Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamics of tolterodine

Objective: To determine whether cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of tolterodine by investigating potential differences in pharmacokinetics and pharmacodynamics (heart rate, accommodation, and salivation) of tolterodine and its 5-hydroxymethyl metabolite between poor metabolizers and extensive metabolizers of debrisoquin (INN, debrisoquine).
Methods: Sixteen male subjects (eight extensive metabolizers and eight poor metabolizers) received 4 mg tolterodine by mouth twice a day for 8 days followed by a single intravenous infusion of 1.8 mg tolterodine for 30 minutes after a washout period. Doses were given as the tartrate salt. The pharmacokinetics of tolterodine and 5-hydroxymethyl metabolite were determined, and the pharmacodynamics were measured.
Results: The mean systemic clearance of tolterodine was significantly lower ($p < 0.001$) among poor metabolizers (9.0 ± 2.1 L/hr) compared with extensive metabolizers (44 ± 13 L/hr), resulting in a fourfold longer elimination half-life ($p < 0.001$). The terminal half-life of the 5-hydroxymethyl metabolite (2.9 ± 0.4 hours) was slightly longer than that of the parent compound (2.3 ± 0.6 hours) among extensive metabolizers, but the 5-hydroxymethyl metabolite was undetectable in the serum of poor metabolizers. Only minor differences in pharmacodynamic effects after tolterodine dosage were observed between the groups. Tolterodine caused a similar decrease in salivation in both panels. The decrease occurred when the concentration of unbound tolterodine and 5-hydroxymethyl metabolite among extensive metabolizers was comparable with that of tolterodine among poor metabolizers.
Conclusions: Tolterodine is extensively metabolized by CYP2D6 with high specificity. Despite the effect on pharmacokinetics, the CYP2D6 polymorphism does not appear to be of great importance in the antimuscarinic effect, probably because of the additive action of parent drug and active metabolite. (Clin Pharmacol Ther 1998;63:529-39.)

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Large interindividual variation in drug response and therapeutic outcome is not uncommon, and a leading contributing factor is a corresponding variation in the capability to metabolize drugs. One example is cytochrome P450 2D6 (CYP2D6) polymorphism (debrisoquin [INN, debrisoquine]–sparteine hydroxylase), which exhibits an incidence of poor metabolism of about 7% among white persons.[1] A large number of drugs, such as antidepressants, neuroleptic agents, antiarrhythmic agents, several β–adrenergic receptor antagonists and some opioids, have been shown to be metabolized by the CYP2D6 enzyme.[2,3] Individualization of dosage is necessary for some of these drugs.[4] Moreover, if a drug is metabolized by CYP2D6 to an active metabolite, the activity of the enzyme may be an important determinant of the effectiveness of treatment. Certain drugs, such as codeine[5] and encainide,[6] are activated by CYP2D6. Therefore poor metabolizers may be nonresponders to such therapy. Conversely, with drugs that are inactivated by CYP2D6, poor

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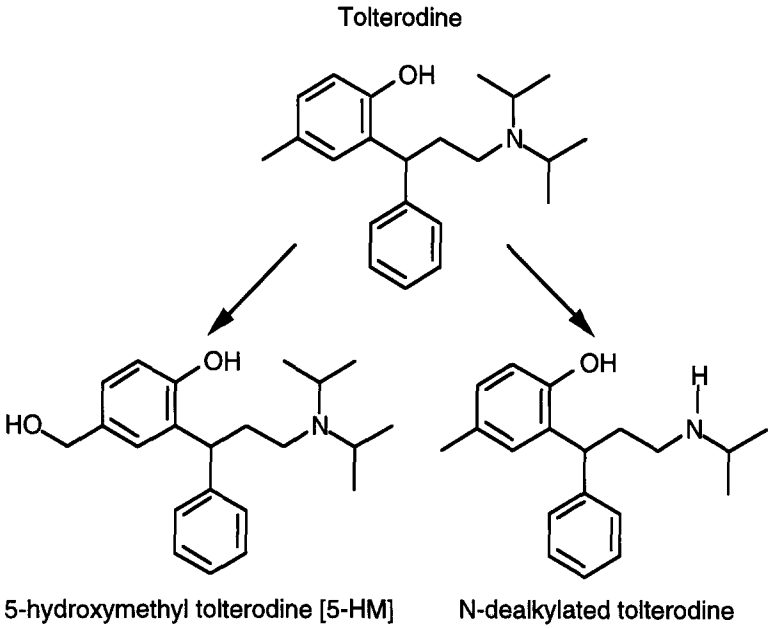

Fig. 1. Tolterodine, *(R)-N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine and the primary metabolites of tolterodine.

metabolizers may accumulate the drug and experience adverse effects at "normal" dosages.

Tolterodine is a new antimuscarinic drug for the management of overactive bladder with symptoms of frequency or urge incontinence.[7] Preclinical studies have shown that tolterodine has high antimuscarinic potency in guinea pig and human detrusor muscle and displays favorable selectivity for the urinary bladder over salivary glands in vivo.[8] Studies have suggested that tolterodine exerts a marked inhibitory effect on bladder function among both healthy volunteers[9] and patients with urinary urge incontinence.[10] Among healthy volunteers, tolterodine was rapidly absorbed, with a high first-pass metabolism. This led to considerable interindividual variation in serum concentration.[11] Two hepatic oxidative metabolic pathways for tolterodine have been identified—hydroxylation and *N*-dealkylation (Fig. 1).[11] The concentration-effect relation suggests a pharmacologically active metabolite. Preclinical studies have shown that the 5-hydroxymethyl metabolite (5-HM) of tolterodine (PNU-200577) is pharmacologically active and equipotent compared with tolterodine in vitro.[12] Stahl et al.[9] reported results for a healthy volunteer with a half-life of tolterodine of 15 hours, which is six times longer than average. This person subsequently was phenotyped with debrisoquin and found to be a poor metabolizer (data on file). This finding, along with a number of unpublished observations, indicates that CYP2D6 may be involved in the metabolism of tolterodine. The aim of this study was to investigate potential differences in pharmacokinetics and pharmacodynamics (effect on heart rate, accommodation, and salivation) of tolterodine and its 5-HM between poor metabolizers and extensive metabolizers of debrisoquin.

METHODS

Subjects. Sixteen healthy male volunteers were recruited for the study from more than 1000 healthy Swedish subjects previously phenotyped with debrisoquin.[13] Eight volunteers were classified as poor metabolizers of debrisoquin (metabolic ratio >12.6) and eight were extensive metabolizers (metabolic ratio <1.0). The lower metabolic ratio of less than 1.0 was chosen arbitrarily to exclude intermediate metabolizers. The mean (±SD) demographic characteristics for the extensive metabolizers were as follows: age, 29 ± 7 years; body weight, 76 ± 7 kg; and height, 1.79 ± 0.06 m. The mean characteristics for the poor metabolizers were as follows: age, 30 ± 8 years; body weight, 76 ± 8 kg; and height, 1.81 ± 0.04 m. The two panels were matched for age (±2 years) and body weight (±20%). The study was approved by the ethics committee of Huddinge University Hospital, and each volunteer gave witnessed verbal informed consent before the study.

Study design. Volunteers received 4 mg oral tolterodine twice a day for 8 days, followed by a single intravenous infusion of 1.8 mg tolterodine for 30 minutes after a washout period (at least 7 days). Doses of tolterodine are given as the tartrate salt. Each volunteer fasted overnight before the first (day 1) and last (day 8) days of oral administration of tolterodine and before the intravenous infusion. Smoking and consumption of alcohol and caffeine-containing beverages were prohibited the day before dosing and for 24 hours afterward.

Assessment. On days 1 and 8, venous blood samples were taken before administration of tolterodine; at 10, 20, 30, and 45 minutes; and at 1, 1½, 2, 4, 6, 8, 10, 12, and 24 hours (24 hours on day 8 only) after administration. Among poor metabolizers, the 6- and 10-hour samples were changed to 32 and 48 hours on day 8. Blood samples were obtained before the start of the intravenous infusion; at 5, 10, 20, and 30 minutes during the infusion; and at 5, 10, 20, 30 minutes and 1, 2, 4, 6, 8, 10, and 12 hours after termination of the infusion. The 6- and 10-hour samples were replaced by samples at 24 and 26 hours among poor metabolizers. Urine was collected during the last interval of oral administration (0 to 12 hours) and after the intravenous infusion.

One day before drug administration, baseline recordings of pharmacodynamic measurements (heart rate, supine blood pressure, visual accommodation, and salivation) were performed for 8 hours. Heart rate and blood pressure were measured twice before tolterodine administration and repeated in connection with blood sampling. Recordings were performed simultaneously with an automatic, noninvasive, digital blood pressure meter (UA-751; A & D Company Ltd., Tokyo, Japan). An electrocardiogram was obtained, and near point of vision and salivation were measured twice before tolterodine administration on days 1 and 8 and at 10 and 30 minutes and 1, 2, 4, 8, and 12 hours after drug administration. Recordings also were obtained before infusion; at 30 minutes during infusion; and at ½, 4, 8, and 12 hours after cessation of the infusion.

Electrophysiologic measurements were obtained with a computerized 12-lead electrocardiograph (Megacart; Siemens Elema, Solna, Sweden), and QT, QT_c, PQ, and QRS duration were calculated automatically. Near point of vision was determined according to the Royal Air Force near-point rule by means of a convergence meter (Clement Clarke, International Ltd., Harlow, England). Basal whole-mouth salivation was measured by means of absorption into three preweighed cotton rolls[14] (Celluron; Hartmann, Heidenheim-Brentz, Germany).

Adverse events were assessed by means of spontaneous reports,observation, and questioning at regular intervals. The intensity of the adverse event was rated on a three-point scale (mild, moderate, or severe) by a research clinician. Laboratory values were assessed before and at the end of the study, and vital signs data were screened for trends.

Analytical method. Determination of tolterodine and 5-HM levels in blood, serum, and urine was performed with a specific and sensitive capillary gas chromatography–mass spectrometry assay.[15] Extraction of the analytes was performed with liquid-liquid or solid-phase extraction before derivation with a silyl-reagent. The derivatives were quantified by means of selected ion-monitoring mass spectrometry with deuterium-labeled internal standards and a single-level calibration curve. With this technique the accuracy (interday and intraday) for both analytes was within 87% to 110% over the range from 0.90 to 210 nmol/L. Precision was better than 9%. Urinary concentrations of tolterodine and 5-HM also were assessed after incubation of samples with β-glucuronidase (Boehringer Mannheim, GmbH, Mannheim, Germany).

Data analysis. All data are expressed as mean ± SD, except when indicated otherwise. In the regression analysis of tolterodine data (performed with PCNONLIN [version 4.1][16]), equations 1 and 2[17] were fitted simultaneously to intravenous and oral data, as follows:

$$C_{iv} = \frac{R_{inf}}{V_c} \sum_{i=1}^{n} \left[\frac{C_i}{-\lambda_i} \cdot \left(1 - e^{\lambda_i \cdot T}\right) \cdot e^{-\lambda_i \cdot t'} \right] \quad (1)$$

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

in which R_{inf} is the infusion rate, V_c is the apparent volume of the central compartment, n is the number of exponential terms, C_i is the fractional intercept, λ_i is the corresponding rate constant, t is time, and T is time during the infusion and then becomes a constant, t_{inf} (duration of infusion), after the cessation of the infusion, k_a is the absorption rate constant, and F is the extent of bioavailability. A weighting scheme of $1/\hat{c}^2$, in which a constant relative error is assumed, gave the overall best fit. The choice of model was made with respect to residual plots and parameters precision. A lag-time (t_{lag}) was included for oral data. The volume of distribution at steady state (V_{ss}), systemic clearance (CL), bioavailability (F), and elimination half-life ($t_{½\beta}$) were estimated

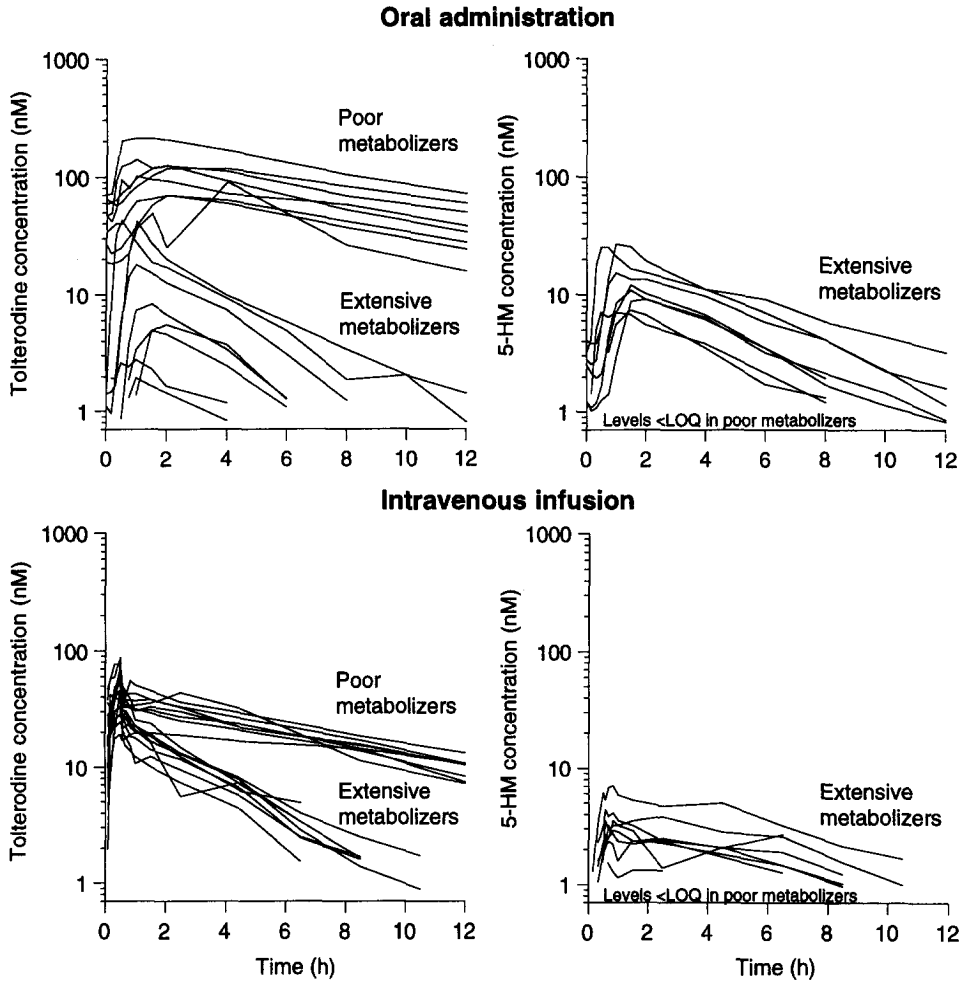

Fig. 2. Serum concentration–time profiles of tolterodine and the 5-hydroxymethyl metabolite (5-HM) after oral administration of 4 mg tolterodine tartrate twice a day **(top panel)** and intravenous infusion of 1.8 mg tolterodine tartrate **(bottom panel)** for extensive metabolizers ($n = 8$) and poor metabolizers ($n = 8$).

according to standard equations.[17,18] Noncompartmental analysis of tolterodine and 5-HM data was performed to determine the metabolite–parent compound ratio for area under the serum concentration–time curve (AUC) and terminal half-life ($t_{½z}$) of 5-HM. The AUC was obtained by means of linear trapezoidal rule[17] with extrapolation to infinity by means of division of the last calculated data point by the terminal slope (λ_z) derived from the 2- to 24-hour interval. Statistical analysis for pharmacokinetic variables was performed with the Student t test for unpaired data. Differences were considered to be significant at $p < 0.05$.

The pharmacologic effect of tolterodine on salivation was expressed as the area under the effect curve for the first 8 hours (AUEC) and computed according to the linear trapezoidal rule. In the concentration-effect relation, the effect was transformed by use of the relative change from the baseline values computed as follows:

$$E = \frac{E_i - E_{0,i}}{E_{0,i}}$$

in which E_i is the value of the salivary effect at time i, and $E_{0,i}$ is the corresponding value at baseline.

RESULTS

Pharmacokinetics. The individual serum concentration–time profiles of tolterodine and 5-HM at steady state (oral) and after intravenous infusion are shown in Fig 2. There was a distinct difference in serum tolterodine con-

Table I. Pharmacokinetic parameters of tolterodine after simultaneous fit of oral multiple-dose data (4 mg twice daily) and intravenous infusion data (1.8 mg) after administration of tolterodine to extensive and poor metabolizers

Volunteer No.	t_{lag} *(hr)*	t_{max} *(hr)*	C_{max} *(nmol/L)*	*F (%)*	V_{SS} *(L)*	*CL (L/hr)*	$t_{½\beta}$ *(hr)*
Extensive metabolizers							
1	0.36	1.0	18 (5.9)	27	89	35	1.9
2	0.63	1.0	1.9 (0.63)	40	158	53	2.1
3	0.27	0.5	43 (14)	58	135	33	3.6
4	1.0	2.0	5.5 (1.8)	11	134	40	2.4
11	0.49	1.5	8.3 (2.7)	13	101	41	1.9
12	0.72	1.5	4.9 (1.6)	15	154	69	1.8
15	0.49	1.0	43 (14)	40	90	31	2.6
16	0.10	1.0	2.8 (0.90)	6.8	147	52	2.4
Mean	0.51	1.2	16 (5.2)	26	126	44	2.3
SD	0.28	0.5	17 (5.7)	18	28	13	0.6
Poor metabolizers							
5	0.30	2.0	71 (23)	89	181	13	9.9
6	0.30	2.0	123 (40)	99	110	8.1	10
7	0.31	4.0	89 (29)	48	102	9.7	7.5
8	0.30	1.0	101 (33)	75	111	7.7	10
9	0.33	1.0	212 (69)	170	104	8.9	8.2
10	0.75	2.0	117 (38)	77	87	5.9	11
13	0.29	1.0	141 (46)	120	118	10	8.3
14	0.74	2.0	71 (23)	49	110	8.6	9.0
Mean	0.42	1.9	116* (38)	91†	115	9.0*	9.2*
SD	0.20	1.0	46 (15)	40	28	2.1	1.2

Values in parentheses are micrograms per liter.
CL, Systemic clearance; C_{max}, peak serum concentration; F, absolute bioavailability; t_{lag}, lag-time; t_{max}, time to reach C_{max}; $t_{½\beta}$, elimination half-life; V_{SS}, volume of distribution at steady state.
*$p < 0.001$ versus extensive metabolizers.
†$p < 0.002$ versus extensive metabolizers.

Table II. Pharmacokinetic values of 5-HM after oral administration (4 mg twice daily) and metabolic ratios of tolterodine among extensive metabolizers

				$AUC_{tolterodine}/AUC_{5\text{-}HM}$		
Volunteer No.	t_{max} *(hr)*	C_{max} *(nmol/L)*	$t_{½z}$ *(hr)*	*Single dose*	*Steady state*	*Infusion*
1	1.0	15 (5.2)	3.0	0.84	0.78	3.3
2	1.5	7.3 (2.5)	2.5	ND	0.24	3.4
3	0.5	25 (8.6)	3.0	0.94	0.99	3.4
4	2.0	9.1 (3.1)	3.0	0.51	0.49	ND
11	1.5	11 (3.7)	2.7	0.68	0.59	4.4
12	1.5	12 (4.1)	2.5	0.50	0.37	2.6
15	1.0	27 (9.1)	3.7	1.1	0.89	2.3
16	0.5	7.0 (2.4)	2.7	0.16	0.32	3.2
Mean	1.2	14 (4.8)	2.9	0.59	0.58	3.3
SD	0.5	7.7 (2.6)	0.4	0.38	0.28	0.67

Values in parentheses are micrograms per liter.
AUC, Area under the serum concentration–time curve; t_{max}, time to reach C_{max}; C_{max}, peak serum concentration; $t_{½z}$, terminal half-life associated with the terminal slope (λ_z) of the semilogarithmic serum concentration–time curve; ND, not determined.

centrations between the panels of the extensive metabolizers and those of the poor metabolizers. The 5-HM levels for extensive metabolizers were similar to those of tolterodine, but 5-HM was not quantifiable among poor metabolizers. The pharmacokinetic parameters of tolterodine are given in Table I. Tolterodine was rapidly absorbed. Absorption half-life was 0.41 ± 0.23 hour among extensive metabolizers and 0.53 ± 0.40 hour

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