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 14C-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 [14C]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 glucuronic 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 [14C]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, emepironium, 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 14C-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 Pålman, 1997). In the present study, the metabolism of [14C]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. [14C]Tolterodine (labeled at the benzylic methyl group) (fig. 1), tolterodine (PNU-200583), 5-HM1 [(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). β-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 [14C]tolterodine (4.2 MBq/mg) and an iv dose of 1.0 mg/kg [14C]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 [14C]tolterodine (4.2 MBq/mg). Blood from the orbital plexus was collected into heparinized tubes 15 min after drug admin-
**Human Liver Microsomes.** Human liver microsomes were obtained from Human Biologies, 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 −20°C until use in the incubation experiments.

**Plasma and Serum.** Human plasma and serum were obtained from a patient who died of myocardial infarction and examined by HPLC for the presence of tolterodine and its metabolites. Tolterodine was extracted from plasma and serum by solid-phase extraction using a Sep-Pak Plus C18 column (Waters Associates, Milford, MA). The extract was evaporated to dryness and then dissolved in 30 μl of methanol.

**Metabolite Identification.** Metabolites were identified by comparison of their retention times and mass spectra with those of authentic standards. Mass spectra of the metabolites were obtained by electron impact ionization at 70 eV using a Finnigan MAT TSQ 700 triple-stage quadrupole mass spectrometer equipped with an electrospray ionization interface. The solvent flow rate was set to 1 ml/min, and the mobile phase and gradient described above were used. Aliquots of 100 μl were analyzed. The sheath gas was set to 80 psi, and the electrospray voltage was 4.5 kV and 200°C, respectively.

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**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 min, and minor peaks were evident at 11–13 min and 28–30 min.
Electrospray-ionization MS of metabolites showed prominent peaks corresponding to the protonated molecular ion ([M+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 [M+H]⁺ ions) with those of the corresponding reference standards (figs. 3–5). The 14C-labeled fragment ions of the metabolites appeared 2 amu larger than the nonlabeled 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 the peak at 20 min represented 5-CM. These metabolites constituted 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 (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 [14C]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 [M+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 three different metabolites, i.e. 5-HM, N-dealkylated 5-HM glucuro-
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 β-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 dealkylated amino groups. The mass spectra contained diagnostic fragments 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 [14C]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 [14C]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 formation of metabolites. N-Dealkylated tolterodine and 5-HM were
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, and a metabolite hydroxylated in the unsubstituted benzene ring, 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, conjugates of both tolterodine and its metabolites were formed by glucu-
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ronidation. In contrast, rats also formed metabolites by oxidation of the unsubstituted benzene ring to form mono- and dihydroxylated metabolites, and the urinary metabolite pattern showed gender differences. The major metabolites in dogs and mice, 5-CM and N-dealkylated 5-CM, were not detected in rat urine. A possible cause of the different metabolite pattern in rats might be a metabolic switch resulting from the relatively high administered dose (50 mg/kg). However, mice given a similar dose (40 mg/kg) did not form metabolites by oxidation of the unsubstituted benzene ring. The metabolites containing vicinal diols were also methylated. Methylation is not unexpected and occurs mainly with phenols containing vicinal diols, e.g. catechols (Mulder, 1982) and metabolites of terodiline (Nørén et al., 1985). Terodiline has a molecular structure similar to that of tolterodine. Extensive metabolism and a gender difference are well documented in rats (Shapiro et al., 1995). In connection with toxicological studies, rats are a well-researched species and are often used as a primary species in preclinical safety evaluations during drug development. However, rats can be a poor choice in some situations. One such case is when rats metabolize and excrete the drug so extensively that relevant systemic levels of intact drug are difficult to maintain during toxicological studies. Another case is when the metabolite pattern in blood does not reflect that of humans as a result of more extensive metabolism; consequently, rats are not properly exposed to the drug and/or active metabolites, as are human subjects. General pharmacokinetic studies in rats have indeed shown that the systemic levels of tolterodine are very low, considering the administered dose (Kankaanranta and Påhlman, 1997). Furthermore, as a result of the different metabolic profile in rats, systemic levels of the pharmacologically active metabolite 5-HM are also very low. Rats were therefore excluded as a main species in the preclinical safety evaluation of tolterodine.

The metabolic profiles of mice and dogs showed similarities to those of human subjects (Brynée et al., 1997), and the major metabolites in the urine from these species were 5-CM and N-dealkylated 5-CM. The only phase II metabolites that were identified were glucuronides. The only phase II metabolites that were identified were glucuronides. The major metabolites in dogs and mice, 5-CM and N-dealkylated 5-CM, were not detected in rat urine. A possible cause of the different metabolite pattern in rats might be a metabolic switch resulting from the relatively high administered dose (50 mg/kg). However, mice given a similar dose (40 mg/kg) did not form metabolites by oxidation of the unsubstituted benzene ring. The metabolites containing vicinal diols were also methylated. Methylation is not unexpected and occurs mainly with phenols containing vicinal diols, e.g. catechols (Mulder, 1982) and metabolites of terodiline (Nørén et al., 1985). Terodiline has a molecular structure similar to that of tolterodine. Extensive metabolism and a gender difference are well documented in rats (Shapiro et al., 1995). In connection with toxicological studies, rats are a well-researched species and are often used as a primary species in preclinical safety evaluations during drug development. However, rats can be a poor choice in some situations. One such case is when rats metabolize and excrete the drug so extensively that relevant systemic levels of intact drug are difficult to maintain during toxicological studies. Another case is when the metabolite pattern in blood does not reflect that of humans as a result of more extensive metabolism; consequently, rats are not properly exposed to the drug and/or active metabolites, as are human subjects. General pharmacokinetic studies in rats have indeed shown that the systemic levels of tolterodine are very low, considering the administered dose (Kankaanranta and Påhlman, 1997). Furthermore, as a result of the different metabolic profile in rats, systemic levels of the pharmacologically active metabolite 5-HM are also very low. Rats were therefore excluded as a main species in the preclinical safety evaluation of tolterodine.

The metabolic profiles of mice and dogs showed similarities to those of human subjects (Brynée et al., 1997), and the major metabolites in the urine from these species were 5-CM and N-dealkylated 5-CM. The only phase II metabolites that were identified were glucuronides, and the concentrations of these were highest in mice. At higher doses in mice, the relative concentrations of intact tolterodine and N-dealkylated tolterodine were increased, whereas the concentrations of 5-HM and the acid metabolites were decreased, indicating dose-dependent biotransformation.

Recently, we reported that the formation of 5-HM and N-dealkylated tolterodine in humans is catalyzed by cytochrome P450 2D6 and 3A4, respectively (Postlind et al., 1998). Further biotransformation to the acid metabolites via the aldehydes is most likely catalyzed by alcohol and aldehyde dehydrogenases. However, the metabolic capacity of cytochrome P450 2D6 in humans is much lower, in comparison with the 3A4 isoenzyme (Shimada et al., 1994). A possible explanation for the altered metabolism observed with the higher oral dose in mice is therefore that the isoenzymes involved in the formation of 5-HM and the acid metabolites were saturated. Consequently, the relative concentrations of tolterodine and N-dealkylated tolterodine, as well as their glucuronide conjugates, were increased.

In vitro studies have become an increasingly important tool in pharmaceutical research (Chiu, 1993; Rodrigues, 1994). Subcellular fractions, slices, recombinant enzymes, and cell cultures are routinely used in the screening for candidate drugs, the selection of species for toxicological studies, and the prediction of the situation in humans. Although results obtained from the use of microsomes are limited, the data often yield a good representation of the in vivo situation, in terms of the major metabolic pathways in which cytochromes P450 are involved. Incubation of tolterodine with liver microsomes in vitro yielded a good qualitative prediction of in vivo metabolism, although the carboxylated metabolites were missing because of the lack of alcohol and aldehyde dehydrogenases in the microsomal system. Furthermore, the metabolites formed in incubations with liver microsomes from mice and dogs were very similar to those observed with human microsomes, which is in accordance with the results from in vivo studies.

In conclusion, the metabolism of tolterodine was extensive. Mice and dogs showed similar metabolite patterns, which correlated with that observed for humans. Tolterodine was metabolized along two different pathways in these species, with the more important being the stepwise oxidation of the 5-methyl group attached to the benzene ring to yield 5-HM and then, via the aldehyde, 5-CM. The other pathway involved dealkylation of the nitrogen. In the subsequent phase II metabolism, tolterodine and the metabolites were conjugated with glucuronic acid to various degrees. Rats exhibited a different metabolic profile, with metabolites also being formed by hydroxylation in the unsubstituted benzene ring of the tolterodine molecule.

### References


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Data are mean ± SD of three incubations.
antagonist, is metabolized by cytochromes P450 2D6 and 3A in human liver microsomes. Drug Metab Dispos 26:289–293.