Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity

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Abstract. The aim of this study was to determine the pharmacokinetics, pharmacodynamics, and safety of tolterodine following single oral and intravenous doses in healthy volunteers. A secondary aim was to identify major urinary metabolites and determine mass balance. Single oral doses of 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 mg of tolterodine (as the tartrate salt) were given to 17 healthy male volunteers. Two intravenous doses (0.64 and 1.28 mg) were administered to 8 of the volunteers and mass balance was studied after a single oral dose of 5 mg (^{14}C)-tolterodine in 6 subjects. Tolterodine was rapidly absorbed following oral administration (time to peak serum concentration 0.9 ± 0.4 h). The absolute bioavailability was highly variable, ranging from 10 to 70%. The volume of distribution at steady-state ranged from 0.9 to 1.6 l/kg and systemic clearance ranged from 0.23 to 0.52 l/h/kg, which resulted in a terminal half-life of 2 – 3 h. Tolterodine exhibited high first-pass metabolism and 2 hepatic metabolic pathways were identified: oxidation and dealkylation. Independent of route of administration, < 1% of the parent compound was excreted unchanged in urine. Five metabolites were structurally identified in urine. Following oral administration of (^{14}C)-tolterodine, the excretion of radioactivity into urine and feces was 77 ± 4.0% and 17 ± 3.5%, respectively. Tolterodine decreased stimulated salivation after 3.2 mg, increased heart rate after 6.4 mg, and nearpoint of vision after 12.8 mg. Six of 8 subjects reported micturition difficulties after a dose of 12.8 mg. The lack of a direct relationship between tolterodine serum concentrations and effects on stimulated salivation suggested the presence of pharmacologically active metabolite(s).

Key words: tolterodine – pharmacokinetics – mass balance – healthy volunteers – active metabolite

Introduction

Disorders of micturition may be divided into disturbances of the storage function or the emptying function of the urinary bladder. The main symptoms of disturbances of the storage function are frequency, urgency, and incontinence. In man there are reasons to believe that normal bladder contractions as well as contractions associated with bladder overactivity are mediated mainly by muscarinic receptor stimulation [Andersson 1993]. For this reason, antimuscarinic drugs are often used for treatment of detrusor overactivity.

Quaternary ammonium compounds, such as emepronium bromide and propantheline bromide, are commonly used in the treatment of bladder overactivity. These drugs have documented effects on bladder function when given parenterally [Blaivas et al. 1980, Ulmsten and Andersson 1977]. However, peripheral antimuscarinic adverse effects such as dry mouth, accommodation paralysis, and tachycardia have limited the effectiveness of these agents. Dose titration is often necessary because of poor bioavailability and high interindividual variation following oral administration [Sundwall et al. 1973, Vose et al. 1981]. Oxybutynin, which is a well documented drug, is currently considered to be the drug of choice in the treatment of

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patients with bladder overactivity [Yarker et al. 1995]. The utility of this agent is restricted by a high incidence of adverse effects, such as dryness of the mouth [Cardozo et al. 1987].

No currently available therapeutic agent has a selective action on the muscarinic receptors of the bladder. A drug with a high antimuscarinic potency and a more bladder-selective action is therefore desired. Preclinical data have shown that tolterodine ((R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine) exerts a high antimuscarinic potency in guinea pig and human detrusor muscle [Naerger et al. 1995, Nilvebrant et al. 1994]. It has also been shown that tolterodine displays a favorable tissue selectivity for the urinary bladder over salivary glands in the anesthetized cat [Gillberg et al. 1994].

Preliminary studies in healthy volunteers suggest that tolterodine exerts a marked inhibitory effect on micturition [Stahl et al. 1995]. The objective of the present study was to determine the pharmacokinetics, pharmacodynamics, and safety of tolterodine following single oral and intravenous (i.v.) doses in healthy volunteers. A secondary aim was to identify major urinary metabolites of tolterodine following oral administration and to quantify urinary/fecal excretion (mass balance).

Subjects, material and methods

Study drugs

Tolterodine is a weak base (pKa 9.9) with an octanol/phosphate buffer partition coefficient (log D) at room temperature of 1.8 at pH 7.3 (data on file [Pharmacia & Upjohn AB]). For the purposes of this study, tolterodine (as the tartrate salt) was prepared as water solutions (150 ml) for use in dose escalation studies while a solution of (^{14}C)-tolterodine (labelled in the α-position, 95% radiochemical purity), together with unlabelled tolterodine, was prepared for determination of mass balance. Oral solutions of tolterodine were prepared by the Pharmacy, Lund University Hospital, Sweden, while i.v. solutions of tolterodine were prepared by Pharmacia and Upjohn AB, Stockholm, Sweden.

Subjects

A total of 23 male Caucasian volunteers were included in the 3 parts of the study (oral dose escalation, i.v. administration, and mass balance determination). All volunteers were judged to be healthy by clinical examination, electrocardiography, and evaluation of laboratory parameters prior to study enrolment. Seventeen volunteers participated in the oral dose escalation studies. Their mean (± standard deviation, SD) demographic characteristics were: age 28 ± 7 years, body weight 77 ± 10 kg, and height 1.81 ± 0.04 m. Eight of these subjects subsequently received tolterodine i.v., while 6 additional volunteers received (^{14}C)-tolterodine orally for determination of mass balance. The mean (± SD) demographic characteristics of these 6 volunteers were: age 45 ± 6 years, body weight 75 ± 4 kg, and height 1.80 ± 0.06 m. Each participant provided informed written consent and the study protocol was approved by the Ethics Committee of the University of Lund, Sweden.

Study design

The subjects fasted overnight (from 10 p.m.) before drug administration and they abstained from food until a standardized lunch was given (4 h after drug administration). No other drugs were allowed for 2 weeks prior to and 48 h after each administration. In addition, smoking and the consumption of alcohol and caffeine-containing beverages were restricted prior to and for 48 h after drug intake.

In the dose escalation part of the study, tolterodine was given as a single oral dose of 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, or 12.8 mg. Two subjects per dose were included in the lower dose interval (0.2 – 1.6 mg), while 8 subjects received 3.2, 6.4 and 12.8 mg, respectively. Blood samples (10 ml) were drawn into Vacutainer tubes without additives prior to and at 0.33, 0.66, 1, 2, 3, 4, 6, 8, and 24 h after drug administration. After coagulation at room temperature for approximately 0.5 – 1 h the blood samples were centrifuged (1,000 g for 10 min). Serum was immediately separated, frozen, and stored at –20° C pending analysis. Urine was collected quantitatively 0 – 24 h and 24 – 48 h after tolterodine dosage. Heart rate and blood pressure (supine) were simultaneously recorded by an automatic, noninvasive, digital blood pressure meter (UA-751, A and D Company Ltd, Japan). Nearpoint of vision was determined using a RAF nearpoint rule (Clement Clarke Ltd., UK). Stimulated salivation was measured with a slightly modified method used by Dollery et al. [1976]. The subjects chewed 1 tablet of paraffin (Orion Diagnostica, Espoo, Finland) alternately on the left and right side of the mouth for 5 min. All saliva was carefully collected in a plastic cup and weighed in order to calculate salivation flow (g/5 min). Measurement of heart rate, blood pressure, nearpoint of vision and stimulated salivation were performed prior to and at 0.25, 0.75, 1.25, 1.75, 2.25, 2.75, 3.25, 3.75, 4.75, 5.25, 5.75, 6.25, 6.75, 7.25, and 7.75 h after the administration of tolterodine.

Eight of the 17 subjects included in the dose escalation also received tolterodine i.v. Two subjects received a 5-min infusion of tolterodine 0.64 mg while all 8 subjects received an i.v. infusion of tolterodine 1.28 mg over 10 min. Blood samples (10 ml) were drawn prior to and immediately after the infusion, and at 0.33, 0.66, 1, 2, 3, 4, 6, 8, and 24 h after completion of the infusion. Quantitative collection of urine and measurement of heart rate, blood

pressure, nearpoint of vision, and stimulated salivation were performed as described above.

An additional 6 subjects were included in the mass balance investigation. Each subject received a single 5 mg (110 µCi) oral dose of (^{14}C)-tolterodine. Fecal samples were collected quantitatively in 24 h intervals for 7 days and urine in the intervals 0 – 4, 4 – 8, 8 – 24, 24 – 48, 48 – 72, 72 – 96, 96 – 120, 120 – 144, and 144 – 168 h after drug administration. Urine samples (0 – 24 h) used for identification of tolterodine metabolites were adjusted to pH 3.5 – 4.0 with 2 M H_2SO_4 in 0.5 M ascorbic acid to prevent oxidative processes. All serum, urine and fecal samples were stored frozen at –20° C until analysis.

All spontaneously reported adverse events were recorded and laboratory parameters were again determined for all volunteers at study end.

Analytical procedure

Tolterodine concentrations in serum and urine were determined using gas chromatography/mass spectrometry, with a deuterated analogue as the internal standard. Urinary concentrations of tolterodine were also assessed following incubation of samples with β-glucuronidase (Boehringer Mannheim, Germany). Tolterodine and its internal standard were synthesized by the Department of Medicinal Chemistry, Pharmacia and Upjohn AB, Stockholm, Sweden. The analytes were extracted from 1 – 2 ml of alkalised (pH 11 – 14) sample into 5 ml pentane/diethyl ether (1 : 3 v/v). After evaporation of the organic phase to dryness, in a stream of nitrogen, the residue was derivatized with 50 µl BSTFA (N,O-bis-(trimethylsilyl)-trifluoroacetamide). Separation was achieved on a fused silica capillary column (HP Ultra 1 or 2, 25 m – 0.22 mm, 0.33 µm), using temperature programming. Detection was performed with an HP 5970 or 5971 MSD mass selective detector (Hewlett Packard, USA). The ions m/z 382 and m/z 387 were focused for single-ion monitoring of tolterodine and its internal standard, respectively. Standard curves prepared in serum were linear within the range 0.5 – 50 µg/l. The limit of detection was 0.5 µg/l. The interday variation for tolterodine in the concentration range 1.9 – 47.2 µg/l was < 7% and the accuracy varied between 100 and 111%.

Measurements of total radioactivity were performed in aliquots of the oral solution and urine. Samples were diluted with Ultima Gold (Packard, USA) and radioactivity measured by liquid scintillation spectrometry (Canberra Packard TR 2500, USA). Fecal samples were homogenized in water (3 – 4 times the fecal weight) and aliquots were dried and combusted (Packard Sample Oxidizer Model 307, USA). Radioactivity was subsequently measured in Carbosorb/Permafluor (Packard, USA) by liquid scintillation spectrometry.

Urinary metabolites were extracted on Amberlite XAD-2 (17 × 180 mm, conditioned with methanol and water), eluted with methanol, and concentrated under reduced pressure. The different metabolites were fractionated by preparative reversed-phase liquid chromatography on a Prep Pak column packed with 6 µm Nova Pak C18 particles (Waters Millipore, MA, USA). The analytes were eluted with a methanol gradient in water and the radioactive fractions were collected and concentrated. Radioactive fractions were further purified on an analytical reversed-phase column and finally analyzed by Frit-FAB liquid chromatography/mass spectrometry. Unconjugated metabolites were silylated and analyzed by gas chromatography/mass spectrometry with electron impact ionisation.

Data analysis

All data are expressed as mean ± SD, except where indicated. Noncompartmental analysis was performed using PCNonlin (version 4.2) for extravascular administration [Statistical Consultants 1986]. The area under the serum concentration-time curve was obtained by linear trapezoidal approximation [Gibaldi and Perrier 1982] with extrapolation to infinity by dividing the last predicted data point by the terminal slope, λz (derived from the 2 – 24 h interval). Oral clearance (CL/F), assuming complete absorption, and terminal half-life ($t_{1/2}$) were calculated according to standard methods [Rowland and Tozer 1995].

In the regression analysis, a biexponential model (equations 1 and 2) [Gibaldi and Perrier 1982] was fitted simultaneously to i.v. and oral serum concentration data (in order to stabilize the model and to get a better estimate of bioavailability):

$$C_{i.v.} = \frac{R_{inf}}{V_c} \sum_{i=1}^{n} \left[\frac{C_i}{-\lambda_i} \cdot \left(1 - e^{\lambda_i \cdot \theta}\right) \cdot e^{-\lambda_i \cdot t} \right] \quad (1)$$

$$C_{p.o.} = \frac{F \cdot Dose \cdot k_a}{V_c} \sum_{i=1}^{n} \left[\frac{C_i}{\lambda_i - k_a} \cdot e^{-k_a \cdot t} + \frac{C_i}{k_a - \lambda_i} \cdot e^{-\lambda_i \cdot t} \right] \quad (2)$$

where θ is t during the infusion and becomes the constant t_{inf} (duration of infusion) after cessation of the infusion.

Generally, a lag-time (t_{lag}) needed to be included for oral data. The model was fitted to the data by weighted least squares regression using the weighting factor $1/c^2_{calc}$, which assumes that the coefficient of variation (CV) of error on the concentration measurements was constant. The choice of model was made with respect to several criteria to assess the goodness of fit of the models to experimental data. These criteria were as follows: the objective function, the scatter of the plot of the residuals, and the precision of each parameter. The volume of distribution at steady-state (V_{SS}), systemic serum clearance (CL), absorption half-life ($t_{1/2a}$), bioavailability (F) and mean residence time (MRT)

Table 1 Pertinent kinetic estimates obtained after simultaneous fit of oral data (3.2, 6.4, and 12.8 mg) and infusion data (1.28 mg) after administration of tolterodine to healthy volunteers.

Parameter	3.2 mg (n = 4)			6.4 mg (n = 3)			12.8 mg (n = 5)		
	Mean	Range	CV (%)	Mean	Range	CV (%)	Mean	Range	CV (%)
C_{max} (µg/l)	6.2[a]	< 0.7 – 13	74	9.6[b]	2.5 – 17	63	25[b]	6.8 – 54	56
t_{max} (h)	0.8[a]	0.7 – 1.0	19	0.9[b]	0.7 – 1.5	33	1.1[b]	0.3 – 2.0	53
F (%)	43	23 – 74	51	34	23 – 48	38	33	10 – 60	55
V_{SS} (l/kg)	1.4	0.9 – 1.6	25	1.4	1.1 – 1.6	18	1.3	1.1 – 1.4	13
CL (l/h/kg)	0.36	0.24 – 0.46	27	0.37	0.23 – 0.47	34	0.43	0.32 – 0.52	18
MRT (h)	4.1	2.9 – 6.7	44	4.2	2.8 – 7.0	57	3.0	2.7 – 4	9.3
$t_{1/2\beta}$ (h)	3.2	2.4 – 52	41	3.3	2.3 – 5.3	51	2.4	2.1 – 2.9	13
CL/F (l/h/kg)[c]	1.6[d]	0.38 – 3.1	63	2.4[b]	0.56 – 5.4	83	1.7[b]	0.71 – 4.8	76

[a] = based on 7 subjects, [b] = based on 8 subjects, [c] = estimated by noncompartmental analysis, [d] = based on 6 subjects, C_{max} = peak serum concentration, t_{max} = time to C_{max}, F = bioavailability, V_{SS} = volume of distribution at steady-state, CL = systemic serum clearance, MRT = mean residence time, $t_{1/2\beta}$ = elimination half-life, CL/F = oral clearance, CV = coefficient of variation

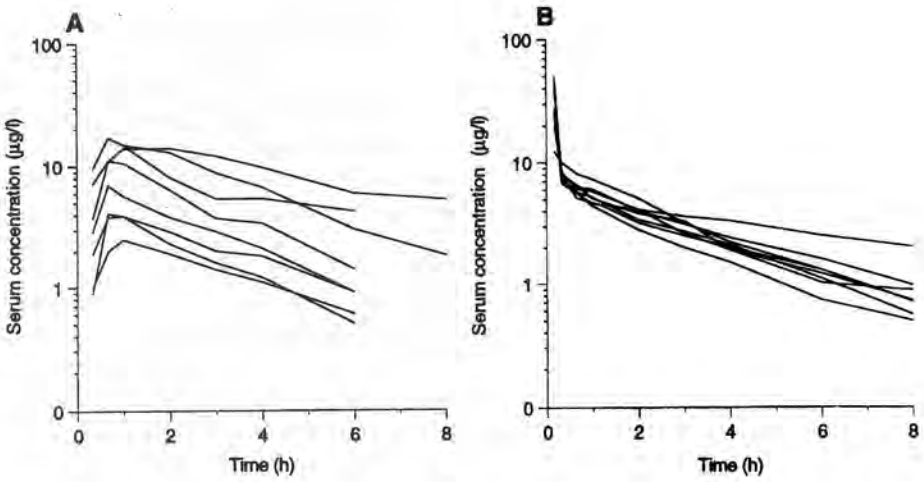

Fig. 1 Serum concentration time profiles of tolterodine after 6.4 mg oral (panel A) and 1.28 mg intravenous (panel B) single-dose administration of tolterodine to 8 healthy volunteers.

were estimated according to standard equations [Gibaldi and Perrier 1982].

Radioactivity in urine and feces was determined quantitatively and described as a function of time.

Results

All subjects complied with the study protocol and completed the trial. Since only 2 subjects per dose level were included for the lower oral doses of 0.2 – 1.6 mg this presentation will emphasize the pharmacokinetics and pharmacodynamics after tolterodine doses of 3.2, 6.4, and 12.8 mg (8 volunteers per group).

Pharmacokinetics

Pharmacokinetic parameters from the noncompartmental analysis and the simultaneous fit to oral and i.v. data are presented in Table 1 and serum concentration time profiles after 6.4 mg oral and 1.28 mg i.v. administration in Figure 1. Tolterodine was rapidly absorbed at all dose levels, time to peak serum levels (t_{max}) following oral administration was 0.8 – 1.1 h. A proportional increase in mean peak serum concentration (C_{max}) (6.2 – 25 µg/l) was observed at doses of 3.2 – 12.8 mg. CL/F showed high interindividual variability (range 0.38 – 5.4 l/h/kg) without any obvious dose relationship. Mean $t_{1/2}$ was constant (2.5 – 3.0 h) with increasing dose. After a mean t_{lag} of 0.3 ± 0.3 h, tolterodine was absorbed with a $t_{1/2a}$ of 0.4 ± 0.3 h. The initial distribution phase was rapid ($t_{1/2\alpha}$ < 0.33 h). Bioavailability exhibited high variability between individuals, ranging from 10 to 74%, while V_{SS} and CL ranged from 0.9 to 1.6 l/kg and from 0.23 to 0.52 l/h/kg, respectively. On the basis of these results, MRT and elimination half-life ($t_{1/2\beta}$) were estimated to be 3 – 7 h and 2 – 3 h, respectively. Renal excretion of unchanged tolterodine was < 1% during the first 48 h and was independent of dose and route of administration. Similar results were obtained when urine samples were incubated with β-glucuronidase prior to analysis.

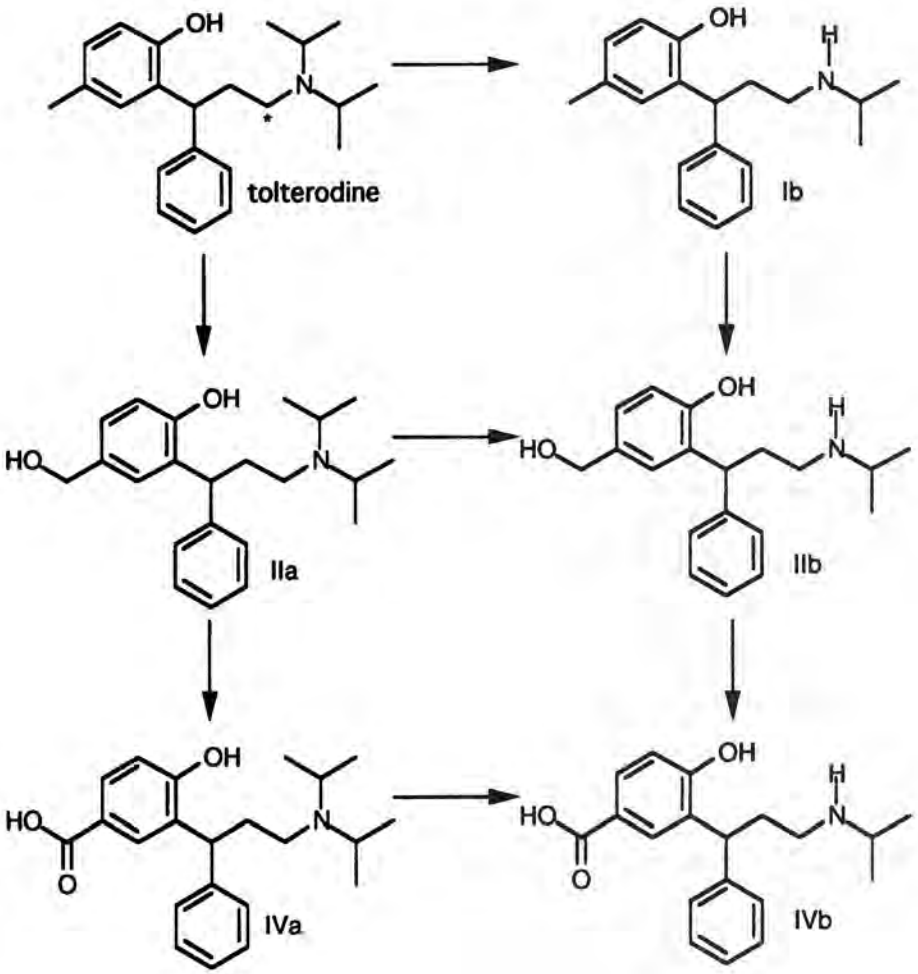

Fig. 2 Identified urinary metabolites after a single 5 mg oral dose of (^{14}C)-tolterodine in healthy volunteers. All metabolites (and tolterodine) were also identified as glucuronides. The position of (^{14}C)-labelling is indicated (*) in the tolterodine molecule.

Mass balance and metabolism

Within 7 days from drug administration, 94 ± 2.5% of the total amount of radioactivity administered was recovered (77 ± 4.0% and 17 ± 3.5% in urine and feces, respectively). Most of the radioactivity (74 ± 5.8%) was excreted in urine and feces within 24 h.

The structures of tolterodine metabolites identified in the 0 – 24 h urine samples are shown in Figure 2. Although the relative concentrations of the metabolites varied between subjects, the carboxylic acid metabolite (IVa) and the dealkylated carboxylic acid metabolite (IVb) were consistently the predominant metabolites in all samples analyzed. The latter 2 metabolites accounted for 80 ± 17% of total urinary radioactivity (IVa, 51 ± 14.0%, IVb, 29 ± 6.0%). The remaining 20% of radioactivity were accounted for by the hydroxylated metabolite (IIa) along with its dealkylated form (IIb), intact tolterodine, dealkylated tolterodine and their glucuronide conjugates. Fecal samples contained 2 major metabolites with similar retention times to the IVa and IVb metabolites, while no peak with a retention time corresponding to that of intact tolterodine was observed.

Pharmacodynamics

The effects of tolterodine 3.2, 6.4, and 12.8 mg on mean heart rate, nearpoint of vision, and stimulated salivation are shown in Figure 3. Tolterodine was associated with a dose-dependent increase in heart rate, the onset of which was fairly rapid with time to maximal effect around 1.3 – 1.8 h. The maximum increase in heart rate observed in volunteers who received tolterodine 12.8 mg was 19 ± 5 beats/min. Nearpoint of vision was not affected at doses of 3.2 and 6.4 mg, although considerable interindividual variability was apparent. In contrast, a mean increase of 32 mm was observed at a dose of 12.8 mg. Following a transient increase in stimulated salivation (most probably as a result of water intake, 300 ml, and the slightly bitter oral solution), a rapid decrease in salivary flow was observed. The maximum decrease in salivary flow was attained within 1.3 – 1.8 h after drug administration and at 12.8 mg an almost

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