

Urodynamic and Other Effects of Tolterodine: A Novel Antimuscarinic Drug for the Treatment of Detrusor Overactivity

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Tolterodine, a novel compound intended for treatment of urgency and urge incontinence, has been characterized as a potent muscarinic receptor antagonist in pharmacological *in vitro* and *in vivo* studies. In cats, tolterodine was shown to reduce bladder pressure at doses significantly lower than those affecting salivation. To predict clinical effectiveness, an open pilot study was performed in healthy male volunteers. Efficacy was measured by cystometry and by spontaneously reported effects after administration of a single oral dose of tolterodine, 6.4 mg, given as a water solution. Tolterodine had distinct inhibitory effects on urinary bladder function, both at 1 and 5 hours post-dose. At 1 hour, but not at 5 hours post-dose tolterodine also significantly reduced stimulated salivation. In addition to the objectively demonstrated changes in urodynamic parameters, most volunteers experienced voiding difficulties. No significant changes in blood pressure, heart rate, or near point of accommodation were registered. Tolterodine, in the dosage used, was both objectively and subjectively shown to exert a marked inhibitory effect on micturition in healthy subjects, and the data suggest a more pronounced effect on bladder function than on salivation.

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INTRODUCTION

Available evidence suggests that muscarinic receptors mediate not only the detrusor contraction of normal voiding, but also the main part of contraction in bladder overactivity associated with urge and urge incontinence [Andersson, 1993]. Anticholinergic treatment would therefore seem to be the logical choice for treatment of detrusor overactivity, but the results of such treatment are often disappointing [Andersson, 1988; Wein et al., 1994]. Contributing to this may be low bioavailability, particularly with quarternary compounds, and side effects, such as dryness of the mouth, accommodation difficulties, and increased heart rate. Anticholinergics with

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selectivity for the urinary bladder are desirable, but none of the drugs currently in clinical use has any such preference.

In the development of new drugs for treatment of detrusor hyperactivity, the intention has been to find substances with a selective action on the detrusor muscle, thereby avoiding the systemic side effects. Tolterodine is a new muscarinic receptor antagonist intended for treatment of urgency and urge incontinence. It is a potent and competitive antagonist at muscarinic receptors in guinea pig as well as human detrusor muscle [Nilvebrant et al., 1994, 1995], and in cats, the drug was shown to reduce bladder pressure at doses significantly lower than those affecting salivation [Gillberg et al., 1994].

The present study was undertaken to investigate the urodynamic effects of tolterodine administered to healthy male volunteers as a single oral dose. In addition, changes in blood pressure, heart rate, stimulated salivation, and near point of accommodation were registered, and serum concentrations were measured.

MATERIALS AND METHODS

Twelve male subjects were recruited for the study. Their mean age was 24 years (range 21–29 years) and their mean body weight 77 kg (range 68–87 kg). They were all judged to be healthy by clinical examination, 12-lead ECG, routine laboratory tests and a urine culture and were without any previous history of significant illness. Each subject gave his written informed consent to participation, and the study protocol was approved by the Ethics Committee of the University of Lund, Sweden.

The subjects were fasting from 10 pm on the preceding evening and abstained from food on the trial day until lunch was served (4 hours after the administration of tolterodine). However, coffee and tea without sugar and cream were allowed in the morning of the study day. The subjects received 6.4 mg of tolterodine (Pharmacia, Uppsala, Sweden) orally as an aqueous solution (6.4 mg/150 ml), a dose that in previous phase I studies had been shown to produce a clear-cut reduction of stimulated salivary secretion. This dose was assumed to be too high for clinical use, but was deliberately chosen to secure effects on the bladder. No other drugs or alcohol were allowed during 48 hours prior to and 24 hours after drug intake.

Urodynamic Investigation

The urodynamic measurements were performed according to the routines at the Department of Urology, University of Lund, Sweden, using a Life-Tech 1106 Urolab equipment. Two 8 Fr baby-feeding catheters were inserted into the bladder for infusion and pressure recording. The rectal pressure, considered approximately equal to the intraabdominal pressure, was recorded simultaneously to correct for an increase in intravesical pressure as caused by an increase in intraabdominal pressure. For this purpose a balloon catheter applied to an external pressure transducer was used and placed 5–10 cm into the rectum. Saline of body temperature was infused into the bladder at a rate of approximately 50 ml/min. The volumes at which the subject experienced the first sensation of bladder filling (FS) and the normal desire to void (ND) were noted. The maximum detrusor pressure ($p_{\text{det,max}}$) was recorded during micturition alongside the catheters. Each time this procedure was executed twice consecutively. Finally, the bladder was filled until ND, the catheters were removed

and the maximum flow rate (Q_{\max}) was registered during natural micturition. The volume of residual urine (V_{res}) was measured prior to the urodynamic investigations (true residual urine) and during the second cystometry in each session (that is, after micturition with the catheters present). The above mentioned investigations were performed thrice on the trial day, that is, prior to and 1 and 5 hours following the administration of tolterodine.

Measurements of Other Pharmacologic Effects

Heart rate and supine blood pressure (both simultaneously recorded by an automatic, non-invasive, digital blood pressure meter, Model UA-751, A&D Company Ltd., Japan), near point of accommodation (R.A.F. Near point rule, Clement Clarke, Ltd., England) and stimulated salivation (see below) were measured before (prior to the baseline cystometry) and 15 and 45 minutes and 1 h 45 min, 2 h 15 min, 2 h 45 min, 3 h 15 min, 3 h 45 min, 4 h 45 min, 5 h 45 min, 6 h 15 min, 6 h 45 min, 7 h 15 min and 7 h 45 min after drug intake. The ability to accommodate for near vision was measured binocularly by moving a block of fine print along the above rule balanced on the subject's nose and recording the nearest point (distance in mm) at which the letters were still clearly distinguishable. For this test the subjects were told to retain their visual correction. All baseline measurements were done after 10–20 minutes' rest in the supine position. For heart rate, blood pressure, and stimulated salivation, the baseline values consisted of one measurement only, but for accommodation, the baseline values were the means of two recordings. The baseline measurements were performed on average 70–90 minutes prior to drug intake, and the interval between the first and second near point recording was approximately 10 minutes. At each of the time points, the recordings of the physiologic variables occurred in the following order: heart rate and blood pressure simultaneously, accommodation for near vision and finally, salivation. In addition, a one-lead ECG strip was obtained in conjunction with each heart rate and blood pressure recording. For the salivation test, the subject was asked to swallow all saliva, whereupon one paraffin tablet (Orion Diagnostica, Espoo, Finland) was chewed for 5 minutes alternately on the left and right side. All saliva was continuously spat out into a plastic cup and the salivation flow was calculated as weight of saliva collected during 5 minutes (g/5 min).

Blood Sampling

Blood samples of 10 ml were drawn from an antecubital vein via an indwelling catheter (Venflon) into Vacutainer tubes (Becton Dickinson) without additives, prior to and 20 and 40 minutes and 1, 2, 3, 4, 6 and 8 hours after drug administration. The samples were kept at room temperature for 1 hour, followed by centrifugation (1000g for 10 min). Serum was then immediately separated and frozen. These samples were stored at -20°C until analysis.

Analysis of Tolterodine

Tolterodine was analyzed by capillary gas chromatography and mass spectrometry [Palmér and Stenberg, to be published].

TABLE I. Effects on Urodynamic Parameters of a Single Dose of 6.4 mg of Tolterodine Given Orally as an Aqueous Solution to Healthy Male Volunteers

	0 h cystometry		1 h cystometry		5 h cystometry	
	Before	At	Before	At	Before	At
V _{res} ml	20 (22)	13 (24)	124 (128)*	234 (131)	208 (148)*	202 (159)
P _{det,max} cm H ₂ O		56 (17)		41 (13)*		43 (9)*
Q _{max} ml/s		25 (7)		18 (7)*		20 (5)*
FS ml		218 (71)		282 (80)*		282 (76)*
ND ml		395 (100)		421 (76)		490 (98)*

Measurements were performed at baseline (0 hour), 1 and 5 hours after administration. Mean values are given with 1 SD within parentheses. The results from the second cystometry in each investigation was used for calculations. The number of subjects is twelve, except for P_{det,max} (n = 10).

* $P < 0.05$ vs. baseline. For ND the difference between 1 and 5 hours was also statistically significant ($P < 0.05$).

Adverse Effects

Each subject was questioned in a non-leading way about any symptoms that deviated from his normal status. Approximately 1 week after each subject had completed the study he was subjected to routine laboratory testing, a 12-lead ECG-recording, urine culture and a physical examination.

Data Analysis and Statistics

Comparisons between the three different occasions (baseline, 1 and 5 hours after drug intake) were made for the following urodynamic variables: 1) V_{res} prior to each of these time points, 2) V_{res} during cystometry, 3) volume at FS, 4) volume of ND, 5) P_{det,max}, and 6) Q_{max}. The second cystometry at each of the mentioned three time points was regarded as the valid one, since the subjects had no previous experience of urodynamic investigations. Statistics thus consistently refer to the second investigation (variables 2–5 above). For the variables, an ANOVA, including multiple comparisons with the Ryan-Einot-Gabriel-Welsh Multiple Range Test [Ramsey, 1978], was executed on the 0.05 level of statistical significance. Values of the effect variables are given as means \pm standard deviations (mean \pm 1 SD) and are presented vs. time together with the corresponding 95% confidence intervals of the means. From the serum concentrations of tolterodine the following pharmacokinetic data were derived: maximum concentration (C_{max}), its corresponding time point (t_{max}), the elimination rate constant (k_e) and elimination half-life (t_{1/2}). All pharmacokinetic data are presented as mean \pm 1 SD, except for t_{max}, which is expressed as median and range.

RESULTS

Urodynamic Effects

The mean values of the urodynamic effect variables are given in Table I. For each of them, there was a statistically significant difference between investigations before and after tolterodine intake ($P < 0.05$).

The mean V_{res} was higher during the second cystometry compared to the first

one both at 1 and 5 hours after the administration of tolterodine (234 vs. 181 ml, and 202 ml vs. 175, at 1 and 5 hours, respectively). The same was true for FS (282 vs. 235 ml, and 282 ml vs. 243 ml, respectively), but for ND only at 5 hours (490 vs. 435 ml). This tendency was not seen for the corresponding baseline measurements. For $p_{\text{det,max}}$ the difference between the first and the second cystometry at 1 and 5 hours was not obvious.

Four subjects were unable to void at baseline, probably because too short a time had elapsed since the previous micturition. These subjects had the largest initial residual volumes (32–75 ml). Further, three and four subjects, respectively, could not void prior to the investigations at 1 and 5 hours, most likely due to a pharmacologic effect. Two subjects were excluded from the mean calculations of $p_{\text{det,max}}$ because of their inability to void at 1 hour. Hence, the detrusor pressures (9 and 0 cm H₂O, respectively) measured in these cases are not comparable to those of the others.

Since the subjects were undergoing several catheterizations during the study day, it was difficult to evaluate the micturition problems reported. However, the subjects seemed able to separate actual voiding problems and the burning sensation from the urethra seen as a result of the manipulations. Taking this uncertainty into account, at least eight subjects had voiding difficulties, seven of them also in the afternoon during the last urodynamic procedure, approximately 5 hours after drug intake. One subject experienced micturition problems 10 hours following drug administration. Before the 1 hour cystometry, another subject felt that the bladder had been not completely emptied, and in accordance with this, the volume of residual urine was considerable (175 ml). Before the 5 hour cystometry, however, voiding was experienced as normal, yet the volume of urine remaining in the bladder following micturition was now 375 ml.

For one subject (No. 7), whose pharmacokinetics differed from that of the others (see below), V_{res} prior to each investigation amounted to 35, 10 and 4 ml (at baseline, 1, and 5 hours, respectively). The initial residual volume (35 ml) was probably an overestimation of the true V_{res} , since this subject was unable to micturate before the investigation. The residual volume of urine during cystometry was 0, 30 and 10 ml for baseline, 1 and 5 hours, respectively. FS was 280, 290 and 300 ml at the same time points, ND 430, 425 and 505 ml, $p_{\text{det,max}}$ 74, 54 and 50 cm H₂O, and Q_{max} 18, 25 and 18 ml/s.

Other Pharmacologic Effects

Tolterodine caused a significant mean maximum decrease (72%, related to the basal value) of stimulated salivation, 45 min after drug intake (Fig. 1). At approximately 5 hours after dose, salivation was normalised.

Tolterodine had no effect on the diastolic and systolic blood pressures. In relation to the basal value, there was a non-significant increase in heart rate (Fig. 2), and in the near point of vision (data not shown).

Pharmacokinetics

The mean C_{max} was 5.6 ± 2.8 $\mu\text{g/L}$, excluding subject No. 7 whose C_{max} was 21.4 $\mu\text{g/L}$ (Fig. 3). In seven subjects C_{max} occurred at 0.67 hours, in four (including subject No. 7) at 1 hour and in one at 0.33 hours after the intake of tolterodine. Mean

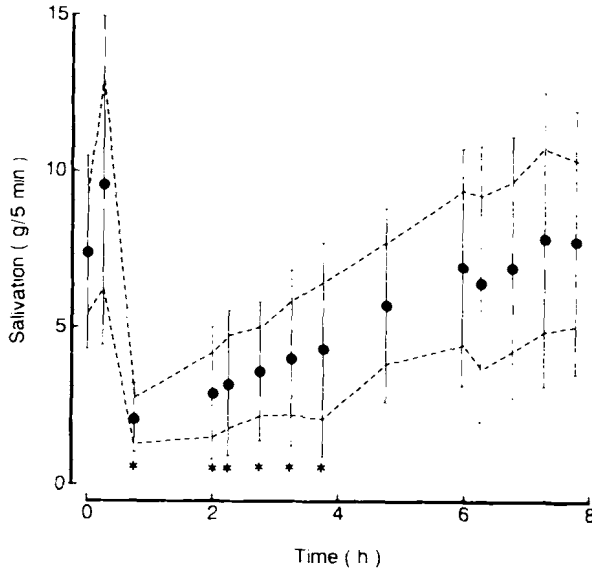


Fig. 1. Mean stimulated salivation vs. time after 6.4 mg tolterodine given orally as an aqueous solution to 12 healthy male volunteers. Solid lines are standard deviations and broken lines are 95% confidence limits.

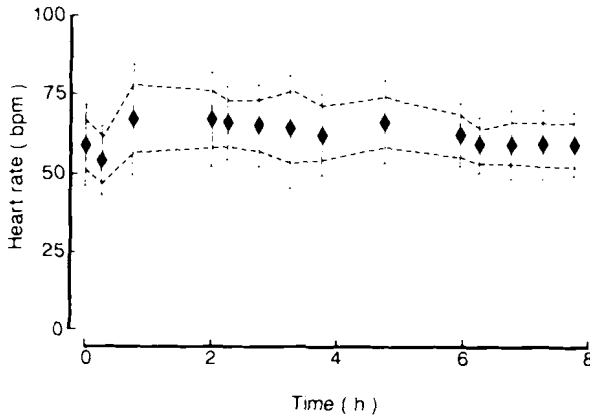


Fig. 2. Mean resting heart rate vs. time after 6.4 mg tolterodine given orally as an aqueous solution to 12 healthy male volunteers. Solid lines are standard deviations and broken lines are 95% confidence limits.

$t_{1/2}$ was 2.5 ± 0.4 hours, again excluding subject No 7 ($t_{1/2}$ 15.0 hours), and mean k_e was 0.28 ± 0.046 h^{-1} .

Adverse Effects

All subjects reported dry mouth, commencing 8–72 minutes (mean 37 minutes) following the administration of tolterodine. The duration ranged between 69 minutes

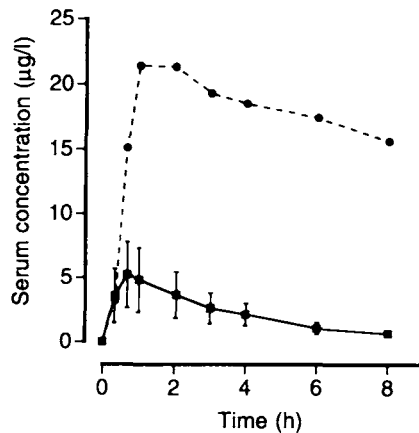


Fig. 3. Mean (\pm S.D.) serum tolterodine concentrations in 11 healthy male subjects after an oral dose of 6.4 mg as an aqueous solution (solid line). The data from subject No. 7 are shown separately (broken line).

and 9 hours (mean 4 hours). Two individuals also reported dry throat. Five of the volunteers reported dry hands, and in two of them, the symptom was accompanied by a sensation of dry feet.

Other symptoms reported were change of taste, increased sensitivity to light, problems focusing, hoarseness, hazy vision, and nasal congestion.

All post study physical and laboratory examinations including 12-lead ECG and urine culture were found to be normal.

DISCUSSION

In the normal human detrusor, the emptying contraction *in vivo* and the contraction evoked by electrical stimulation of nerves *in vitro* has been suggested to be mediated mainly, if not exclusively, through muscarinic receptor stimulation [Sjögren et al., 1982; Sibley, 1984; Kinder and Mundy, 1985; Craggs et al., 1986], because these responses can be more or less completely blocked by atropine. In support of this suggestion, atropine [Cullumbine et al., 1955] and other anticholinergic drugs can produce an almost complete paralysis of the bladder when injected intravenously in normal humans.

Tolterodine is a potent and competitive antagonist at human bladder muscarinic receptors. In electrically stimulated bladder strips, tolterodine effectively and concentration-dependently reduced the contractile responses, and the receptor specific binding of $(-)^3\text{H-QNB}$ in homogenates of urinary bladder from humans was effectively inhibited by tolterodine in a concentration-dependent manner [Nilvebrant et al., 1994, 1995]. Intravenous infusion of tolterodine (0.01–1 mg/kg) to anaesthetised cats resulted in a dose-dependent inhibition of urinary bladder contractions induced by acetylcholine and of salivation evoked by electrical nerve stimulation [Gillberg et al., 1994]. The effect of urinary bladder contractions occurred at significantly lower doses than the effect on salivary secretion. In contrast, oxybutynin was significantly more potent in inhibiting salivary secretion than urinary bladder contractions; atropine was equally effective on both parameters.

In the present study, tolterodine had a pronounced effect on bladder function in healthy volunteers when given orally. The main urodynamic effects of tolterodine consisted of an increase in V_{res} , reflecting an incomplete emptying of the urinary bladder, and a decreased $p_{det,max}$. These findings are consistent with a potent antimuscarinic action on the lower urinary tract. The mean baseline V_{res} prior to the urodynamic investigation was probably an overestimation of the true baseline V_{res} , since four of the subjects included in the mean calculations were unable to void at baseline. Thus, although three and four subjects, respectively, were unable to micturate prior to the urodynamic procedure at 1 and 5 hours, the difference in mean V_{res} prior to cystometry (that is, the "true" V_{res}), and therefore the drug effect, is likely to be underestimated. The V_{res} during each cystometry disclosed a similar increase. However this volume does not constitute a true V_{res} since it was assessed following micturition with indwelling catheters in position.

Tolterodine also influenced the other urodynamic variables investigated. A decreased urinary flow rate was found. However, the rates were still within the normal range. There was an increase in ND which coincides well with an assumed decrease in detrusor contractility, and also in the volume of FS. Even if significant, the changes in FS should be interpreted with caution because of its large interindividual variability.

As expected, tolterodine in the dose used (6.4 mg), caused a distinct decrease in stimulated salivation. The effect was, however, shorter-lasting than the effect on bladder function, and at 5 hours, when the effects on the bladder were still as pronounced as at 1 hour post dose, stimulated salivation was normalised. No significant effects on heart rate, blood pressure, or near point of accommodation were found, despite the high tolterodine dose that was used. This suggests that if any side effect will be dose-limiting in clinical practice, it is likely to be reduced salivation, rather than effects on the heart or the eye.

The pharmacokinetics of tolterodine, as found in this pilot study, revealed a rapid absorption with a mean time for maximal serum concentration of less than 1 hour, and a serum half life of about 2.5 hours. In one of the 12 subjects, the pharmacokinetics of the drug differed markedly from that of the others. This subject had a maximal serum tolterodine concentration almost four times higher than the mean, and a serum half-life of 15 hours. Despite this, the urodynamic effects were not conspicuous. These findings suggest that tolterodine is metabolised to active metabolites, and that the subject was a slow metabolizer.

Thus, tolterodine, in the dosage used, was both objectively and subjectively shown to exert a powerful inhibitory effect on micturition in healthy subjects. Even if the drug reduced stimulated salivation, the results suggest that a selective effect on the bladder, as demonstrated in an animal model [Gillberg et al., 1994], and be obtained also in humans. Overall the drug had an acceptable adverse effect profile. Taking into account the relatively large residual volumes produced in this study on healthy volunteers, and the distinct effects on stimulated saliva secretion, a dose of 6.4 mg of tolterodine seems too high a dose for future patients.

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