

Effect of Terbinafine on Theophylline Pharmacokinetics in Healthy Volunteers

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Twelve healthy volunteers were enrolled in an open-label, randomized, crossover study. Subjects received single doses of theophylline (5 mg/kg) with and without multiple-dose terbinafine, and 11 blood samples were collected over 24 h. The study phases were separated by a 4-week washout period. Theophylline serum data were modeled via noncompartmental analysis. When the control phase (i.e., no terbinafine) was compared to the treatment phase (terbinafine), theophylline exposure (the area under the serum concentration-time curve from time zero to infinity) increased by 16% ($P = 0.03$), oral clearance decreased by 14% ($P = 0.04$), and half-life increased by 24% ($P = 0.002$). No significant changes in other theophylline pharmacokinetic parameters were evident.

Terbinafine is an oral allylamine antifungal agent for the treatment of onychomycosis that has recently been introduced to the American market (2). It is highly effective in treating both fingernail and toenail infections (1). The drug is extensively metabolized via various pathways, including N-demethylation and N-oxidation. Schuster has shown that terbinafine metabolism utilizes only a small fraction (<5%) of the total hepatic cytochrome P-450 (CYP450) capacity of humans (11). Therefore, the propensity of terbinafine for drug interactions is thought to be small.

Various drug interactions have been reported with the use of terbinafine, but none have been deemed to be clinically significant (3, 8). One of the reported interactions is that with caffeine. Caffeine is metabolized primarily to 1,7-paraxanthine via the CYP1A2 system (6, 14). Theophylline is also largely metabolized through the CYP1A2 pathway (6). As theophylline has a narrow therapeutic index, it is important to assess whether theophylline and terbinafine interact. The objective of this study was to assess the impact of multiple doses of terbinafine on single-dose theophylline pharmacokinetic parameters in an open-label, randomized, crossover study.

The study was approved by the Institutional Review Board of The Mary Imogene Bassett Hospital. Written informed consent was obtained from each subject. Twelve volunteers were included in the study, and they met the following criteria. (i) They were healthy as determined by medical history and a laboratory screening (i.e., electrolytes, glucose, urea, creatinine, and hepatic function tests [aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and total bilirubin]) performed within 10 days of commencing the study. (ii) Female volunteers were either surgically sterile or using an effective form of nonhormonal birth control for 3 months prior to the study and willing to continue using it during and for the 3 months after the study. (iii) For females, a negative prestudy urine pregnancy test was required. Subjects were excluded from the study if they met any of the following criteria: (i) an abnormal value on medical history or laboratory screening; (ii)

obesity, defined as a total body weight greater than 30% above the upper limit of the ideal for the subject's height and body frame (based on Metropolitan Life Insurance tables); (iii) exposure to drugs other than acetaminophen in the 10 days prior to study entry; (iv) a history of allergy or intolerance to theophylline, caffeine, or terbinafine; (v) a history of smoking or use of nicotine delivery devices within 12 months prior to study initiation; (vi) a history of alcohol or drug abuse; and (vii) donation of blood in the 8 weeks prior to study initiation. Subjects were asked to abstain from caffeinated beverages, chocolate, charbroiled meats, cruciferous vegetables (e.g., broccoli, cauliflower, brussels sprouts, and cabbage), and alcohol for 48 h prior to and for the duration of the study, as these have been shown to impact CYP1A2 drug metabolism (15).

By using a computerized random-number generator, we randomized subjects to receive the following regimens in random order with a 1-month washout period between the two phases: (i) theophylline at 5 mg/kg of total body weight (TBW) and (ii) 250 mg of terbinafine (Lamisil; lot no. 20593; Novartis Pharmaceuticals Corporation, East Hanover, N.J.) by mouth once daily for 4 days plus theophylline at 5 mg/kg of TBW 2 h after the final terbinafine dose. Theophylline doses were administered as Aminophylline Oral Solution USP (lot no. 961525; Roxane Laboratories Inc., Columbus, Ohio), which contained 90.3 mg of anhydrous theophylline per 5 ml of solution. One predose blood sample was taken, and 10 postdose blood samples were collected at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 8.0, 12.0, and 24.0 h. Each 7-ml blood sample was collected from an indwelling catheter, which was flushed with 5 ml of 0.9% sodium chloride before and after sample collection. Samples

TABLE 1. Subject demographics

Parameter	Mean \pm SD	Range
Age (yr)	41 \pm 8	27-54
TBW (kg)	79 \pm 14	61-104
Ideal body weight (kg)	70 \pm 7	59-84
Creatinine clearance ^a (ml/min/1.73 m ²)	103 \pm 17	72-125
Theophylline dose (mg)	345 \pm 27	307-397

^a Calculated by the method of Cockcroft and Gault (4).

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TABLE 2. Pharmacokinetic parameters in two treatment phases^a

Treatment phase	C_{\max} (mg/liter)	T_{\max} (min)	k_{el} (h^{-1})	$t_{1/2}$ (h)	AUC _{0-∞} (mg · h/liter)	CL/F (ml/min/kg of TBW)	V/F (liters/kg of TBW)
Without terbinafine	11.1 ± 1.8	34 ± 24	0.076 ± 0.014	9.3 ± 1.7	124 ± 22	0.62 ± 0.17	0.48 ± 0.08
With terbinafine	11.8 ± 3.1	39 ± 27	0.061 ± 0.009	11.5 ± 1.6	144 ± 26	0.53 ± 0.13	0.53 ± 0.15
<i>P</i> value	0.46	0.16	0.003	0.002	0.03	0.04	0.06

^a The values shown are means ± standard deviations.

were centrifuged within 2 h of collection, and sera were transferred to storage containers and frozen at -80°C until assay.

Theophylline samples were analyzed by using the Opus Magnum automated immunoassay system (Behring Diagnostics, Westwood, Mass.). Each sample was analyzed in duplicate. If the difference between the two values was greater than 15%, two more analyses were performed. The mean of the assays was used in the analysis. The range of detection for the assay was 0.36 to 40.0 µg/ml. The intra-assay precision percent coefficients of variation were 4.5% at 7.1 µg/ml and 4.8% at 23.2 µg/ml, while the interassay coefficients of variation were 4.9% for 7.2 µg/ml and 2.3% for 24.2 µg/ml.

Theophylline concentration data were analyzed by using the TopFit Version 2.0 computer software (12). This program utilizes a nonlinear least-squares regression analysis method. Modeling of the concentration-time data was performed by using noncompartmental analysis and a weighting function of $1/y^2$. Goodness of fit was determined by evaluating the standard errors of the parameter estimates and by visual examination of the residuals. The following pharmacokinetic parameters were obtained: area under the serum concentration-time curve from time zero to infinity (AUC_{0-∞}), total oral clearance (CL/F [*F* denotes bioavailability]), maximum concentration of drug in serum (C_{\max}), time to maximum concentration of drug in serum (T_{\max}), oral volume of distribution (V/F), elimination rate constant (k_{el}), and half-life ($t_{1/2}$).

A power calculation using an α level of 0.05, a β level of 0.10, and an estimated clinically significant 25% reduction in the treatment group found that a sample size of 12 was necessary to find a difference. Descriptive statistics were calculated for subject demographic parameters. As the data were not normally distributed and the sample size was small, the non-parametric Wilcoxon signed-rank test was used to compare treatment phases. A *P* value of ≤ 0.05 was considered to be statistically significant. Data are presented as means ± standard deviations.

Demographic parameters for the 12 subjects (six males and six premenopausal females) are presented in Table 1. The mean theophylline dose administered was 345 mg. Table 2 illustrates the mean pharmacokinetic parameters for subjects on and off terbinafine. Administration of terbinafine caused statistically significant changes in the theophylline k_{el} , $t_{1/2}$, AUC_{0-∞}, and CL/F. A 24% increase in the theophylline $t_{1/2}$ was observed when terbinafine was given with theophylline. The use of terbinafine also caused a 16% increase in AUC_{0-∞} and a 14% reduction in CL/F. No significant changes were noted in C_{\max} , T_{\max} , or V/F.

The two drugs were relatively well tolerated. When terbinafine and theophylline were coadministered, the adverse effects reported were shakiness or jitteriness (seven subjects), light-headedness (one subject), and dizziness (one subject). When theophylline was administered alone, shakiness or jitteriness (six subjects), dizziness (one subject), palpitation (one subject), and headache (one subject) were reported. These were all

short-lived, and none of the subjects required any medical intervention. With terbinafine, two subjects experienced dyspepsia and one had a headache.

Theophylline is a methylxanthine compound used for the treatment of asthma and chronic obstructive pulmonary disease (9, 16). Because of its low therapeutic index and large pharmacokinetic intra- and interindividual variability, monitoring of its concentration in serum is necessary to ensure efficacy and prevent toxicity (5, 13). Interactions have been reported between theophylline and various drugs, including rifampin, carbamazepine, cimetidine, and ciprofloxacin (7). The first two drugs are inducers of theophylline metabolism and increase its clearance by approximately 50%. The risk associated with these interactions is the development of subtherapeutic theophylline concentrations. In contrast, cimetidine and ciprofloxacin inhibit theophylline metabolism, thereby increasing theophylline concentrations and potentially predisposing individuals to toxicity.

A previous study by Wahlander and Paumgartner (14) found that terbinafine reduced caffeine clearance by 21%. Caffeine and theophylline are both methylxanthines and are metabolized via similar pathways (6). The findings of this study are therefore consistent with those of the prior investigation. Terbinafine has also been shown to interact with other drugs, including rifampin, cimetidine, terfenadine, and cyclosporine (8). None of these interactions were deemed to be clinically significant. A study by Schuster (11) showed that terbinafine had a weak affinity for CYP450 enzymes and was bound to less than 5% of those tested in liver samples from cadaveric renal transplant donors. The exact mechanism for the interaction observed in our subjects is therefore unclear. It is possible that terbinafine caused some disruptions in the CYP450 reductase membranes and thereby inhibited its action on theophylline metabolism mediated via the CYP1A2 pathway (10, 11).

In the present study, administration of multiple doses of terbinafine increased the single-dose theophylline $t_{1/2}$ by 24%, increased the AUC_{0-∞} by 16%, and reduced the CL/F by 14%. Although it is difficult to predict the impact of these results on daily theophylline dosing as used in clinical practice, it appears that these pharmacokinetic changes may predispose individuals to accumulation of theophylline and unwanted toxicity. A study evaluating the effect of terbinafine on steady-state theophylline is needed to confirm this finding. Until such a study is undertaken, clinicians prescribing terbinafine to patients on chronic theophylline therapy should be cautious. Closer monitoring of theophylline concentrations in serum may be indicated when terbinafine therapy is initiated, especially in those sensitive to theophylline concentration changes or those maintained at concentrations at the upper end of the therapeutic range.

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REFERENCES

1. **Anonymous.** 1996. Terbinafine for onychomycosis. *Med. Lett.* **38**:72–74.
2. **Balfour, J. A., and D. Faulds.** 1992. Terbinafine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. *Drugs* **43**:259–284.
3. **Billstein, S. (Novartis Pharmaceuticals Corporation, East Hanover, N.J.)**. Personal communication.
4. **Cockcroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* **16**:31–41.
5. **Jennings, T. S., A. N. Nafziger, L. Davidson, and J. S. Bertino.** 1993. Gender differences in hepatic induction and inhibition of theophylline pharmacokinetics and metabolism. *J. Lab. Clin. Med.* **122**:208–216.
6. **Kalow, W., and B. K. Tang.** 1993. The use of caffeine for enzyme assays: a critical appraisal. *Clin. Pharmacol. Ther.* **53**:503–514.
7. **Kelly, H. W.** 1996. Mechanisms and principles of theophylline pharmacokinetic drug interactions, p. 497. *In* P. D. Hansten and J. R. Horn (ed.), *Drug interactions and updates quarterly*—1996. Applied Therapeutics, Vancouver, Wash.
8. **Novartis Pharmaceuticals Corporation.** 1996. Lamisil product monograph. Novartis Pharmaceuticals Corporation, East Hanover, N.J.
9. **Ramsdell, J.** 1995. Use of theophylline in the treatment of COPD. *Chest* **107**(Suppl.):206S–209S.
10. **Sarkar, M. A., and B. J. Jackson.** 1994. Theophylline *N*-demethylations as probes for P4501A1 and P4501A2. *Drug Metab. Disp.* **22**:827–834.
11. **Schuster, I.** 1985. The interaction of representative members from two classes of antimycotics—the azoles and the allylamines—with cytochromes P-450 in steroidogenic tissues and liver. *Xenobiotica* **15**:529–546.
12. **Tanswell, P., and J. Koup.** 1993. TopFit: a PC based pharmacokinetic/pharmacodynamic data analysis program. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **31**:514–520.
13. **Troger, U., and F. P. Meyer.** 1995. Influence of endogenous and exogenous effectors on the pharmacokinetics of theophylline: focus on biotransformation. *Clin. Pharmacokinet.* **28**:287–314.
14. **Wahllander, A., and G. Paumgartner.** 1989. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur. J. Clin. Pharmacol.* **37**:279–283.
15. **Watkins, P. B.** 1992. Drug metabolism by cytochromes P450 in the liver and small bowel. *Gastroenterol. Clin. N. Am.* **21**:511–526.
16. **Weinberger, M., and L. Hendeles.** 1996. Theophylline in asthma. *N. Engl. J. Med.* **334**:1380–1388.