Peer reviewed article

The pharmacokinetic profile of fesoterodine: Similarities and differences to tolterodine

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Summary

Background: Fesoterodine is a new antimuscarinic agent developed for the treatment of overactive bladder. Fesoterodine itself is inactive and is rapidly and extensively converted by ubiquitous esterases to its principal active moiety, 5-hydroxymethyl tolterodine (5-HMT). 5-HMT is formed via biotransformation of both fesoterodine and tolterodine, albeit by different metabolising enzymes, viz. esterases and CYP2D6 respectively. Tolterodine is a potent muscarinic receptor antagonist and has been used for the treatment of overactive bladder for over ten years. The objective of this study was to establish the pharmacokinetic profile of fesoterodine and to highlight its potential pharmacokinetic advantages over tolterodine.

Design: Single-centre, open-label, randomised, 4-way crossover study in a total of 24 healthy male volunteers. Single oral doses of 4, 8, or 12 mg fesoterodine were administered after an overnight fast. In addition, the 8 mg dose was also administered after a standard high-fat and high-calorie breakfast. Blood and urine samples for the analysis of 5-HMT were collected before and multiple times after drug administration for pharmacokinetic analysis.

Results: The mean peak plasma concentration (C_{max}) of 5-HMT and the mean area under the time versus concentration curve (AUC) increased proportionally with the fesoterodine dose. These two parameters were some 2-fold higher in CYP2D6 poor metabolisers, whereas the time to peak plasma concentration (t_{max}) and half life ($t_{1/2}$) were not influenced by the dose or the CYP2D6 metaboliser status. If fesoterodine was taken following a high-fat breakfast, we observed small increases in C_{max} and AUC. In spite of these modest genetic influences and food effects on the pharmacokinetics of fesoterodine, the overall interindividual variability in C_{max} levels was relatively little compared to previously published reports using tolterodine.

Conclusions: Due to the esterase-mediated cytochrome P450-independent formation of 5-HMT and involvement of multiple metabolic and renal excretion pathways in the elimination of 5-HMT, the effects of patient-intrinsic and -extrinsic factors on the pharmacokinetics of fesoterodine are only modest, with some 2-fold higher 5-HMT exposure. Therefore, in contrast to tolterodine, no reduction of fesoterodine dosage is required under conditions of reduced elimination. In most cases of drug interaction or renal/hepatic impairment, the fesoterodine dose may be increased to 8 mg/day based on individual patients' response, or patients may be required to remain at the initial recommended dose of 4 mg/day.

Key words: drug interactions; fesoterodine; 5-hydroxymethyl tolterodine; muscarinic antagonists; pharmacokinetics; tolterodine

This study was supported by Pfizer Inc and Schwarz Bio-Sciences GmbH.

H.U.S. is supported by an independent basic research grant from the Swiss National Science Foundation: grant no. 310000-107526. He also reports receiving consulting fees from GlaxoSmithKline, Ception Therapeutics, Novartis, Gene Signal, Nycomed, and Pfizer. B.M. is employed by Pfizer.

Introduction

Fesoterodine is a new antimuscarinic drug in development for the treatment of overactive bladder. Antimuscarinic drugs mediate their effects by blocking muscarinic receptors, which are expressed within the bladder [1]. However, muscarinic receptors are also expressed outside the bladder, explaining the side effects of receptor antagonism that are in particular dry mouth, constipation, and blurred vision. Available drugs include oxybutynin [2], darifenacin [3], trospium [4], solifenacin [5], and tolterodine [6].

Both tolterodine and fesoterodine share the same active metabolite, 5-HMT. However, how 5-HMT is generated differs between the two drugs. Tolterodine is converted to 5-HMT by the cytochrome P450 2D6 enzyme system (CYP2D6) [7]. In contrast, fesoterodine is rapidly hydrolysed by non-specific esterases to 5-HMT [8]. There-

fore, generation of the active metabolite does not require CYP2D6, which suggests some differences in pharmacokinetics between tolterodine and fesoterodine. Further, while tolterodine has antimuscarinic activity similar to that of 5-HMT, fesoterodine is inactive, undetectable in plasma after oral dosing and functions as a prodrug of 5-HMT.

The objective of this trial was to investigate the pharmacokinetic profile of 5-HMT following single dose administration of fesoterodine, and to compare the established parameters with those known from earlier studies performed with tolterodine. In addition, we separately analysed the data in CYP2D6 extensive and poor metabolisers who were genetically phenotyped before the study.

Materials and methods

Subjects

The study was conducted in 24 healthy white males, whose eligibility criteria were (1) age 18–50 years, (2) body mass index between 20–28 kg/m^2, and (3) absence of clinically relevant deviations from normal following physical examination and vital sign assessments. Subject eligibility assessments included medical history, physical examinations with haemodynamics (including blood pressure and heart rate), 12-lead electrocardiogram (ECG), genotyping for CYP2D6 status, and laboratory screening. The presence of the following conditions precluded subject participation: (1) abnormal laboratory or clinical findings at prestudy testing, (2) any acute disease or respiratory or cardiovascular condition, (3) urinary retention or other disturbance of bladder function, (4) narrow angle glaucoma, myasthenia gravis, or digestive tract disturbance. All subjects provided written informed consent before initiation of the study procedures. The protocol was approved by an independent ethics/IRB committee (Freiburger Ethik-Komission, Freiburg, Germany), and the trial was conducted in accordance with the principles of the Helsinki Declaration.

Study design

This was a single-centre, open-label, randomised, 4-way crossover study in healthy male volunteers with a washout phase of at least seven days between treatment periods. Single oral doses of 4, 8, or 12 mg fesoterodine were administered after an overnight fast. In addition, the 8 mg dose was also administered after a standard high-fat and high-calorie breakfast (1027 kcal, 65 g fat, 73 g carbohydrates, 36 g protein). Plasma samples were collected at the following time points: 0 (predose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, and 36 h postdose. Urine samples were collected as follows: 0 (predose), 0–6, 6–12, 12–24, and 24–36 h postdose. Plasma and urine samples were stored at –70 °C until analysis.

Pharmacokinetic analysis

5-HMT concentrations in plasma and urine were measured using validated liquid chromatography tandem mass spectrometry with lower limits of quantification of 0.02 ng/mL (plasma) and 1.0 ng/mL (urine) respectively. A deuterated isotope of 5-HMT was used as the internal standard (IS). The samples were basified with an equal volume of 1M carbonate buffer, pH 10. The analytes were isolated by liquid-liquid extraction using 5 mL of hexane/ethyl acetate (1:1 v/v). The dried residues were reconstituted in the acetonitrile/10 mM ammonium acetate pH 3 (35:65 v/v) mobile phase (100 mL for plasma and 200 mL for urine samples). The extracted samples (10 mL) were injected onto the LC-MS-MS instrument: API 365 for plasma and API 100 for urine samples (PE Biosystems, Foster City, CA). The analyte peaks were sufficiently separated from endogenous compounds on a narrow-bore liquid chromatography Symmetry Shield RP8 column (Waters, Milford, MA) at a flow rate of 0.2 mL/min and a runtime of six min. Electrospray triple stage mass spectrometry (ionspray voltage 4600 V and temperature 380 °C) in the positive mode was used to detect 5-HMT and IS at the $[M+H]^+$ ion (mass-to-charge ratio transitions of 342→223 and 348→229 respectively). All concentration calculations were based on the peak area ratios of 5-HMT to its IS. The calibration curves (0.02–20 ng/mL for plasma and 1.0–500 ng/mL for urine) were characterised by the regression coefficient, slope, and intercept using a 1/x-weighted linear regression. Concentrations of 5-HMT in the quality-control samples were determined by inverse prediction from the calibration curve.

The following PK parameters for each subject in each treatment group were calculated using standard noncompartmental pharmacokinetic methods [9]: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve (AUC) from time zero until the time of the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity (AUC_{0-inf}), terminal elimination half-life ($t_{½}$), total amount excreted in urine (Ae), and renal clearance (CL_R). The estimate for CL_R was calculated as the quotient of the cumulative amount excreted in urine and the AUC over the corresponding interval.

Safety analysis

Safety was monitored by assessing adverse events, vital signs, ECG recording, and laboratory tests. Adverse events were continuously recorded. Vital sign data were measured at the prestudy examinations; during each period before dosing; 3, 6, 10, 15, 24, and 36 h after drug administration, and at the poststudy examination (each measure was obtained after three min. rest in a supine position). 12-lead ECGs were recorded prestudy; during each period before dosing; 5, 10, 24, and 36 h after drug administration; and poststudy. Safety laboratory assessments were conducted the day after drug administration in each period.

Statistical analysis

Descriptive statistics were conducted for all pharmacokinetic and safety parameters. C_{max} and AUC of 5-HMT were assessed for dose proportionality, genotype, and food effects using ANOVA. The genotype effect was tested using the mean sum of squares for subject within genotype group as the relevant error term. In order to assess dose proportionality, point estimates and the corresponding 90% confidence intervals were calculated for dose-normalised C_{max} and AUC ratios for the 4 mg fasted versus 8 mg fasted, and 12 mg fasted versus 8 mg fasted treatment comparisons. For the assessment of food effect, point estimates and the corresponding 90% confidence intervals were calculated for C_{max} and AUC ratios for the 8 mg fed versus 8 mg fasted treatment comparison.

Results

5-HMT plasma concentrations are dependent on the fesoterodine dose

A total of 24 subjects were enrolled and completed the study. Plasma concentrations of 5-HMT increased proportionally with fesoterodine dose. Mean C_{max} were 2.3 ng/mL (4 mg fesoterodine), 4.8 ng/mL (8 mg fesoterodine), and 7.3 ng/mL (12 mg fesoterodine) in the fasted state (fig. 1). Accordingly, mean AUC0-t also increased with dose (table 1). Statistical analysis of dose-normalised C_{max} and AUC values concluded linear pharmacokinetics of 5-HMT following the administration of 4, 8, and 12 mg fesoterodine in the fasted state. Mean t_{max} and mean $t_{1/2}$ remained unchanged with fesoterodine dose (table 1).

Interestingly, mean C_{max} and mean $AUC_{0\text{-}t}$ significantly increased approximately 1.30- and 1.18-fold, respectively, after a standard high-fat and high-calorie meal (fig. 1 and table 1). The 90% confidence intervals for the fed versus fasted treatment ratios were 123% to 141% and 110% to 127% for C_{max} and AUC respectively. The confidence interval for C_{max} ratio was contained entirely within the pre-specified acceptance range of 70% to 143%; however, the range for the AUC ratios was just outside the upper limit of the acceptance range of 80% to 125%. Mean t_{max} was not affected. However, there was a small, but statistically significant, reduction in mean $t_{1/2}$ by dosing in the fed state (table 1).

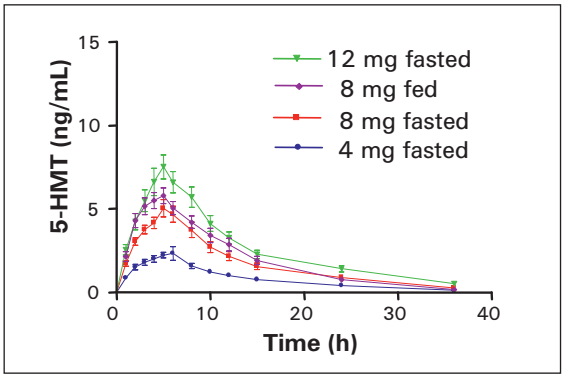

Figure 1

Plasma concentrations of 5-HMT after administration of fesoterodine in healthy subjects irrespective of CYP2D6 status. Data are presented as means ± standard error of the mean (SEM).

5-HMT plasma concentrations are dependent on the CYP2D6 status

Since tolterodine and 5-HMT are known to be metabolised by CYP2D6 [7], all subjects were characterised regarding their CYP2D6 status. For an assessment of the effect of CYP2D6 status on the pharmacokinetics of 5-HMT, 16 of the 24 subjects in this study were enrolled as extensive metabolisers (EM) and 8 as poor metabolisers

Table 1

Plasma pharmacokinetic parameters of 5-HMT following administration of fesoterodine.

	CYP2D6 metaboliser status					
Parameter/ fesoterodine dose	**EM & PM (n = 24)**		**EM (n = 16)**		**PM (n = 8)**	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Cmax (ng/mL)						
4 mg fasted	2.7 (2.0)	0.9–10.9	2.1 (1.1)**	0.9–5.6	4.0 (2.9)**	2.0–10.9
8 mg fasted	5.2 (2.4)*	2.4–11.6	4.1 (1.2)*,**	2.4–7.4	7.3 (2.9)*,**	4.5–11.6
12 mg fasted	8.0 (3.8)	3.3–17.6	6.4 (2.0)**	3.3–11.1	11.2 (4.6)**	6.5–17.6
8 mg fed	6.7 (2.4)*	3.3–12.4	5.6 (1.5)*,**	3.3–9.5	8.9 (2.4)*,**	5.9–12.4
$AUC_{0\text{–}inf}$ (ng×h/mL)						
4 mg fasted	30.7 (15.7)	11.9–68.9	23.8 (11.4)**	11.9–62.8	44.5 (14.2)**	29.0–68.9
8 mg fasted	66.6 (33.2)*	30.8–157.4	50.8 (18.5)*,**	30.8–107.8	98.2 (34.4)*,**	54.3–157.4
12 mg fasted	101.7 (54.9)	45.8–278.5	80.1 (28.5)†,**	45.8–162.1	148.2 (70.4)‡,**	89.4–278.5
8 mg fed	74.5 (33.7)*	39.1–151.8	58.7 (20.2)*,**	39.1–124.8	106.1 (34.0)*,**	62.9–151.8
$t_{½}$ (h)						
4 mg fasted	7.6 (2.1)	4.5–13.0	7.6 (2.1)	4.5–13.0	7.6 (2.2)	5.4–10.4
8 mg fasted	8.7 (3.1)*	4.1–16.6	9.2 (3.6)*	4.1–16.6	7.8 (1.5)*	5.4–10.1
12 mg fasted	9.4 (3.7)	4.2–20.4	9.3 (4.1)	4.2–20.4	9.8 (2.8)	5.7–13.3
8 mg fed	6.0 (1.7)*	3.9–11.2	5.7 (1.8)*	3.9–11.2	6.6 (1.2)*	5.3–9.1
T_{max} (h)						
4 mg fasted	5.0+	2.0–6.0	5.0	2.0–6.0	5.0	5.0–6.0
8 mg fasted	5.0+	3.0–6.0	5.0	3.0–6.0	5.0	5.0–6.0
12 mg fasted	5.0+	3.0–8.0	5.0	3.0–6.0	5.0	4.0–8.0
8 mg fed	5.0+	2.0–10.0	4.5	2.0–10.0	5.0	3.0–6.0

+n = 22; †n = 15; ‡n = 7.

EM = extensive metaboliser; PM = poor metaboliser

*, p <0.05 between fasted and fed; **, p <0.05 between EM and PM

(PM). When we separately analyzed EM and PM regarding the pharmacokinetics of 5-HMT following administration of fesoterodine, we found significantly increased mean C_{max} levels in PM compared with EM (approximately 2-fold; fig. 2, table 1). Accordingly, mean AUC_{0-t} was increased in PM compared with EM (approximately 2-fold; table 1). These results were not due to differences in the baseline characteristics between PM and EM groups (table 2). In contrast, mean t_{max} and mean $t_{1/2}$ did not differ between PM and EM. Fesoterodine exhibits flip-flop PK in that the terminal half-life of 5-HMT reflects the extended-release rate from the fesoterodine formulation. Due to flip-flop kinetics, modest changes in metabolic clearance, as demonstrated on the basis of CYP2D6 metaboliser status, do not affect the terminal half life of 5-HMT. As a result, for 5-HMT the time to reach steady state and the accumulation ratio, each determined by the half life, are likewise not expected to differ between CYP2D6 EMs and PMs. Additionally, the influence of a standard high-fat and high-calorie meal before fesoterodine administration was similar in both groups (table 1).

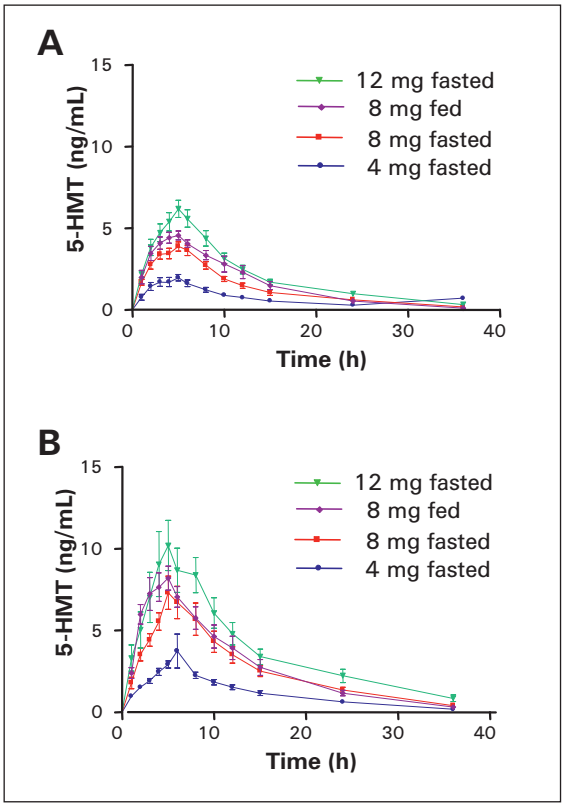

Figure 2

Plasma concentrations of 5-HMT after administration of fesoterodine in rapid (A) and slow (B) metabolisers. Data are presented as means ± standard error of the mean (SEM).

5-HMT urine concentrations are dependent on the CYP2D6 status

The mean excretion of 5-HMT in urine was significantly increased in PM compared with EM (approximately 2-fold). Moreover, consistent with the slightly higher AUC of 5-HMT in the fed state, there was a small but statistically significant increase in the urinary excretion of 5-HMT following administration of fesoterodine under these conditions. In contrast, the mean renal clearance was affected neither by the CYP2D6 nor the fed status (table 3).

Fesoterodine safety

Fesoterodine was well tolerated across all the dose levels studied, the most frequently occurring adverse effects being dry mouth and headache. The frequency of dry mouth was highest in the 12-mg-dose group, occurring in 4 out of 24 subjects. All adverse effects reported were either mild or moderate in intensity. There were no severe adverse events and none that necessitated withdrawal of a subject from the study. There were no apparent differences in the number of adverse effects reported in PM compared with EM.

Table 2

Baseline demographics.

Characteristic	EM (n = 16) mean (SD)	PM (n = 8) mean (SD)
Age (yr)	33.1 (7.1)	35.1 (6.1)
Weight (kg)	76.1 (7.6)	81.1 (5.4)
Height (cm)	178 (7.6)	178 (4.3)
BMI (kg/m²)	23.9 (2.0)	25.7 (1.4)

BMI = body mass index; EM = extensive metaboliser; PM = poor metabolizer

Table 3

Urinary pharmacokinetic parameters of 5-HMT following administration of fesoterodine.

	CYP2D6 metaboliser status		
Parameter/ fesoterodine dose	**EM & PM mean (SD)**	**EM mean (SD)**	**PM mean (SD)**
CL_R (mL/min)			
4 mg fasted	273 (79) n = 24	293 (85) n = 16	228 (37) n = 8
8 mg fasted	266 (60) n = 24	270 (66) n = 16	259 (49) n = 8
12 mg fasted	257 (64) n = 24	264 (67) n = 16	242 (59) n = 8
8 mg fed	267 (57) n = 22	267 (69) n = 14	267 (31) n = 8
Ae (µg)			
4 mg fasted	446 (171) n = 24	374 (120)** n = 16	609 (164)** n = 8
8 mg fasted	981 (471) n = 24	753 (252)** n = 16	1437 (486)** n = 8
12 mg fasted	1391 (552) n = 24	1138 (333)** n = 16	1896 (569)** n = 8
8 mg fed	1166 (473) n = 22	910 (247)** n = 14	1615 (442)** n = 8

CL_R = renal clearance; Ae = amount excreted in urine; EM = extensive metaboliser; PM = poor metaboliser
**, p <0.05 between EM and PM

Except for a slight increase in white blood cells and change of differential blood count in one subject with cold symptoms (sore throat and rhinitis), there were no abnormal clinical laboratory findings. Physical examination and 12-lead ECG, and vital signs did not exhibit any clinically relevant changes in this subject population. There were no absolute corrected QT intervals in the ECG greater than 500 milliseconds or changes from baseline exceeding 60 milliseconds. Thus no clinically relevant QT changes were noted in the on-treatment and poststudy ECG evaluations.

Discussion

Fesoterodine is a new antimuscarinic drug which demonstrated clinical efficacy in overactive bladder syndrome [10–12]. Treatment effects appeared to be more pronounced with fesoterodine 8 mg compared with fesoterodine 4 mg or tolterodine 4 mg [10]. Although fesoterodine and tolterodine are metabolised in different ways, the main active metabolite generated from both drugs is 5-HMT. In contrast to tolterodine, fesoterodine is not detectable in blood due to rapid conversion into 5-HMT by non-specific esterases [8]. Tolterodine is metabolised by CYP2D6 [7].

Because CYP2D6 activity varies between different individuals due to genetic differences [13], the amount of 5-HMT that is formed from tolterodine may also vary considerably. Indeed, it was found that the C_{max} of the active moieties after 4 mg tolterodine administration in plasma ranges between approximately 1 and 100 ng/mL [14], whereas, in the case of fesoterodine 4 mg administration, 5-HMT C_{max} varied between 1 and 10 ng/mL, about an order of magnitude narrower range than tolterodine [15]. In our study, although the mean C_{max} of 5-HMT was some 1.7-fold higher in CYP2D6 PMs vs EMs (table 1), the individual C_{max} values across both genotypes were maintained within this range. Therefore, the risk of adverse effects seems to be lower after fesoterodine compared with tolterodine. However, in spite of these theoretical considerations, the frequency of antimuscarinic adverse events, such as dry mouth and constipation, appeared to be similar between fesoterodine and tolterodine [10].

CYP2D6 exhibits a low capacity in general and is therefore easily saturated by substrate and/or inhibited, resulting in pharmacokinetic drug interactions [16]. It is known to be involved in the oxidation of 20–30% of the most commonly described drugs, including those acting on the cardiovascular or the central nervous system. For instance, amiodarone, a class III antiarrhythmic drug, is a potent inhibitor of CYP2D6 [17]. Propranolol, a nonselective beta-adrenergic blocking agent, was also reported to inhibit CYP2D6 activity [18]. In addition, the antidepressants fluoxetine and paroxetine are inhibitors of CYP2D6 [19]. Fesoterodine is not metabolised by CYP2D6, which is a single predominant pathway for tolterodine. In contrast to fesoterodine, its active moiety, 5-HMT, is metabolised by CYP2D6 along with equally predominant CYP3A4 metabolism as well as renal excretion. [8]. This explains why the CYP2D6 status influenced 5-HMT pharmacokinetics, at least regarding C_{max} and AUC, after fesoterodine administration. Although the differences between EM and PM were statistically significant in our experimental setting, at each dose level the ranges of the C_{max} and AUC values overlapped between the EMs and PMs (table 1). Since the $t_{1/2}$ of 5-HMT was unaffected by CYP2D6 status, it can be expected that the time to reach steady state and the extent of systemic accumulation at steady state is similar in EM and PM subjects.

We observed statistically significant increases in C_{max} and AUC of 5-HMT in the fed compared with the fasted group. The increases in 5-HMT exposures in the fed state were, however, small and did not affect the frequency of adverse effects in our study. It is equally not expected that the small increases in C_{max} would change the efficacy of the drug, an assumption recently confirmed in clinical studies [10, 11].

Unlike the CYP2D6-mediated metabolism of tolterodine to 5-HMT, the formation of 5-HMT is mediated by non-specific and ubiquitous esterases and involvement of multiple metabolic (comparable contributions from CYP3A4 and CYP2D6) and renal excretion pathways in the elimination of 5-HMT [8], the effects of patient-intrinsic (hepatic/renal impairment of CYP2D6 deficiency) and extrinsic factors (CYP3A4 or CYP2D6 inhibition) on the pharmacokinetics of fesoterodine are only modest, with approx. 2-fold higher 5-HMT exposure. This may generate an advantage compared to tolterodine [8]. As a result, in patients with varying degrees of renal or hepatic impairment, or those taking CYP3A4 or CYP2D6 inhibitor concomitantly, fesoterodine dosage may either be limited to 4 mg/day or increased cautiously to 8 mg/day, without requiring doses lower than the standard recommended ones. This is in contrast to tolterodine, for which a dosage of 2 mg/day, half the standard dose, is recommended under situations of reduced elimination. Taken together, we confirmed in this study that fesoterodine is safe and the pharmacokinetics of its active moiety, 5-HMT, is robust and largely independent of CYP pharmacogenetics and fed status.

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