

## BIOTRANSFORMATION OF TOLTERODINE, A NEW MUSCARINIC RECEPTOR ANTAGONIST, IN MICE, RATS, AND DOGS

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### ABSTRACT:

Tolterodine is a new muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and other symptoms associated with an overactive bladder. The *in vivo* metabolism of  $^{14}\text{C}$ -labeled tolterodine was investigated in rats, mice, and dogs by analysis of blood and urine samples, whereas *in vitro* metabolism studies were performed by incubation of [ $^{14}\text{C}$ ]tolterodine with mouse, rat, dog, and human liver microsomes in the presence of NADPH. Tolterodine was extensively metabolized *in vivo*. Mice and dogs showed similar metabolite patterns, which correlated well with that observed in humans. In these species, tolterodine was metabolized along two different pathways, with the more important being the stepwise oxidation of the 5-methyl group to yield the 5-hydroxymethyl metabolite of tolterodine and then, *via* the aldehyde, the 5-carboxylic acid metabolite. The other pathway involved dealkylation of the nitrogen. In the subsequent phase II metabolism, tolterodine and the metabolites were conjugated with glu-

ronic acid to various degrees. Rats exhibited more extensive metabolism and a markedly different metabolite pattern, with metabolites also being formed by hydroxylation of the unsubstituted benzene ring. In addition, a gender difference was observed, with male rats showing more extensive metabolism than females. Incubation of [ $^{14}\text{C}$ ]tolterodine with liver microsomes yielded a total of five metabolites with rat liver microsomes and three with mouse, dog, and human liver microsomes. The 5-hydroxymethyl metabolite of tolterodine and *N*-dealkylated tolterodine were major metabolites in all incubations, representing 83–99% of total metabolism. Although the extent of metabolism varied among species, the metabolic profiles were similar. However, rat liver microsomes also formed metabolites hydroxylated in the unsubstituted benzene ring. These results show that the metabolism of tolterodine in mice and dogs corresponds to that observed in humans, whereas rats exhibit a different metabolite pattern.

Tolterodine [(*R*)-*N,N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-phenylpropanamine] is a new muscarinic receptor antagonist that was specifically developed for the treatment of urinary urge incontinence and other symptoms associated with an overactive bladder. Treatment of an overactive bladder is primarily based on the use of muscarinic receptor antagonists, *e.g.* propantheline, emepronium, and oxybutynin (Andersson, 1988; Wein *et al.*, 1994), and oxybutynin is currently considered to be the drug of choice for the treatment of such symptoms (Yarker *et al.*, 1995). Although the efficacy of oxybutynin has been well demonstrated, the occurrence of classic antimuscarinic adverse events (*e.g.* dry mouth) often leads to discontinuation of treatment (Cardozo *et al.*, 1987). Tolterodine is characterized by favorable tissue selectivity for the urinary bladder over salivary glands (Nilvebrant *et al.*, 1997).

The pharmacokinetic profile of tolterodine after oral administration to humans is characterized by rapid absorption and a terminal half-life of 2–3 hr. The excretion of drug-related substances in urine and feces was 77 and 17% of the administered dose, respectively (Brynne *et al.*, 1997). After oral administration of  $^{14}\text{C}$ -labeled tolterodine to mice and dogs, approximately equal amounts of radioactivity were recovered in the urine and feces, whereas rats excreted 80% of the administered radioactivity in the feces. The terminal half-life of tolterodine was approximately 2 hr in these species (Kankaanranta and Pählman,

1997). In the present study, the metabolism of [ $^{14}\text{C}$ ]tolterodine was investigated by characterization of the biotransformation products formed *in vivo* by mice, rats, and dogs and *in vitro* by liver microsomes from these species and humans.

### Materials and Methods

**Chemicals.** [ $^{14}\text{C}$ ]Tolterodine (labeled at the benzylic methyl group) (fig. 1), tolterodine (PNU-200583), 5-HM<sup>1</sup> [(*R*)-*N,N*-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)phenylpropanamine, PNU-200577, labcode DD 01], 5-CM (PNU-200579), and *N*-dealkylated tolterodine (PNU-200578) were synthesized at Pharmacia & Upjohn AB (Uppsala, Sweden).  $\beta$ -Glucuronidase (*Escherichia coli*, product no. 127051) was obtained from Boehringer Mannheim (Mannheim, Germany) and arylsulfatase (*Aerobacter aerogenes*, product no. S1629) from Sigma Chemical Co. (St. Louis, MO). All other chemicals were of reagent grade and were obtained from usual commercial sources.

***In Vivo* Experiments.** *Dogs.* Six beagle dogs (three male and three female) were each administered an oral dose of 1.5 mg/kg [ $^{14}\text{C}$ ]tolterodine (4.2 MBq/mg) and an iv dose of 1.0 mg/kg [ $^{14}\text{C}$ ]tolterodine. Blood samples were collected at 1 hr after the oral dose and at 20 min after the iv dose. Serum was prepared by allowing the blood to coagulate for 30 min, followed by centrifugation at 1200g for 10 min. Urine was collected cumulatively at 0–8 hr and 8–24 hr after administration of the oral and iv doses.

*Mice.* Male and female mice (CD-1 strain) were each administered a single oral dose of 4 or 40 mg/kg [ $^{14}\text{C}$ ]tolterodine (4.2 MBq/mg). Blood from the orbital plexus was collected into heparinized tubes 15 min after drug admin-

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<sup>1</sup> Abbreviations used are: 5-HM, 5-hydroxymethyl metabolite of tolterodine;

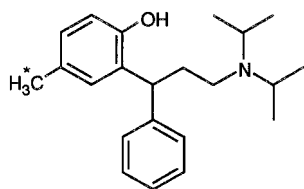


FIG. 1. Chemical structure of tolterodine.

\*, position of the radiolabel.

istration. Samples from five mice in each group were pooled and centrifuged to prepare plasma, which was immediately stored at  $-20^{\circ}\text{C}$  until analysis.

Urine was collected in separate experiments in which mice were administered a single oral dose of 4 mg/kg [ $^{14}\text{C}$ ]tolterodine (0.6 MBq/mg). Animals were subsequently placed in individual metabolism cages and urine was collected at 0–6 hr and 6–24 hr, in containers surrounded by solid carbon dioxide.

**Rats.** Four Sprague-Dawley rats (two male and two female) were placed in individual metabolism cages and administered an oral dose of 50 mg/kg [ $^{14}\text{C}$ ]tolterodine (0.2 MBq/mg). Urine was collected at 0–12 hr and 12–24 hr after dosing. All urine samples were stored at  $-20^{\circ}\text{C}$  until analysis.

**In Vivo Sample Preparation. Urine.** Dog urine was centrifuged and analyzed directly. Urine from mice was centrifuged, and metabolites were extracted by solid-phase extraction using a Supelco Visoprep SPE vacuum manifold and Isolute  $\text{C}_{18}$ (EC), 1-g, 6-ml cartridges that had been sequentially conditioned with methanol and 20 mM ammonium acetate (pH 4.5). Urine (3 ml) was applied, and the cartridges were washed with 2 ml of 20 mM ammonium acetate (pH 4.5). Metabolites were eluted with 2 ml of methanol/20 mM ammonium acetate (pH 4.5) (80:20, v/v). The eluate was evaporated to dryness and then diluted in 30  $\mu\text{l}$  of methanol and 270  $\mu\text{l}$  of 20 mM ammonium acetate (pH 4.5). The extraction yield was 98–100%.

Hydrolysis of conjugated metabolites in rat urine was performed by incubation of urine samples (450  $\mu\text{l}$ ) with 450  $\mu\text{l}$  of 0.1 M ammonium acetate (pH 5.5) and either 20  $\mu\text{l}$  of  $\beta$ -glucuronidase or 30  $\mu\text{l}$  of arylsulfatase, for 16 hr at  $37^{\circ}\text{C}$ . The hydrolyzed metabolites were extracted with Sep-Pak PLUS  $\text{C}_8$ , 125- $\text{\AA}$ , solid-phase cartridges, which were conditioned before use by the sequential passing of 5 ml of methanol and 5 ml of 20 mM ammonium acetate (pH 4.5) through the cartridges. Urine was applied, the cartridges were washed with 4 ml of 0.1 M ammonium acetate (pH 5.5)/methanol (95:5, v/v), and metabolites were eluted with 3 ml of methanol/0.1 M ammonium acetate (pH 5.5) (50:50, v/v). The extract was evaporated to dryness and dissolved in 400  $\mu\text{l}$  of 20 mM ammonium acetate (pH 4.5) before analysis.

**Plasma and Serum.** The plasma and serum samples were treated with acetone (2 times the sample volume) and centrifuged to precipitate proteins. The supernatants were transferred to new vials, and the pellets were washed twice with aliquots of acetone/20 mM ammonium acetate (pH 4.5) (1:1, v/v). The combined supernatant and pellet extract was evaporated to dryness and dissolved in 20 mM ammonium acetate (pH 4.5) containing 10% methanol. The extraction yield was  $101 \pm 11\%$  (mean  $\pm$  SD).

**In Vitro Experiments. Preparation of Microsomes from Mouse, Rat, and Dog Liver.** Livers from untreated male mice (CD-1 strain), male Sprague-Dawley rats, and male Beagle dogs were used. The microsomal fraction was prepared from a 20% (w/v) liver homogenate in 0.25 M sucrose containing 1 mM EDTA and 10 mM Tris-HCl buffer (pH 7.4). The homogenate was centrifuged at 20,000g for 20 min, and the resulting supernatant was then centrifuged at 100,000g for 60 min. The microsomal pellet was suspended in one half the original volume of 0.1 M potassium pyrophosphate buffer (pH 7.4) with 1 mM EDTA, homogenized, and centrifuged at 100,000g for 60 min. The resulting microsomal pellet was subsequently suspended and homogenized in 100 mM potassium phosphate buffer (pH 7.4) containing 20% glycerol and 0.1 mM EDTA, to a total volume of 0.5–1 ml/g of liver. Microsomes were immediately stored at  $-70^{\circ}\text{C}$ . During the preparation procedure, the temperature was maintained as close to  $+4^{\circ}\text{C}$  as possible.

**Protein Determination.** The protein content of microsomal fractions was determined as described by Lowry *et al.* (1951), using bovine serum albumin as the standard. The measured protein concentrations in the liver microsomes

**Human Liver Microsomes.** Human liver microsomes were obtained from Human Biologics, Inc. (Phoenix, AZ). Microsomes were prepared from five frozen liver samples. Approximately equal amounts of microsomal protein from the samples were pooled, and the protein concentration was determined to be 20 mg/ml, as described by Lowry *et al.* (1951). Microsomes were stored at  $-70^{\circ}\text{C}$  until use in the incubation experiments.

**Incubations.** For each species, incubations were performed in triplicate. The incubation mixtures contained 100 mM potassium phosphate buffer (pH 7.4), 1 mM NADPH, 50  $\mu\text{g}$  of [ $^{14}\text{C}$ ]tolterodine, and 1 mg of liver microsomal protein, in a final volume of 1 ml. The reaction was started by the addition of 25  $\mu\text{l}$  of an aqueous solution of [ $^{14}\text{C}$ ]tolterodine, to yield a final concentration of 154  $\mu\text{M}$ . The incubations were performed at  $37^{\circ}\text{C}$  for 60 min and were terminated by the addition of 1 ml of acetone. Control incubations in which NADPH was omitted were performed as described above. The samples were stored at  $-20^{\circ}\text{C}$  for at least 1 hr before analysis. Before analysis, microsomal protein was precipitated by centrifugation at room temperature, and the acetone was evaporated with a stream of nitrogen at  $37^{\circ}\text{C}$ . A 200- $\mu\text{l}$  aliquot of the remaining supernatant from each incubation was analyzed.

**Analysis. HPLC Analysis.** Quantification of the *in vitro* incubation products was performed by HPLC using two LKB 2150 pumps, an LKB 2152 LC controller, a Beckman 171 radioisotope detector, a Beckman 110B solvent-diluting module, a Supelco PKB 100 (2-cm) precolumn, and a Supelco PKB 100 (150- $\times$  4.5-mm) column. The mobile phase was 20 mM ammonium acetate (pH 4.5) in methanol. The solvent flow rate was 1 ml/min, and a gradient of decreasing polarity (0 min, 10% methanol; 5 min, 20% methanol; 35 min, 45% methanol; 40 min, 100% methanol; 50 min, 100% methanol) was used.

**MS.** Metabolic profiles and mass spectra of the metabolites in the *in vivo* samples from mice and dogs and from *in vitro* incubations were obtained by analysis by HPLC coupled to electrospray-ionization MS. The system consisted of an autosampler and a quaternary pump (HP1050; Hewlett-Packard) connected to a Supelco PKB 100 (2-cm) precolumn and a Supelco PKB 100 (150- $\times$  4.5-mm) column. A stream splitter diverted approximately 80% of the flow to a UV detector (Pharmacia UV-M monitor, set at 280 nm) coupled to a radioactivity detector (Packard Radiomatic A525) and 20% to a triple-stage quadrupole mass spectrometer equipped with an electrospray-ionization interface (TSQ 700; Finnigan MAT). The solvent flow rate was set to 1 ml/min, and the mobile phase and gradient described above were used. Aliquots of 100  $\mu\text{l}$  were analyzed. The sheath gas was set to 80 psi, and the electrospray voltage and capillary temperature were 4.5 kV and  $200^{\circ}\text{C}$ , respectively.

Rat urine, hydrolyzed by  $\beta$ -glucuronidase, was fractionated by the HPLC method used for the *in vitro* samples. Collected fractions were evaporated and fractionated using a second HPLC system with a Zorbax SB-CN guard column (12.5  $\times$  4 mm) and a Zorbax SB-CN column (150  $\times$  4.6 mm). The gradient was as follows: 0 min, 10% methanol; 20 min, 50% methanol; 25 min, 100% methanol.

Metabolites in the HPLC fractions of rat urine were analyzed by GC/MS, as trimethylsilyl derivatives, after treatment with 50  $\mu\text{l}$  of *N,O*-bis(trimethylsilyl)trifluoroacetamide overnight. Mass spectra of the trimethylsilyl-derivatized metabolites were obtained using an HP5890A gas chromatograph connected to a TSQ 70 mass spectrometer with electron impact ionization at 70 eV. The gas chromatograph was equipped with an on-column injector and a DB-1 capillary column (15 m  $\times$  0.32 mm; film thickness, 0.25  $\mu\text{m}$ ). One-microliter aliquots of the derivatization mixture were injected, and the column temperature was maintained at  $110^{\circ}\text{C}$  for 1 min after injection and then increased to  $290^{\circ}\text{C}$  in 7 min. The mass spectrometer was scanned between 35 and 700 amu, with a cycle time of 0.7 sec.

## Results

**Dog Urine.** The general appearance of the radiochromatograms, with respect to the relative concentrations of the metabolites, did not reveal any obvious intraindividual or gender differences. However, the total amount of radioactivity recovered in the urine samples did vary. Fig. 2a shows a typical radiochromatogram of urine collected at 0–8 hr after a 1.5 mg/kg oral dose. The chromatogram contained major metabolite peaks at retention times of 15–16 min and 18–20

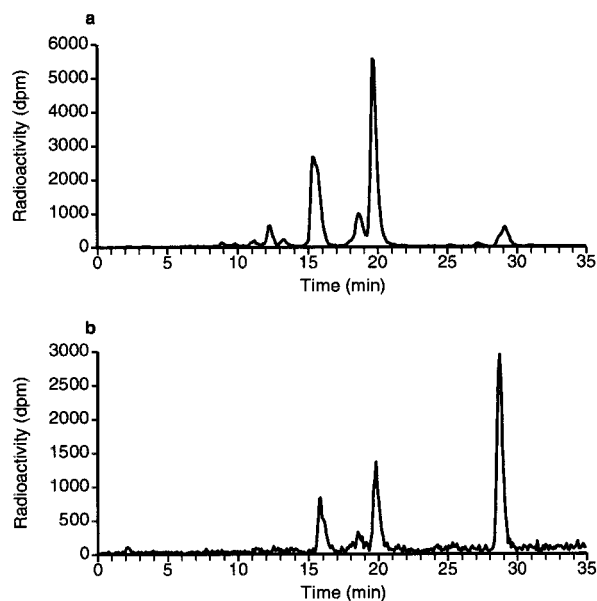


FIG. 2. Radiochromatograms of urine collected at 0–8 hr (a) and serum collected at 1 hr (b) after oral administration of [ $^{14}\text{C}$ ]tolterodine (1.5 mg/kg) to a female dog.

Electrospray-ionization MS of metabolites showed prominent peaks corresponding to the protonated molecular ion ( $[\text{M}+\text{H}]^+$ ) for each metabolite and was useful in distinguishing the metabolites in the unresolved peaks at 15–16 min and 28–30 min. 5-HM, 5-CM, and *N*-dealkylated tolterodine metabolites were identified by comparing the retention times and product-ion mass spectra (obtained by collision-induced dissociation of the  $[\text{M}+\text{H}]^+$  ions) with those of the corresponding reference standards (figs. 3–5). The  $^{14}\text{C}$ -labeled fragment ions of the metabolites appeared 2 amu larger than the non-labeled fragment ions of the reference standards. The identities of most of the other metabolites were deduced from the fragmentation patterns of the product-ion mass spectra. Thus, the product-ion mass spectra of glucuronide conjugates contained peaks showing the loss of the glucuronide moiety ( $-176$  amu) and intense peaks identical to those of the product-ion mass spectra of the corresponding aglycon. Several key fragments in the mass spectra of the *N*-dealkylated metabolites were identical to those of metabolites that were not dealkylated (table 1). The proposed molecular structures of identified metabolites are summarized in fig. 6. The most abundant peak (19.7 min) in the urinary metabolic profile of dog urine represented 5-CM, with its corresponding glucuronide conjugate (18.7 min). The other major peaks, at 15–16 min, were not completely resolved and contained two metabolites, 5-HM and *N*-dealkylated 5-CM. These major metabolites constituted approximately 70–80% of the total radioactivity in the urine samples. The peak at 12.4 min was *N*-dealkylated 5-HM. The unresolved peaks at approximately 29 min contained intact tolterodine and its corresponding glucuronide conjugate. Trace amounts of 5-HM glucuronide and *N*-dealkylated tolterodine were also observed in some of the samples.

The metabolite pattern in urine from dogs that had received an iv dose of 1 mg/kg was similar to that observed after the 1.5 mg/kg oral dose. However, the concentration of intact tolterodine in urine was much higher after iv administration.

**Dog Serum.** The metabolite pattern observed in serum collected 1 hr after oral administration of 1.5 mg/kg contained three major peaks, at retention times of approximately 16, 20, and 29 min (fig. 2b). The peak at 16 min represented 5-HM and *N*-dealkylated 5-CM, whereas

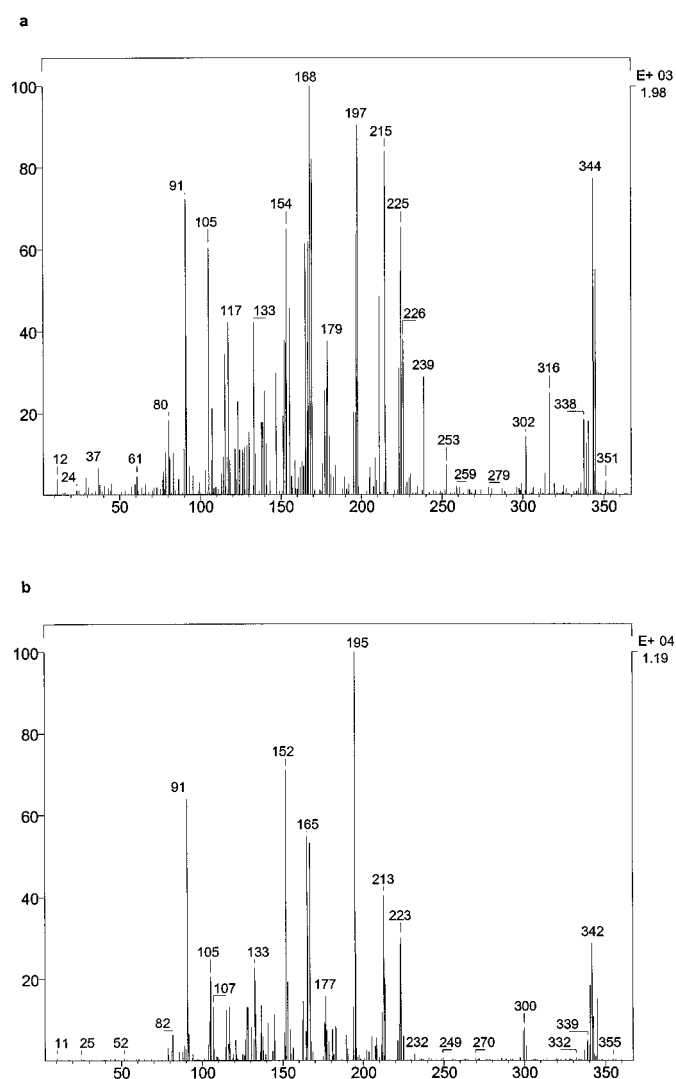


FIG. 3. Product-ion mass spectra of 5-HM (a) and the corresponding synthesized reference standard (b).

30–60% of the total radioactivity in serum samples. The most abundant peak (24–65% of total radioactivity), at a retention time of 29 min, corresponded to intact tolterodine. The 1 mg/kg iv dose yielded a metabolite pattern that exhibited a higher relative concentration of intact tolterodine but was otherwise similar to that observed after oral administration.

**Mouse Urine.** The major metabolites found in dog urine were also observed in mouse urine (fig. 7a), although the relative concentrations of *N*-dealkylated and conjugated metabolites were higher in mouse urine. The radiochromatogram of mouse urine collected at 0–6 hr after oral administration of 4 mg/kg [ $^{14}\text{C}$ ]tolterodine contained major peaks at retention times of 15–20 min, *i.e.* 5-CM and the corresponding glucuronide at 20 and 18 min, respectively, *N*-dealkylated 5-CM and 5-HM at 16 min, and *N*-dealkylated 5-HM glucuronide and a small amount of *N*-dealkylated 5-CM glucuronide at 15 min. The abundance of the  $[\text{M}+\text{H}]^+$  ion for *N*-dealkylated 5-CM glucuronide at 490 amu was too low to allow a product-ion mass spectrum to be obtained (table 1).

**Mouse Plasma.** The radiochromatograms for plasma samples collected from mice given the 4 mg/kg dose contained two major peaks (fig. 7b). The peaks with a retention time of 15–17 min contained

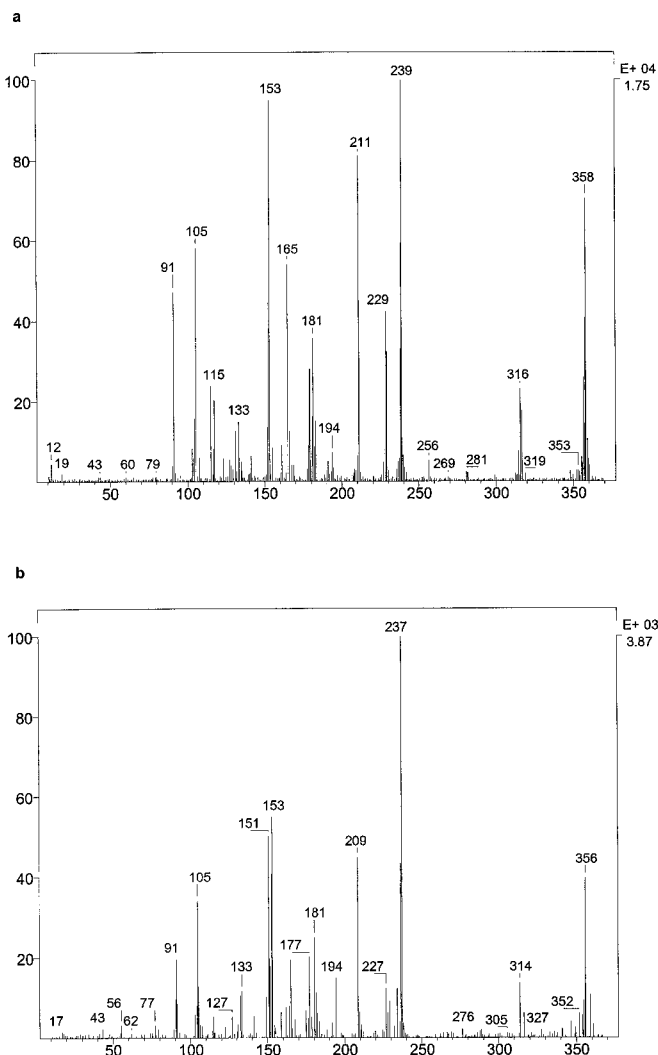


FIG. 4. Product-ion mass spectra of 5-CM (a) and the corresponding synthesized reference standard (b).

nide, and *N*-dealkylated 5-CM. The other major peak corresponded to 5-CM glucuronide. Minor peaks identified represented *N*-dealkylated tolterodine and the corresponding glucuronide and intact tolterodine, at retention times of 27, 29.5, and 30.5 min, respectively. After an oral dose of 40 mg/kg, the relative concentrations of the metabolites in the radiochromatograms were clearly different, in comparison with the metabolic profile after the lower dose. The concentrations of intact tolterodine and *N*-dealkylated tolterodine, together with its glucuronide conjugate, were increased more than proportional to dose, together representing 11% of the radioactivity in plasma at the lower dose and 45% at the higher dose.

**Rat Urine.** The metabolic profile in urine collected at 0–12 hr from rats that had received an oral dose of 50 mg/kg differed from that for dogs and mice. In addition to small amounts of metabolites formed by dealkylation and oxidation of the 5-methyl group, rat urine contained several more-polar metabolites with short retention times (fig. 8). Urine was treated with either  $\beta$ -glucuronidase or arylsulfatase; only treatment with the former affected the appearance of the radiochromatogram. After hydrolysis of glucuronic acid conjugates, the metabolites were tentatively identified from retention times and mass spectra obtained by using GC/MS with trimethylsilyl derivatization. Trimethylsilyl derivatives were formed with the hydroxy and deal-

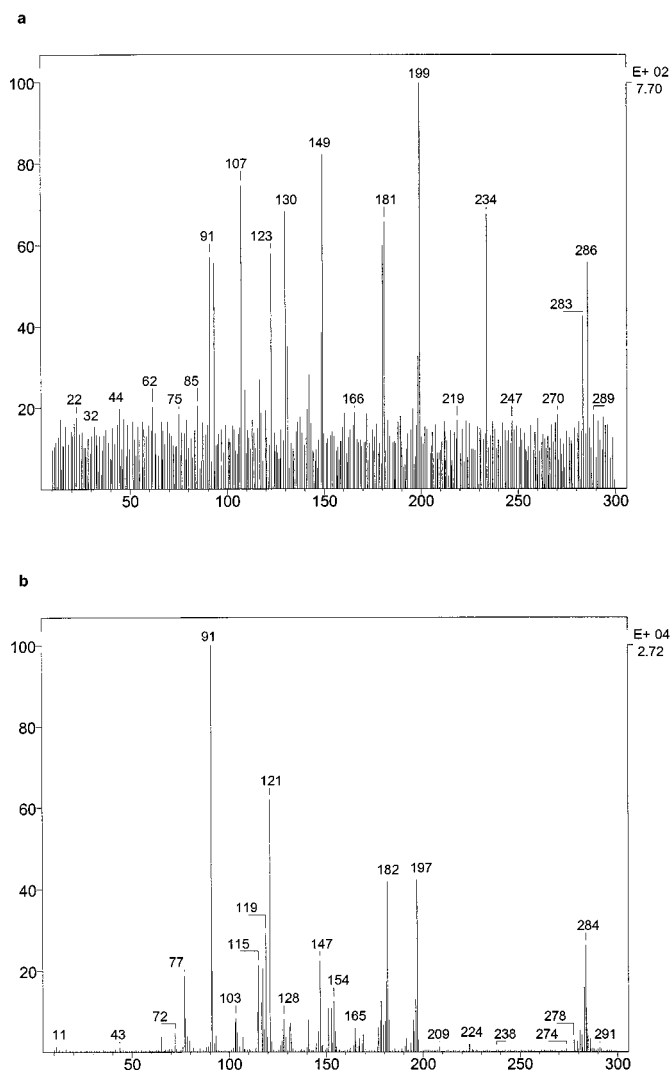


FIG. 5. Product-ion mass spectra of *N*-dealkylated tolterodine (a) and the corresponding synthesized reference standard (b).

ments of the nitrogen moiety and of the diphenyl cation from cleavage of the aliphatic side chain, which facilitated the determination of *N*-dealkylation and hydroxylation in the diphenyl moiety. These rat-specific metabolites were most likely formed by mono- and dihydroxylation of the unsubstituted benzene ring. Three of the metabolites also contained a methoxy group. However, it was not possible to determine the exact sites of hydroxylation from these data. The key MS fragments and tentatively assigned metabolite structures are summarized in table 2. A gender difference was also observed, with urine from male rats containing relatively higher concentrations of these metabolites.

**In Vitro Studies.** Liver microsomes from mice, rats, dogs, and humans converted [ $^{14}$ C]tolterodine into several products in the presence of NADPH. Five metabolites were detected in the radiochromatograms for incubations with rat liver microsomes and three for those with mouse, dog, and human liver microsomes. The major metabolites of [ $^{14}$ C]tolterodine were identified by comparison of their chromatographic retention times with those of reference standards and/or by MS.

Table 3 shows the chromatographic retention times and the protonated molecular ions from the MS analyses, as well as the rates of

TABLE 1

Summary of key MS fragmentation for tolterodine and its metabolites in dog and mouse urine after electrospray ionization and collision-induced dissociation

Metabolite	[M+H] <sup>+</sup>	CID <sup>a</sup> Fragments
Tolterodine	328	286, 199, 182, 149, 123, 91
5-HM	344	302, 225, 215, 197, 154, 133, 105, 91
5-CM	358	316, 239, 229, 211, 194, 181, 165, 153, 133, 105, 91
<i>N</i> -Dealkylated tolterodine	286	199, 181, 149, 123, 91
<i>N</i> -Dealkylated 5-HM	300	223, 213, 195, 177, 165, 167, 152, 133, 105, 91
<i>N</i> -Dealkylated 5-CM	316	239, 229, 211, 181, 165, 153, 133, 105, 91
Tolterodine glucuronide	504	328, 286, 199, 182, 149
5-HM glucuronide	518	342, 233, 213, 195
5-CM glucuronide	534	358, 316, 239, 229, 211, 179, 153
<i>N</i> -Dealkylated tolterodine glucuronide	460	284, 196, 147, 119
<i>N</i> -Dealkylated 5-HM glucuronide	476	213, 167
<i>N</i> -Dealkylated 5-CM glucuronide	490	

<sup>a</sup> CID, collision-induced dissociation.

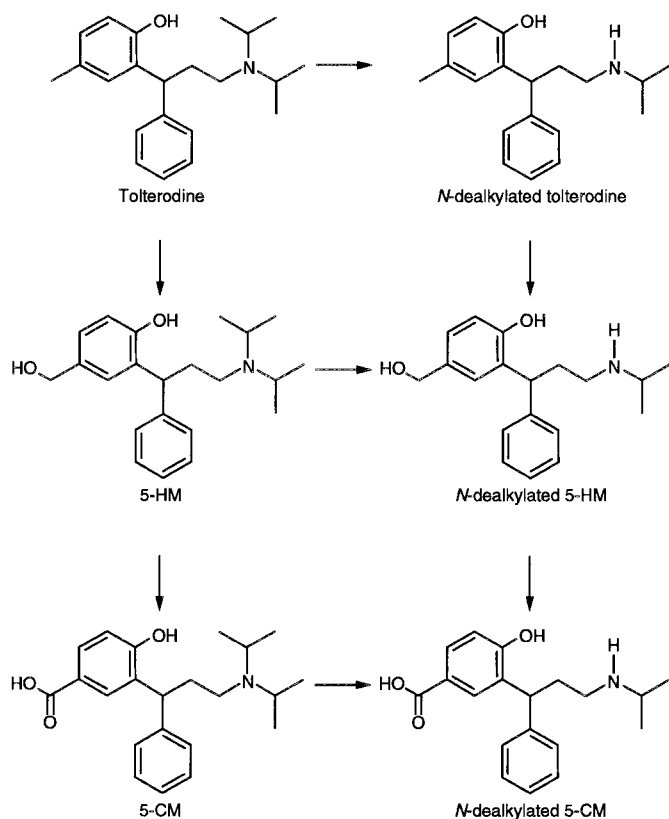


FIG. 6. Metabolic pathway of tolterodine in mice (given 4 mg/kg orally) and dogs (given 1.5 mg/kg orally or 1 mg/kg iv).

major metabolites in all species. Although considerable interspecies differences in the extent of metabolism were apparent, the metabolic profiles were similar. In mice, 5-HM and *N*-dealkylated tolterodine represented approximately 20 and 64% of total metabolism, respectively. One minor product, *N*-dealkylated 5-HM, was also detected. In rats, three major metabolites were formed, *i.e.* 5-HM, didealkylated tolterodine, and *N*-dealkylated tolterodine, representing approximately 5, 11, and 78% of total metabolism, respectively. Minor metabolites included a dihydroxylated product, *N*-dealkylated 5-HM,

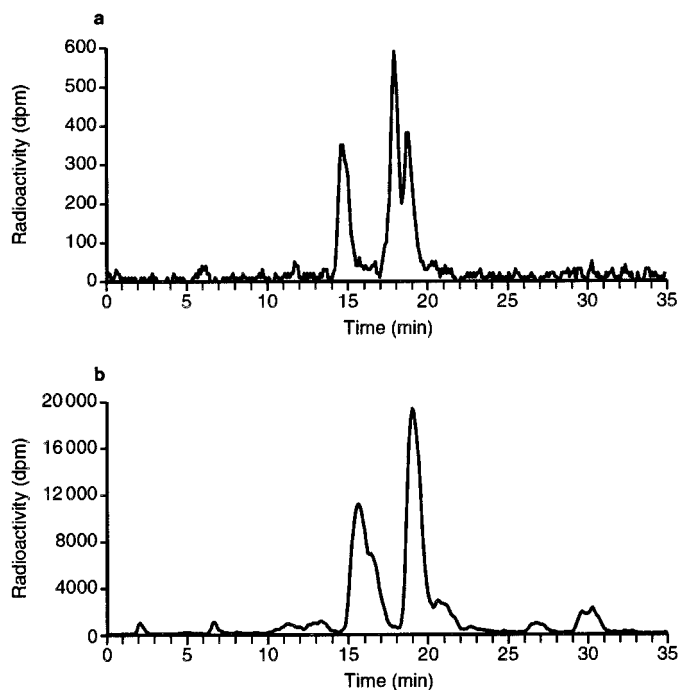


FIG. 7. Radiochromatograms of urine collected at 0–6 hr (a) and plasma collected at 15 min (b) after oral administration of [<sup>14</sup>C]tolterodine (4 mg/kg) to mice.

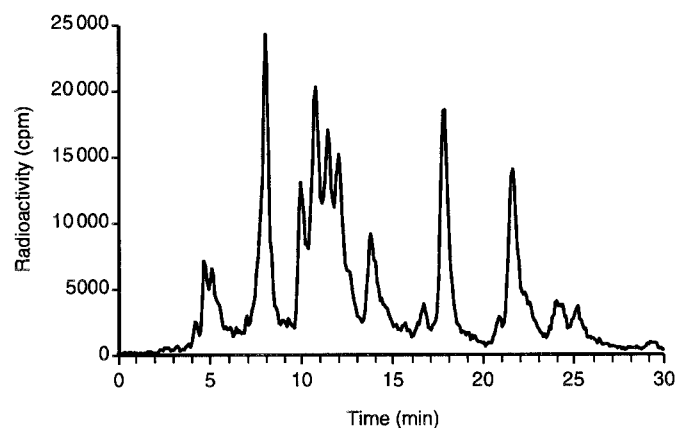


FIG. 8. Radiochromatogram of urine collected at 0–12 hr after oral administration of [<sup>14</sup>C]tolterodine (50 mg/kg) to a rat.

which together represented about 6% of total metabolism. The dihydroxylated product and the product hydroxylated in the unsubstituted benzene ring were detected only in incubations with rat liver microsomes. In dogs and humans, 5-HM represented approximately 39 and 21% and *N*-dealkylated tolterodine represented approximately 47 and 71% of total metabolism, respectively. One minor product, *N*-dealkylated 5-HM, was detected in both species.

## Discussion

Tolterodine is extensively metabolized and similar metabolic profiles were obtained for urine and plasma after oral and iv administration to mice and dogs, indicating that biotransformation takes place predominantly in the liver. Biotransformation products were formed via two major pathways, *i.e.* oxidation of the 5-methyl group in the benzene ring and dealkylation of the nitrogen. Furthermore, conju-

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