of 96 (106) mL, compared with group 3, at 211 (77) mL and 263 (93) mL, an increase of only 52 (92) mL. The cystometric bladder capacity at first desire to void also increased in group 1 (93 to 160 mL) and group 2 (89 to 160 mL), whereas in group 3 there were only minor changes (93 to 120 mL). Changes in the residual urine volume within and between the treatment groups were minimal and clinically irrelevant. The overall assessment of efficacy showed significant differences between the drugs when compared with placebo.

Conclusion Propiverine is a safe and effective drug in the treatment of urgency and urge incontinence; it is as effective as oxybutynin, but the incidence of dry mouth and its severity is less with propiverine than with oxybutynin. The availability of alternative pharmacotherapeutics such as propiverine should reduce the therapeutic failure rate and improves the success rate in the treatment of patients suffering from urgency and urge incontinence.

Keywords Propiverine, oxybutynin, urgency, urge incontinence, controlled trial

Introduction

The treatment of frequency, urgency and urge incontinence, symptoms related to detrusor hyperactivity and hypersensitivity, is based on continence training programmes ('bladder drill') and pharmacotherapy. Propiverine hydrochloride, a tertiary amine (benzylic acid), has special effects on the urinary bladder because it has two modes of action, i.e. spasmolytic activities mediated by calcium antagonism, which are further

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enhanced by its pharmacologically active metabolite propiverine-*N*-oxide, and spasmolytic activities mediated by anticholinergic properties, which are further enhanced by the metabolites des-propyl-propiverine-*N*-oxide and des-propyl-propiverine [1,2] (Table 1). Further analgesic effects might be advantageous for special indications.

In a series of uncontrolled and controlled double-blind clinical trials, the efficacy and the tolerability of propiverine has been widely documented for indications ranging from detrusor hyperreflexia [3], detrusor hypersensitivity and hyperactivity [4] to postoperative adjuvant spasmolytic therapy [5] and the enuretic syndrome [6]. In a dose-optimizing study, the most beneficial dose of propiverine in patients with urge incontinence was verified to be 15 mg twice or three times daily [7].

Oxybutynin hydrochloride is currently the accepted therapeutic standard in the treatment of symptoms related to detrusor instability. Despite its unquestioned efficacy, the high incidence of severe adverse events of oxybutynin limits its tolerability [8,9] and has provoked research for alternative routes of administration with improved tolerability, e.g. intravesical instillation [10], and the development of alternatives like propiverine.

Thus the main objectives of the present study were to confirm the better tolerability of propiverine over oxybutynin and to assess evidence for the equal efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence.

Patients and methods

In a double-blind, randomized, prospective multicentre clinical trial, the treatment results of propiverine, oxybutynin and placebo were compared in a three-armed parallel-group design. After a 1-week 'washout' period, treatments were administered for 4 weeks; 15 mg propiverine (sugar-coated tablets, registered as Detrunorm®/Mictonorm®, Apogepha Arzneimittel GmbH, Dresden, Germany) were administered three times daily (group 1), or 5 mg oxybutynin tablets (registered as Ditropan®/Dridase®) twice daily (group 2), or placebo three times daily (group 3). To ensure the double-blind condition, each of the patients received additional placebos (the double-dummy technique).

Inclusion criteria comprised a history of urgency or urge incontinence, a maximum cystometric bladder capacity of $\leqslant 300$ mL, age $\geqslant 18$ years and body weight $\geqslant 45$ kg. Exclusion criteria were detrusor hyperreflexia, postoperative (bladder) incontinence, infravesical obstruction, a postvoid residual urine (PVR) of $>15\%$ of the maximal cystometric bladder capacity, acute UTIs, angina pectoris, glaucoma, megacolon, clinically relevant cardiac, renal or hepatic dysfunctions, tachy/dysrhythmias, frequency or nocturia due to heart or renal insufficiency, or overt cerebral sclerosis. The following concomitant medications were considered as exclusion criteria: other spasmolytics or anticholinergics, β-sympathomimetics, calcium antagonists, dopamine agonists, prolactin inhibitors, prostaglandin synthesis inhibitors, striated muscle relaxants, or medication for Parkinsonism.

In all, 366 patients were included in the study and could be assessed for tolerability (tolerability group). The random allocation of patients considered a probability ratio of 2 : 2 : 1 among the treatment groups, resulting in 149 patients in group 1, 145 in group 2 and 72 in group 3; 310 patients were evaluable for efficacy (intention-to-treat population, ITT, Table 2). Age, sex and other demographic characteristics, with patients' histories, were equally distributed among the treatment groups (Table 2).

The investigators included patients with urgency or urge incontinence; a restraining stratification procedure was not demanded. In 196 patients sensory urge (sensory bladder disorder) and in 78 motor urge (detrusor instability) were diagnosed. In the remaining patients this differentiation could not be stated with accuracy.

The evaluation of the treatment effects comprised four visits during an observation period of 5 weeks (Table 3). A history and clinical investigation were documented at V1 and to evaluate safety and tolerability, adverse events were elicited by direct questioning at V0, V1 and V4. Additionally, laboratory variables (haematology, clinical chemistry, liver enzymes, analysis of urine, etc.) and an ECG were checked at V0 and V4. Urodynamics were used to assess the treatment effects at V0 and V4. According

Table 1 Pharmacological characteristics of propiverine and oxybutynin

Characteristic	*Propiverine*	*Oxybutynin*
Chemistry	Tertiary amine	Tertiary amine
Format/dosage	Sugar-coated tablets (2–3 × 15 mg/day)	Tablets (2–3 × 5 mg/day)
Half-life (h)	20	1–2.3
Maximum serum level after	2.3 h	1 h
Elimination	By kidney, bile, faeces, elimination of metabolites	By kidney
Mode of action	Calcium antagonistic, spasmolytic, anticholinergic, analgesic	Anticholinergic, spasmolytic, local anaesthetic

Table 2 Patient populations, and the demographic data and patients' history of the intention-to-treat (ITT) population

Characteristic	*Propiverine*	*Oxybutynin*	*Placebo*
Tolerability population (366)	149	145	72
Efficacy population (ITT, 310)	126	121	63
Demography, n *(%)*			
Male	9 (7.1)	8 (6.6)	4 (6.3)
Female	117 (92.9)	113 (93.4)	59 (93.7)
Mean (SD)			
Age (years)	49.6 (13.0)	50.3 (13.5)	47.6 (12.0)
Height (cm)	165.2 (7.1)	163.7 (7.0)	165.2 (6.3)
Weight (kg)	70.9 (13.3)	69.7 (11.8)	70.6 (12.3)
Median (range)			
History of urge incontinence (years)	2.4 (0.1–35.0)	2.4 (0.1–40.0)	2.0 (0.2–40.0)
Patients with previous treatment of urge incontinence, *n* (%)	32 (25.4)	32 (26.4)	21 (33.3)

Table 3 Study design and the protocol for the assessments

	Washout phase		*Therapy phase*	
Feature	*V–1 (−7 days)*	*V0 (day 0)*	*V1 (day 7)*	*V4 (day 28)*
History	+			
Clinical examination	+			+
Randomization		+		
Inclusion/exclusion criteria	+	+		
Blood pressure, pulse rate	+	+	+	+
Laboratory		+		+
Resting ECG		+		+
Cystometry		+		+
Incontinence questionnaire (Gaudenz)		+	+	+
Voiding diaries		+	+	+
Adverse events	+	+	+	+
Anticholinergic symptoms		+	+	+
Assessment of efficacy and tolerability				+

to ICS guidelines, urodynamic analysis of the storage phase consisted of cystometric bladder capacity at first and maximum desire to void, and the measurement of PVR [11]. The technical conditions (patient seated, filling rate 50–70 mL/min, filling medium at body temperature, transurethral catheter of 8–10 F, double-lumen or micro-tip catheter) were maintained constant for the studies before and after treatment. The individual treatment effects were derived from the measured differences between V0 (baseline) and V4 (final evaluation).

The Gaudenz incontinence questionnaire [12] was applied at V0, V1 and V4 to assess the degree of incontinence; 53% of the patients initially had severe urgency and urge incontinence (urge score of 13–26) and 47% had less severe symptoms (urge score <13). Voiding diaries were kept by the patients before and during the treatment period. An overall assessment by the physicians of clinical symptoms and efficacy was scheduled at V4 only.

Because some data were missing, and depending on the variables analysed, patient numbers differed at the assessments. In the statistical assessments, a multiple significance level of 5% was defined as confirming the urodynamic efficacy of propiverine and oxybutynin vs placebo (test for superiority) and to compare both drugs for anticholinergic adverse events (test for equivalence). The results of studies published to date suggested a power of 80% and a withdrawal rate of 10%, giving 150 patients for each active group and 75 patients in the placebo group. For other variables, statistical tests were descriptive and differences considered significant at 5%.

Results

Even during the washout period, there was a remarkably high incidence of adverse events, at 16%, 18% and 13% of groups 1–3, respectively; the final evaluation showed

adverse events in 64%, 72% and 42%, respectively. There was no significant difference between groups 1 and 2, but both were significantly different from group 3. The withdrawal rate was 13%, 11% and 9.7%, respectively, with no significant differences.

The incidence of dry mouth, as documented at V4, is shown in Fig. 1; the difference in total incidence between groups 1 and 2 was significant ($P=0.022$). The severity of dry mouth is also shown in Fig. 1; in particular, severe dry mouth was statistically less frequent in group 1 than in group 2 ($P=0.0093$). The time course of dry mouth also differed; the severity of dry mouth increased in group 2 (18% at V1 and 25% at V4) but not in group 1 (13% at V1 and 12% at V4).

The respective incidence rates of other adverse events in groups 1–3 at V4 were visual disturbance (27%, 18%, 14%), nausea (4.1%, 9.9%, 8.3%) and vomiting (2.1%, 1.4%, 2.8%). In contrast to group 2 and 3, most of the anticholinergic adverse events decreased during treatment (from V1 to V4) only in group 1. Constipation and fatigue increased slightly in all three groups. For visual disturbance, there was a higher, insignificant incidence in group 1 than in group 2, but a decrease over the treatment period was documented only in group 1. The overall assessment of tolerability by the physicians revealed good or excellent attributes in 67% of group 1, compared with 59% and 83% for groups 2 and 3.

Pathological deviations in laboratory variables were recorded in 9.4%, 13% and 2.8% of group 1–3, respectively. The most frequent change was an increase in transaminases, in 2% and 4% of groups 1 and 2, respectively. ECG changes occurred in 0.7%, 2.1% and 2.8% of the three groups, respectively.

In the ITT population, the mean maximum cystometric bladder capacity increased significantly in groups 1 and 2, compared with group 3 (Table 4; $P=0.0105$ and 0.0023, respectively). The capacity at first desire to void also increased significantly in group 1 ($P=0.0209$) and 2 ($P=0.0318$) compared with group 3 (Table 4). Both drugs were equally effective on the two estimates of cystometric bladder capacity. Most patients had sensory urge incontinence; an additional evaluation of urodynamic efficacy in the subpopulations with motor and sensory urge was considered, but these subpopulations could not be contrasted, because there were too few patients in each to permit a valid statistical evaluation. Changes in the PVR within and between the treatment groups were only minimal and clinically irrelevant (Table 4); no patients had urinary retention in any of the groups.

The percentage of patients scoring 13–26 (severe urge) on the Gaudenz questionnaire decreased in all treatment groups (Table 4) but the differences were not significant. The frequency of micturition decreased more in group 1 than in groups 2 and 3, and episodes of urgency also decreased more in groups 1 and 2 than in group 3, but these differences were not significant. Clinical symptoms assessed by physicians differed between groups 1 and 2 and group 3 (Table 4), with similar differences for patients having no change in symptoms. The physicians overall assessment was significantly different for group 1 ($P=0.0013$) and 2 ($P<0.001$) compared with group 3, but there was no significant difference between the active drug groups.

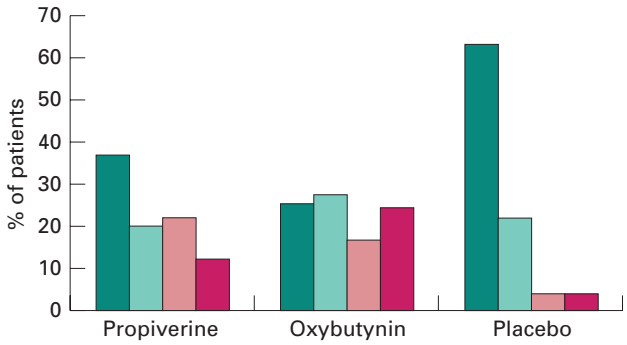

Fig. 1. The severity of dry mouth at V4 in the tolerability population (green, not present; light green, mild; light red, moderate; red, severe). Because some data were missing, total percentages may differ from 100.

Discussion

Dry mouth is the most frequent adverse event and therefore one of the main reasons for patients not complying in clinical practice, thus limiting the therapeutic usefulness of bladder spasmolytics, especially anticholinergics. Under conditions of clinical trials, the rate of adverse events depends on the method of evaluation; studies referring to adverse events reported spontaneously by patients generally document much lower rates [13], while studies using direct questioning about adverse events have higher incidence rates of adverse events, including anticholinergic symptoms [14]. Furthermore, different rates of adverse events in different studies also arise through differences in study population characteristics. According to Macaulay *et al.* [15], patients with sensory urge are more anxious than patients with other forms of incontinence. Frewen [16] also has stressed the psychosomatic nature of urgency and urge incontinence in women, further explaining the relatively high rate of adverse events with both drugs, as well as placebo, during the run-in period and therapy phase in the present study.

Thüroff *et al.* [17] reported an overall incidence of adverse events of 63% for oxybutynin and of 33% for placebo. Considering all adverse events, in the present

Table 4 The assessment of efficacy in the intention-to-treat (ITT) population

	Propiverine		*Oxybutynin*		*Placebo*	
Variable	*V0*	*V4*	*V0*	*V4*	*V0*	*V4*
Mean (SD) cystometric bladder capacity (mL)						
Maximum	222 (77)	311 (125)	226 (75)	322 (123)	211 (77)	263 (93)
Difference		89 (108)		96 (106)		52 (92)
At first desire to void	93	160	89	160	93	120
Mean PVR (mL)	7.0	9.9	7.4	8.2	7.2	7.4
% with severe incontinence (Gaudenz score 13–26)	53	14	56	21	56	22
Voiding diary						
Frequency	10.4	8.5	12.6	10.2	11.5	10.5
Episodes of urgency	9.5	6.4	12.4	9.4	11.3	10.1
Clinical symptoms (%)						
% improved		83		79		68
No change		15		19		32
Overall assessment (%)						
Excellent, good or satisfactory		83		80		60
Unsatisfactory		18		17		40

study the rate of adverse events was lower in group 1 (65%) than in group 2 (73%), despite the comparatively higher dosage of propiverine than oxybutynin. An uncontrolled, dose-optimizing study of propiverine reported comparable efficacy in patients with urge incontinence and urgency for doses of 30 and 45 mg/day [7]. The dosage of propiverine in the present study was selected intentionally to evaluate adverse events in patients known to be susceptible to such events. The 5 mg × 2 dosage for oxybutynin was preferred, because it is usually prescribed in clinical practice and studies show that dosages of 10 and 15 mg/day oxybutynin yielded comparable efficacy, despite 5 mg × 3 resulting in a higher rate of withdrawal [18–20].

Considering the time course of anticholinergic symptoms during the study, the incidence decreased significantly from V1 to V4 in group 1, but was constant or slightly increased in groups 2 and 3. This phenomenon has been documented in long-term tolerability studies of propiverine [4] and requires further investigation as it might have clinical relevance. The severity of dry mouth during the course of the study showed an advantageous trend for propiverine.

The withdrawal rate in all three groups probably reflects patient characteristics; in daily clinical practice, individual dose adjustments are common, reducing adverse events and withdrawal rates while sustaining clinical effectiveness. Furthermore, intolerability to one drug does not necessarily imply intolerability to another. Thus, the availability of a spectrum of pharmacotherapeutic options reduces therapeutic failures and improves the success rate in the treatment of patients. The apparent discrepancy between the lower rate of adverse events and a higher rate of withdrawal with propiverine than with oxybutynin arises because there are many reasons for withdrawal, not just adverse events, i.e. noncompliance of the patients, intercurrent diseases or lost to follow-up. A causal relationship of the ECG changes with the study medication was not confirmed; a recent study detected no increase in cardiac dysrhythmias and tachycardia in an elderly cardiovascular risk population treated with propiverine or placebo [21].

For efficacy, drugs improving urge incontinence should increase bladder capacity, thus reducing voiding frequency. Both the present drugs substantially increased the cystometric bladder capacity at first and at maximal desire to void, in contrast to placebo, confirming the clinical efficacy of propiverine. Comparable improvements in urodynamic values with propiverine and oxybutynin showed that both drugs were equally effective.

From clinical experience it is well known that patients with sensory urge are more difficult to treat than those with motor urge [22,23]. Sensory urge is a very complex problem, being mostly idiopathic, and psychological effects cannot be disregarded. Moreover, just keeping a voiding diary essentially constitutes 'bladder training' [16]. This may be reflected in the remarkable placebo effects in this study. Nevertheless, the significant increase in bladder capacity at first and maximal desire to void under active treatment underlines the beneficial effect of pharmacological relaxation of the detrusor in this group of patients. The present results are comparable with those reported by Thüroff *et al.* [17] for oxybutynin in patients with detrusor hyperactivity. Similarly, the present overall evaluation of efficacy by the physicians concurs with that of other published studies [14,18,24].

Thus propiverine has a favourable safety and efficacy profile, confirming the good clinical experiences with this drug over the past two decades [5].

In conclusion, propiverine is as effective as oxybutynin in patients with urgency and urge incontinence; cystometric bladder capacity increased equally and significantly with propiverine and oxybutynin. The improvement in this major urodynamic variable was also reflected in the efficacy as assessed by the physicians. Although propiverine is equivalent to oxybutynin for treating urgency and urge incontinence, with a comparable risk-benefit relationship, the incidence of dry mouth was less with propiverine than with oxybutynin.

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