World J Urol (2003) 20: 392–399
DOI 10.1007/s00345-003-0321-8

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Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability

Received: 8 January 2002 / Accepted: 15 December 2002 / Published online: 28 March 2003

Abstract Our objectives were to ascertain the tolerability and efficacy of trospium chloride in doses of 20 mg twice daily for long-term therapy (52 weeks) in patients with urge syndrome. The trial comprised a total of 358 patients with urge syndrome or urge incontinence. After randomisation in the ratio of 3:1, participants were treated continuously for 52 weeks with either trospium chloride (20 mg twice daily) or oxybutynin (5 mg twice daily). At intervals of 4–8 weeks, patients were physically examined with measurements of blood pressure and pulse rate, were questioned about any adverse events, checked for compliance and underwent relevant laboratory tests. As an additional safety measure, an ECG was made at 26 and 52 weeks. Urodynamic measurements were performed at the beginning, and at 26 and 52 weeks to determine the maximal cystometric bladder capacity. Among others things, the frequencies of micturition, incontinence and number of urgency events were recorded in patient diary protocols in weeks 0, 2, 26 and 52. The evaluation of vital parameters, laboratory results and ECGs did not show any relevant changes attributable to the action of the anticholinergics. Analysis of the micturition diary clearly indicated a reduction of the micturition frequency, incontinence frequency, and a reduction of the number of urgencies in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 ml after 26 weeks and 115 ml after 52 weeks ($P = 0.001$). Further comparison with oxybutynin did not reveal any statistically significant differences in urodynamic variables between the drugs. Adverse events occurred in 64.8% of the patients treated with trospium chloride and 76.7% of those treated with oxybutynin. The main symptom encountered in both treatment group was dryness of the mouth. For patients on trospium chloride, the estimated risk of an unexpected adverse event was 0.027 per patient per week for all adverse events and 0.009 for dryness of the mouth, resulting in a considerably lower risk during treatment given with trospium chloride than with oxybutynin (0.045 and 0.021, respectively). An overall assessment for each of the drugs reveals a comparable efficacy level and a better benefit-risk ratio for trospium chloride than for oxybutynin due to better tolerability.

Keywords Anticholinergics · Trospium chloride (TCl) · Oxybutynin (OXY) · Detrusor instability · Urodynamic measurement

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Urinary incontinence is among the most pressing health problems of the present day [1, 24]. The prevalence of the condition is estimated at 45% among adults [8, 16, 17, 23], depending on the patient's age, co-morbidity and the techniques used for questioning and examination. With increasing age, urge incontinence—caused by ultrastructural changes in the detrusor muscle of the bladder—comes to predominate [9, 10, 20]. Urge incontinence is evoked by urodynamically measurable, uninhibited contractions of the detrusor muscle of the bladder during

the filling phase, the sphincter apparatus being intact. Clinically, the principal symptoms consist of undue frequency of micturition, nocturia, and overwhelming micturition urgency, sometimes combined with urge incontinence. This results in a serious impairment of the patient's quality of life in almost all spheres of activity [12, 25, 26].

Anticholinergic drugs such as trospium chloride (azonia-3-α-benziloyloxy-8-spiro-1′-pyrrolidinium chloride, $C_{25}H_{30}NO_3Cl$, TCl), a quaternary ammonium derivative with a predominantly muscarinic action, constitute the basic therapy for urinary urge incontinence. In several randomised trials, TCl has proved effective in improving urodynamic variables such as lowering the maximum detrusor pressure and the enlargement of maximum bladder capacity, these being followed by an improvement in the symptoms[2, 6, 13, 15, 19, 22].

Among anticholinergic drugs, TCl is outstanding in two respects. First, in contrast to tolterodine or tertiary amines such as oxybutynin, any passage across the blood-brain barrier can be almost entirely excluded because the TCl molecule is less lipophilic [21]. Central nervous side effects are therefore not to be expected. Second, TCl is excreted mainly unchanged and no pharmacological interactions at the level of the hepatic cytochrome-P-450-system [3] are present. On the contrary, other anticholinergics [4, 5, 7, 14] have been recognised as demonstrating intensive transformation, either to active metabolites or as having drug interaction potential depending on putative metabolic competition.

Methods and materials

Objectives

The study was designed to compare the tolerability and efficacy of TCl and OXY in patients with an unstable bladder over a long-term. It is a prospective randomised, placebo-controlled, multicentre clinical trial over 52 weeks and takes into consideration the relevant ICH/CPMP guidelines recommended for drugs intended for long-term treatment. As a high drop-out rate could be expected in patients suffering from non-life threatening urinary incontinence during a 52 week treatment on placebo alone, an active control group with OXY was included. Patients were randomly divided into two groups in the proportion of 3:1, which further enabled a person to person comparison between the drugs. The larger group was treated with TCl 20 mg twice daily (Spasmolyt-coated tablets, Madaus, Köln) while the second group was treated with OXY in doses of 5 mg twice daily (Dridase, Sanofi-Synthelabo, Berlin). Treatment duration for both groups averaged 54 weeks (range for TCl: 0 days–59 weeks, range for OXY: 1 day–63 weeks).

Patients

Between May 1996 and May 1999, a total of 358 patients were recruited for the trial in Austria, Bulgaria, Czechoslovakia, Germany, Russia and Spain. The corresponding number of centres involved was 11, 1, 14, 20, 3 and 3. The principal diagnoses and inclusion criteria were: (1) urge syndrome (undue frequency of micturition, nocturia, overwhelming urge, wetting), (2) urge incontinence, (3) urge incontinence as one component of mixed incontinence, or (4) urge incontinence due to a neurological condition (detrusor hyperreflexia). Diagnoses were confirmed by pre-trial urodynamic measurements. A follow-up of urodynamic measurements was made at weeks 26 and 52of treatment. Additionally, micturition diaries were reported by participants in four periods of treatment: at 0, 2, 26 and 52 weeks of treatment.

In accordance with the trial plan, all patients were at least 18 years old (Austria: 19 years) and had signed a written consent to take part in the study. All study data were collected with due regard to data protection guidelines. The exclusion criteria are summarised in Table 1.

The trial plan envisaged a total of 11 follow-up appointments. Before starting the actual trial phase, the patient's history was taken, the patient underwent physical examination and was informed of the nature and scope of the study. Inclusion and exclusion criteria were then checked.

The criteria to assess safety and tolerability were adverse events, laboratory data (haematology, clinical chemistry, urinalysis), physical examination, resting ECG and cardiovascular parameters (systolic and diastolic blood pressure, heart rate). Furthermore, a questionnaire on the patient's health, consisting of 20 items, was used. Tolerability was also globally assessed by the investigator and the patient.

Table 1 Exclusion criteria

Absolute tachycardia
Closed-angle glaucoma
Myasthenia gravis
Severe arteriosclerosis of the cerebral vessels
Stress incontinence
Undue frequency of micturition due to heart failure, renal failure or diuretic therapy
Bladder outlet obstruction
Acute urinary tract infection at the beginning of the trial
Hiatus hernia in combination with reflux oesophagitis
Stenosesin the gastrointestinal tract
Megacolon
Colonic ulceration
Allergy or intolerance towards atropine, OXY, TCI or other constituents of the trial medication
Concurrent medication with anticholinergics, tricyclic or tetracyclic antidepressants, α-blockers or β-sympathomimetics within the last 7 days before starting the trial
Urological or gynaecological operations within the last 3 months before starting the trial
Serious illnesses or conditions which would preclude participation in any clinical trial (malignant neoplasms, alcoholism, drug misuse)
Pregnancy or lactation
Participation in any other study

Safety variables

Vital parameters—systolic and diastolic blood pressure together with pulse rate—were measured at the beginning, and at 2, 6, 12, 20, 26, 32, 40 and 52 weeks. At each of these follow-up appointments during treatment, and again after 56 weeks, any side effects were recorded and blood was taken. These blood samples were used to monitor potentially adverse laboratory parameters (blood count, urea, creatinine, LDH, GOT, GPT, uric acid). At 26 and 52 weeks, the patients were systematically questioned with the aid of a checklist. This comprised a 20 point general health assessment together with any side effects of anticholinergic therapy such as nausea, vomiting, constipation, heart palpitations, hot flushes, light sensitivity, double vision and dryness of the mouth. Unweighted addition of the severity grade for each point yielded a summation score (not present = 0, mild = 1, moderate = 2, severe = 3 points).

The recording of a resting ECG at 26 and 52 weeks, together with a check for any additional abnormalities at 56 weeks, completed the investigation of objective safety variables. Finally, the doctor and patient were requested to record their subjective estimation of tolerability in terms of the categories: very good, good, satisfactory or poor.

In accordance with the randomisation plan, the trial medication was issued only in small portions, and "pill-counting" of the medication withdrawn at each follow-up date provided some check on the compliance of the patients.

Efficacy variables

The patient's bladder function was evaluated by urodynamic testing at 26 and 52 weeks. Measurement was performed in accordance with the ICS standards [1] with the patient in a sitting position and the use of an 8-Ch measuring catheter, a lubricant without local anaesthetic and warm filling medium (26–37°C) instilled at a moderately rapid filling rate of 50 ml/min.

Maximum cystometric bladder capacity was the most important urodynamic parameter for the appraisal of efficacy. In addition, records were made of the volume at the first uninhibited detrusor contraction, the volume at first sensation to void, the maximum detrusor pressure at the first unstable contraction together with the volume at the maximum unstable detrusor contraction, residual urine and maximum urinary flow rate.

Using a standardised micturition diary, the patients recorded their frequency of micturition together with the number of episodes of incontinence and their perceptions of urgency over 2 days at the beginning of the study, and again after 2, 26 and 52 weeks.

Patients and the doctors in charge of treatment documented the efficacy of the trial medication under the subjective categories: cured, definite improvement, slight improvement, no improvement or deterioration. A monitoring procedure by Madaus AG, running continuously during the study, had the purpose of ensuring correct data transmission and the completeness of data recording. All printouts of urodynamic measurements were checked for plausibility by the medical division of Madaus.

Statistics

All data were collected for the intention-to-treat-group (ITT) and for the per-protocol group (PP). The safety variables were evaluated descriptively. Following ÓNeill [18], the adverse event rates were divided into three categories:

1. All recorded adverse events.
2. All adverse events possibly or probably associated with the trial medication.
3. All gastrointestinal effects of this classification.

Calculations of a "time-to-event" analysis was made for these three categories and for the adverse event "dryness of the mouth" using the log-rank test. Kaplan-Meier curves were plotted for the censored data.

For the statistical analysis of the efficacy variables, means, medians and standard deviations were determined both for the ITT and PP groups. A significant difference between the two treatment groups was accepted at an α-level of 5% using the t-test or the Mann-Whitney-Wilcoxon test. The Hodges-Lehmann estimator was used to evaluate the median differences between the two treatment groups, given a confidence interval of 95%. The qualitative data were analysed with Fisher's test using a significance level of 5%.

The data from all randomised patients were used for the evaluation of safety variables. The ITT analysis comprised all patients who had not shown any obvious deviations from protocol. For the evaluation of urodynamic measurements, patients were accepted who had at least one measurement during trial medication in addition to an acceptable basic measurement. Micturition protocols were used for ITT analysis, provided that entries had been made before and after ingestion of the trial medication, and that a plausibility check had been carried out. They were regarded as valid if at least four micturitions or incontinence episodes per day had been registered.

Excluded from the PP analysis were those patients who displayed deviations from the protocol, in whom the urodynamic measurement was not in accordance with the trial plan or was not assessable, and in whom there was evidence of more than 20% non-compliance in taking the trial medication (< 80% or > 120%). "Pill counting" showed discrepancies in ten out of 358 patients, these amounting to more than a 20% deviation from the intended trial medication during at least one follow-up appointment.

Results

A total of 358 patients were enrolled for the trial. According to the randomisation plan, 267 were treated with TCl and 90 with OXY (one male patient refused to take TCl). Both treatment groups were comparable with regards to their demographic data and clinical history (Table 2).

Table 2 Demographic data and previous history (ITT)

	TCI ($n = 267$)	OXY ($n = 90$)	Total ($n = 357$)
Female	228 (85%)	78 (87%)	306 (86%)
Male	39 (15%)	12 (13%)	51 (14%)
Smokers	38 (14%)	10 (11%)	48 (13%)
Patients with previous illnesses	184 (69%)	66 (73%)	250 (70%)
Patients with previous medication	101 (38%)	46 (51%)	147 (41%)
Mean age (range), years	54.2 (19–89)	52.2 (19–85)	53.7 (19–89)
Mean body weight (range), kg	72.3 (50–120)	70.4 (50–90)	71.8 (50–120)
Mean height (range), cm	164.8 (144–185)	165.5 (145–183)	165.0 (144–185)

Checklist on general health

The distribution and variability of markers of health characteristics were similar in both trial groups. This indicated, as a first impression, that there were no striking effects of treatment typical for any kind of severe pharmacological intervention. There were no substantial changes in the overall score in either the TCl or OXY groups. More than 95% of the changes scored less than three points in both groups.

Laboratory findings

Apart from minor fluctuations, unrelated to the time course of the trial, the blood picture, nitrogenous metabolites, uric acid, sodium and potassium, GPT and LDH showed no evidence of any changes attributable to the trial medications for either treatment.

Vital signs

Systolic and diastolic blood pressure were uninfluenced by the treatments. A slight increase in the mean pulse rate was observed in patients receiving medication with TCl: when compared with the initial level this amounted to 3 beats/min against 0.1 beats/min in the OXY group. A pulse rate of more than 100 beats/min absolute was noted in 27 patients treated with TCl (10.1%) as compared with six in the OXY group (6.7%). In most cases, this rise was less than 15 beats/min as compared with the initial reading and was observed at only one follow-up appointment. Greater increases in pulse rate were noted in six patients in the TCl group and three patients in the OXY group.

Electrocardiography

Among the patients treated with TCl, abnormal findings were noted in four cases (0,1%) at week 26 and in a further five cases (0,2%) at week 52, the previously recorded ECGs having been normal. In each of an additional seven patients, existing abnormalities had reverted to normal at 26 and 52 weeks. In the OXY group, there were two patients who had abnormal ECGs at 26 weeks. In a further three and four cases respectively, a previously abnormal ECG in the OXY group had reverted to normal at 26weeks and 52 weeks. These abnormalities comprised ventricular or supraventricular extrasystoles, atrioventricular block or ST segment depression as signs of coronary ischaemia. None of these changes was regarded by the investigators as having any relation to the trial medication.

Subjective appraisal of tolerability

In the TCl group at 26 and 52 weeks of treatment, 49% and 63% respectively of the trial physicians assessed tolerability as very good. In the OXY group, the assessment by the trial physicians at the same points showed very good tolerability in 36 and 42%, respectively. Appraisal by the patients gave almost identical results.

Adverse events

Ninety-one patients (25.4%) terminated the study prematurely. These comprised 67 patients from the TCl group (25.0%) and 24 from the OXY group (26.7%). Some of the reasons for premature withdrawal from the study are set out in Table 3.

Other reasons not illustrated in the table such as poor efficacy and compliance, violation of inclusion or exclusion criteria or unknown or not reported reasons were seen in a further 35 and seven participants treated with TCl and OXY, respectively.

In addition, trial medication was prematurely terminated because of serious adverse events (SAEs) in seven cases (TCl: four, OXY: three). SAEs in the TCl group were: recurrent brain infarct with fatal consequences, fatal acute pulmonary embolism associated with metastasising adenocarcinoma of the bronchus, disseminated encephalitis of recent origin and allergic eruption with angio-oedema. The first three events were classified by the trial physician as having no relationship to the trial medication, the allergic reaction was judged as possibly associated with the trial medication.

In the OXY group, the SAEs were: acute urinary retention due to benign hyperplasia of the prostate subsequently dealt with by transurethral resection (relationship probable), tachyarrhythmia which occurred before the first dose of the trial medication and generalised rash of uncertain origin and destabilisation of known diabetes in the 13th and 21st weeks of therapy. In neither of these latter two cases did the trial physician consider that there was any connection with the trial medication.

In all, 719 adverse events were observed in 242 out of 357 patients (67.8%). These comprised 517 events in the TCl group (173/267 patients, 64.8%) and 202 events in the OXY group (69/90 patients, 76.7%). ''Gastro-intestinal system disorders'' were the most common disorders

Table 3 Number of patients and their prevailing reasons to terminate the study

	TCI ($n=267$)	OXY ($n=90$)
Adverse events (classified as having at least a possible association)	10 (3.7%)	6 (6.7%)
Adverse events (classified as having no association)	2 (0.7%)	–
Other serious adverse events	4 (1.5%)	3 (3.3%)
Successful therapy	3 (1.1%)	–
Poor efficacy	8 (3.0%)	2 (2.2%)
Poor compliance	15 (5.6%)	6 (6.7%)

Table 4 Gastrointestinal adverse events (connection possible/probable)

Gastrointestinal adverse events (may be noted under more than one heading)	TCI ($n=267$)	OXY ($n=90$)
Abdominal pain	5 (2%)	–
Constipation	18 (7%)	4 (4%)
Diarrhoea	2 (1%)	2 (2%)
Dyspepsia	13 (5%)	3 (3%)
Dysphagia	9 (3%)	3 (3%)
Dryness of the mouth	87 (33%)	45 (50%)
Nausea	6 (2%)	2 (2%)
Total number of patients	103 (39%)	46 (51%)

Table 5 Frequency of dominating non-gastrointestinal adverse events

Adverse events—non-gastrointestinal (may be noted under more than one heading)	TCI ($n=267$)	OXY ($n=90$)	Totals ($n=357$)
Urinary tract infection	33 (12%)	10 (11%)	43 (12%)
Headache	11 (4%)	8 (9%)	19 (5%)
Visual disturbances	9 (3%)	5 (6%)	14 (4%)
Virus infection	9 (3%)	4 (4%)	13 (4%)
Sleeplessness	10 (4%)	2 (2%)	12 (3%)

for both drugs. Dry mouth (noted by 33% of patients treated with TCl and 50% of those treated with OXY) was the most frequent adverse event contributing to this class. The prominent gastrointestinal adverse events are depicted in Table 4.

The non-gastrointestinal adverse event most frequently mentioned was ''urinary tract infection'' in 43 patients. In 32 cases, this was regarded as having no connection with the trial medication; both treatment groups were affected with equal frequency (12% and 11%, respectively). Other non-gastrointestinal adverse events typically encountered in patients treated with antimuscarinic drugs are mentioned in Table 5.

For the adverse events taken as a whole, the differences between TCl and OXY were significant as regards ''time to event'' ($P<0.01$). There was also a significant difference between the two treatment groups in favour of TCl for the overall total of adverse events having probable or possible connections with the trial medication ($P=0.02$), for all gastrointestinal adverse events with this classification ($P=0.02$) and for dryness of the mouth ($P<0.01$).

When the number of adverse events is viewed in relation to the total number of patients treated and the duration of treatment, the risk of occurrence of an adverse event per patient per week is 0.027 for TCl and 0.045 for OXY, indicating that there is a relative risk of 0.6 in favour of TCl (Table 6).

If adverse events appraised as possibly or probably connected with the trial medication are included in this calculation, the outcome is a risk of 0.016 (TCl) and 0.027 (OXY); for dryness of the mouth the risk is 0.09 for TCl and 0.021 for OXY. This shows that the risk of experiencing dryness of the mouth during OXY medication is higher by a factor of 2.3 than during TCl medication.

Table 6 Incidence and relative risk of adverse events. Incidence indicates the number of patients with adverse events related to the total number of patients treated and the duration of exposure. Incidence may be interpreted as the risk of one patient to experience an adverse event within 1 week

Classification	% of patients		Incidence		Relative risk TCI/OXY
	TCI	OXY	TCI	OXY	
All adverse events	68	77	0.027	0.045	0.60
All adverse events possibly or probably connected with treatment	48	59	0.016	0.027	0.59
All gastrointestinal adverse events possibly or probably connected with treatment	39	51	0.012	0.022	0.55
Dryness of mouth	33	50	0.009	0.021	0.43

Urodynamic measurements

There were 276 patients available for urodynamic evaluation in the ITT section (TCl: 209; OXY: 67). The PP analysis of the variables ''maximum cystometric bladder capacity'' and ''first onset of urgency'' comprised 190 patients (TCl:145; OXY: 45). Comparison of ITT and PP populations did not show substantial differences.

Maximum cystometric bladder capacity

In both treatment groups, the initial bladder capacity was almost identical at 205 ml. In the ITT group, the patients treated with TCl showed increases in maximum cystometric bladder capacity amounting to 92 ml at 26 weeks and 115 ml (Hodges-Lehmann estimator) at 52 weeks. Similarly, the OXY group showed increases of 117 ml and 119.4 ml respectively, signalling that changes were significant in both treatment arms ($P=0.001$).

Calculation of the median differences in the increase in maximum cystometric bladder capacity by the Hodges-Lehmann estimator method revealed a difference between the two treatment arms of –22.0 ml (90% confidence interval −48.0; +1.0 ml) at 26 weeks and –6.0 (90% confidence interval −33.0; +23.0 ml) at 52 weeks. The statistical analysis shows that the two drugs are of comparable efficacy.

Further results on urodynamic variables are listed in Table 7. The increase in volume at the first unstable contraction appeared to be much more pronounced after TCl (mean values: 46.0 ml) than after oxybutynin (36.7 ml). With a median difference of 11 ml in the Hodges-Lehmann test, the differences between the two

Table 7 Urodynamic parameters

Medication	Difference	Max. cystometric bladder capacity (ml)	Volume at first unstable contraction (ml)	Volume at first sensation to void (ml)
TCI	Week 26-start	92.0 $n=203$	63.5 $n=63$	73.6 $n=201$
	Week 52-start	115.0 $n=189$	46.1 $n=51$	78.6 $n=186$
OXY	Week 26-start	117.0 $n=65$	61.2 n = 20	76.93 $n=64$
	Week 52-start	119.4 $n=62$	36.7 $n=18$	70.2 $n=62$

treatment groups are, however, not significant. Analysis of the volume at the first sensation to void ,as well as of other urodynamic parameters measured in the same way, showed no relevant differences between the two treatment groups.

Documentation of micturition in patient diaries

There were on average 1.5 episodes of incontinence per day for TCl and 2.1 episodes per day for OXY at baseline. In both treatment arms, the frequency of incontinence episodes diminished by about one episode at each follow-up attendance.

Frequency of micturition was similar in both treatment arms with initial values of 11.4 (TCl) and 12.5 (OXY) micturitions in 24 h. In the group treated with TCl, this had diminished by 1.2 micturitions/day at 2 weeks, 2.9 micturitions/day at 26 weeks and 3.5 micturitions/day at 52 weeks. Comparable values (Fig. 1) were found in the OXY group (reduction by 1.5/3.4/4.2 micturitions at 2/26/52 weeks).

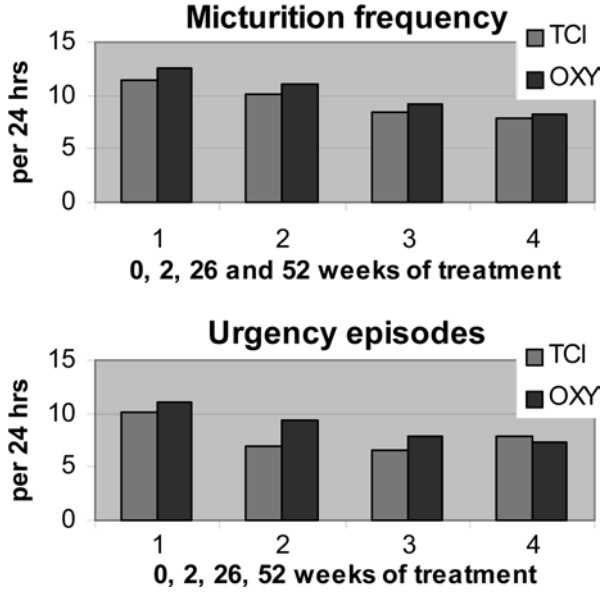

Fig. 1 Twenty four hour micturition and urgency episodes during treatment

There were similar decreases in episodes of urgency, starting at 10.2 per day and decreasing by 1.6 in the second week, 3.2 in week 26 and 3.5 in week 52 among the patients treated with TCl. In the patients treated with OXY, episodes of urgency decreased from the initial value of 11.0 in a similar way (1.7/3.2/3.6).

Subjective appraisal of efficacy

Subjective appraisal of efficacy by the investigators gave comparable results in both treatment groups. After 52 weeks of treatment, 29% (60/207) of the physicians in charge considered the therapeutic outcome for the TCl group as ''cure''; the corresponding figure for OXY was 17% (11/65). Estimates made by the patients gave practically identical figures.

Discussion

The present study is the first controlled, randomised, double-blind design to study the tolerability and efficacy of treatment for urge incontinence with TCl in doses of 20 mg twice daily under the conditions of long-term therapy of 1 year duration in comparison with a standard medication of 5 mg OXY twice daily.

In all, 64.8% of the patients treated with TCl and 76.7% of those treated with OXY experienced adverse events. With the exception of the category ''urinary tract infection'', these occurred in 43 patients and were, as expected, primarily the typical anticholinergic side effects of the two drugs. Although the trial physician postulated a causal connection between the urinary tract infection and the trial medication in 11 cases, the emergence of urinary tract infection can more plausibly be regarded as being associated with the underlying disease than as a side effect of the anticholinergic medication.

Even after 1 year therapy, the overall frequency of adverse events was not higher than in other double-blind investigations of only 2 to 3 weeks duration (Table 8).

Only in one of the latter investigations was the percentage of patients with side effects lower: whereas in the investigation by Alloussi [2] note was taken only of spontaneously reported adverse events, in the present study systematic enquiries were made regarding typical side effects by means of a standardised questionnaire.

Table 8 Randomised controlled studies of the efficacy and tolerability of TCI 20 mg twice daily. An asterisk indicates that differences between groups are not statistically significant

First author source	Diagnose	Study design	Duration of treatment	Max. cystometric bladder capacity means (ml)	Patients with side effects %
Alloussi et al. [2] Placebo: +5.2	Urge syndrom Placebo: 15.2	Placebo controlled	3 weeks	TCI: +79.1	TCI: 19.0
Cardozo et al. [6]	Idiopathic detrusor inst.	Placebo controlled	3 weeks	TCI: +27.2 Placebo: −10.2	TCI: 68 Placebo: 62
Osca-Garcia et al. [19]	Detrusor hype activity/reflexia	Randomised controlled	3 weeks	TCI: +79 OXY: +107	TCI: 64.5 OXY: 94.3
Madersbacher et al. [15]	Detrusor hype reflexia	Randomised controlled	2 weeks	TCI: +96.6 OXY: +163.0*	TCI: 54 OXY: 56
Halaska, this article	Urge syndrom/Urge incont.	Randomised controlled	1 year	TCI: +115 OXY: +119*	TCI: +64.8 OXY: 76.7

The characteristic and most expected side effect of any type of anticholinergic medication is dryness of the mouth caused by a reduction in the flow of saliva. In the TCl group as a whole, this was less frequent (33% versus 50%, $P < 0.01$), was less frequently perceived as serious (2.3% versus 11.1%) and became apparent only at a later stage ($P < 0.01$). The risk per patient per week of experiencing any dryness of the mouth during the trial was estimated 0.009 for TCl and 0.021 for OXY based on prevalence. This risk was therefore 2.3 times higher for OXY than for TCl.

Checks of vital signs, laboratory investigations and ECGs showed no clinically relevant changes under the conditions of continuous long-term therapy of 1 year duration. The ECG changes observed were not typical of any parasympathetic effect on the cardiac conducting system; spontaneous remissions of existing abnormalities were equally frequent and point to a chance effect, unconnected with the treatment.

An increase in the maximum cystometric bladder capacity during medication with TCl of 92 ml was noted at 6 months and an increase of 115 ml after 1 year. This means that cystometric bladder capacity had improved by about 50% of its level at the outset. On direct comparison with double-blind investigations of shorter duration, the therapeutic effect of TCl under the conditions of long-term therapy—measured by the increase in maximum cystometric bladder capacity—showed a tendency to be even more pronounced (Table 8).

Medication with TCl also had a noteworthy effect on other urodynamic variables: after 1 year, the volume at the first unstable contraction had increased by 65 ml and the volume at the first sensation to void had increased by 75 ml. Residual urine and maximum urinary flow remained unchanged (data not shown).

Among patients receiving long-term therapy with OXY in doses of 5 mg twice daily, there was evidence of comparable efficacy as regards the same urodynamic variables. In both the TCl group and the OXY group, the expansion of functional bladder capacity and the reduction in maximum detrusor pressure led to a clinically perceptible improvement in the existing symptoms. The reduction in frequency of micturition by roughly a third of the baseline status, together with a reduction of the frequency of incontinence episodes by around 50%, resulted in impressively positive assessments of efficacy by doctor and patient throughout the entire period of therapy.

Long-term anticholinergic therapy with TCl 20 mg twice daily or OXY 5 mg twice daily can therefore be regarded as safe. With reference to the frequency and severity of typical side effects, TCl has advantages over OXY.

The main conclusions from this investigation can be summarised as follows:

1. For TCl and OXY, the incidence of side effects during 52 weeks long-term therapy was no greater than during short-term therapy of a few weeks duration.
2. Adverse events—in particular dryness of the mouth—were more frequent and began earlier in the OXY group than in the TCl group.
3. A 52 week long-term therapy with TCl or OXY showed comparable efficacy as measured by changes in urodynamic variables.
4. TCl evidenced some tendency to a greater effect—as measured by the urodynamic variable maximum cystometric bladder capacity with an increase by 115 ml at 52 weeks—than in comparable investigations with shorter periods of observation.
5. In conclusion, TCl in doses of 20 mg twice daily has a better risk-benefit profile for long-term therapy than OXY in doses of 5 mg twice daily.

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