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ABSTRACT TITLE:

PHARMACOKINETIC VARIABILITY IS LOWER FOLLOWING ADMINISTRATION OF FESOTERODINE COMPARED WITH TOLTERODINE

Hypothesis / aims of study This open-label, 2-way crossover, within-subject, dose-escalation study compared the pharmacokinetics of the active moiety of fesoterodine (5-hydroxymethyltolterodine [5-HMT]) with that of tolterodine (tolterodine + 5-HMT). Due to the enzymes involved in the formation of 5-HMT after administration of fesoterodine (esterases) versus tolterodine (CYP2D6) and based on preliminary comparisons across studies, we hypothesized that pharmacokinetic variability would be considerably reduced with fesoterodine.

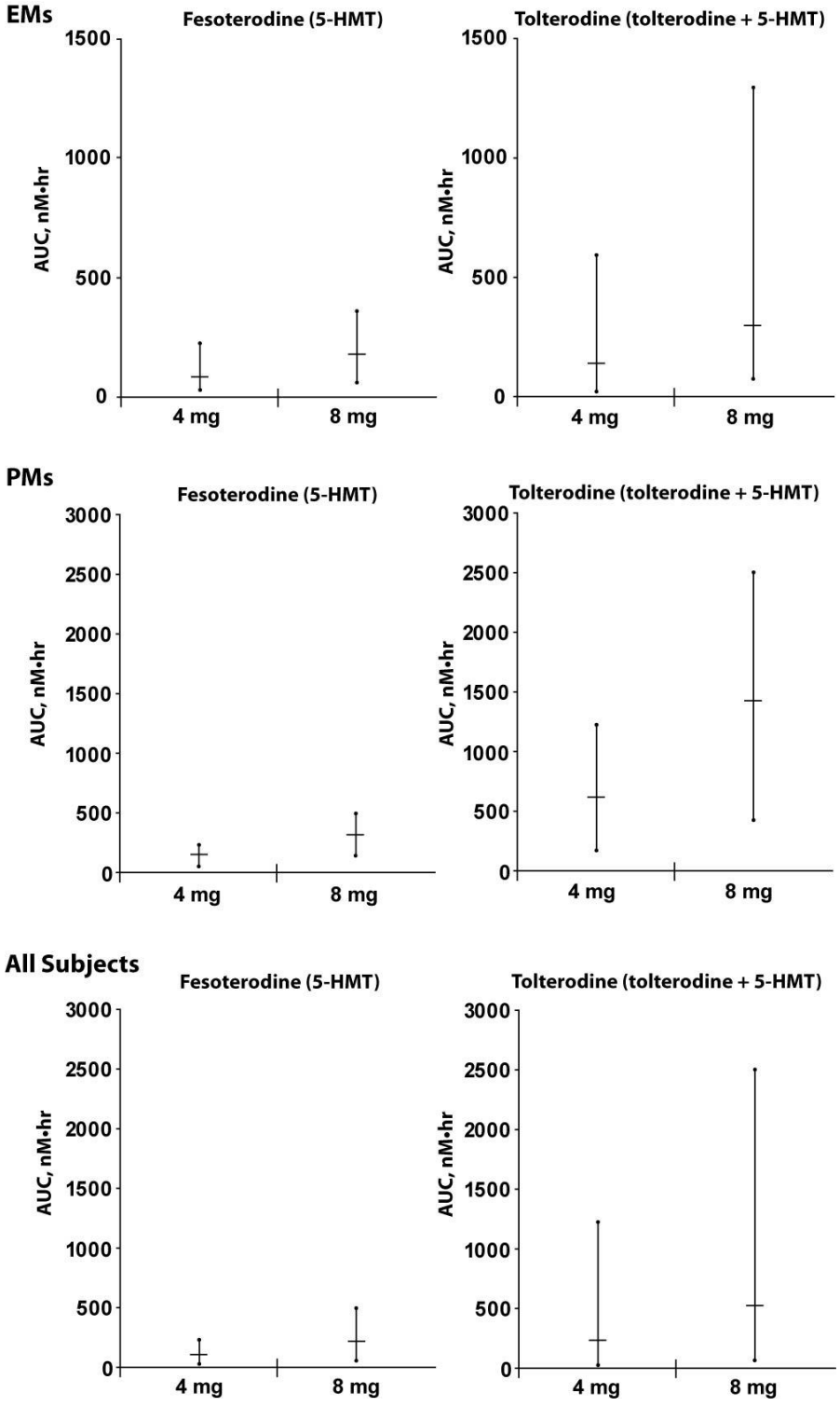
Study design, materials and methods 30 healthy subjects aged 18–55 years and genotyped as CYP2D6 extensive metabolizers (EMs; n=20) or poor metabolizers (PMs; n=10) were enrolled. In period 1, subjects were randomly assigned to receive tolterodine 4 mg once daily followed by tolterodine 8 mg once daily for 5 days each or fesoterodine 4 mg once daily followed by fesoterodine 8 mg once daily for 5 days each. After a washout period of ≥3 days, subjects completed the other treatment in period 2. In each period, blood samples were collected at predose on days 1, 4, 5, 9, and 10 and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, and 24 hours postdose on days 5 and 10; urine was collected over 24 hours postdose on days 5 and 10. Primary endpoints were the concentration versus time profiles, area under the curve from time 0–24 hours (AUC_{0-24}), and maximal concentration (C_{max}). Secondary endpoints included time to C_{max}, half-life ($t_{1/2}$), amount excreted in urine, renal clearance (CLr), and safety measures.

Results The study population consisted of mostly white subjects (90%);19 men (63%) and 11 women (37%) (mean age, 31.9 years; mean weight, 77.4 kg). A total of 29, 28, 28, and 27 subjects given tolterodine 4 mg, tolterodine 8 mg, fesoterodine 4 mg, and fesoterodine 8 mg, respectively, were evaluable for pharmacokinetics. The coefficients of variation for AUC (44%; 45%), C_{max} (43%; 41%), and $t_{1/2}$ (35%, 29%) with fesoterodine 4 mg and 8 mg, respectively, were all lower than those for AUC (91%; 92%), C_{max} (79%; 75%), and $t_{1/2}$ (68%, 62%) with tolterodine 4 mg and 8 mg, respectively. Representative comparisons of fesoterodine and tolterodine treatments, based on mean, minimum, and maximum AUC values of active moiety, are shown in **Figure 1**. Urinary excretion of 5-HMT was 0.49 and 1.02 mg for fesoterodine 4 mg and 8 mg, respectively (all subjects) and 0.38 and 0.71 mg for tolterodine 4 mg and 8 mg, respectively (EMs only). The mean CLr of 5-HMT ranged from 204–267 mL/min, regardless of administered drug or dose level.

Interpretation of results There was considerably less variability in the pharmacokinetics of 5-HMT compared with tolterodine + 5-HMT; this contrast is best illustrated through the maximum/minimum ratios of pharmacokinetic values across EMs and PMs (up to 7- and 40-fold, respectively). Evaluation of the individual contributions from tolterodine and 5-HMT revealed that tolterodine was the prime source of variability after tolterodine administration. Systemic variability was well controlled, and there was substantial urinary excretion of 5-HMT after administration of fesoterodine (in all subjects consistently) or tolterodine (in EMs only).

Concluding message Decreased pharmacokinetic variability with fesoterodine may offer several potential clinical advantages compared with tolterodine, including a more predictable clinical response and avoidance of excessively high or low exposure to active moiety, in part allowing for the development of a higher dose of fesoterodine. Improved tolerability and a lower likelihood of therapeutic failure would be expected with fesoterodine as a result of there being fewer patients with very high or low exposures.

Figure 1. Mean, Minimum, and Maximum AUC Values for Active Moiety After Tolterodine or Fesoterodine Administration to CYP2D6 EMs or PMs and All Subjects



Specify source of funding or grant	This study was funded by Pfizer Inc
Is this a clinical trial?	Yes
Is this study registered in a public clinical trials registry?	No
What were the subjects in the study?	HUMAN
Was this study approved by an ethics committee?	Yes
Specify Name of Ethics Committee	Integ Review 3001 S. Lamar Blvd., Suite 210 Austin, Texas 78704 Phone: (512) 326-3001 Fax: (5120 326-3446 Protocol approval date: July 15, 2008.
Was the Declaration of Helsinki followed?	Yes
Was informed consent obtained from the patients?	Yes