POPULATION VARIABILITY IN THE PHARMACOKINETICS OF TERFENADINE: THE CASE FOR A PSEUDO-POLYMORPHISM WITH CLINICAL IMPLICATIONS

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ABSTRACT

Terfenadine is nearly completely first pass biotransformed. Unmetabolized terfenadine plasma concentrations have been associated with altered cardiac repolarization. During previous drug interaction studies, 2 subjects were found to have quantifiable concentrations of unmetabolized terfenadine with accompanying electrocardiographic repolarization changes while on terfenadine alone. To determine whether these subjects were representative of the population, 150 healthy volunteers (109 males, 41 females, ages 19-49) were screened for their ability to metabolize terfenadine after achieving steady-state. Blood was obtained at known times of maximum terfenadine concentration after dosing. Eleven subjects had quantifiable concentrations of terfenadine demonstrating wide intersubject variability in terfenadine metabolism. Further studies to determine whether such subjects are more susceptible to untoward terfenadine-associated events are underway.

KEY WORDS: terfenadine, metabolism, polymorphism, QT prolongation

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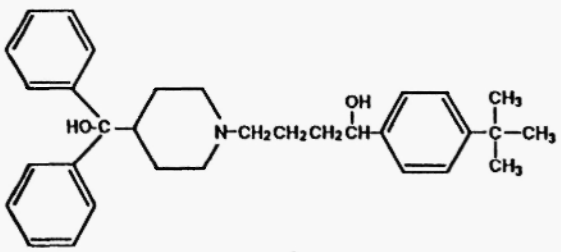
INTRODUCTION

Terfenadine is a widely used non-sedating antihistamine which undergoes nearly complete first pass biotransformation to an active carboxylic acid metabolite /1/ (Figure 1). It is unusual to find unmetabolized parent terfenadine in the plasma of humans taking the drug using current analytic techniques. Cytochrome P-4503A4 is thought to be the specific cytochrome responsible for this oxidative metabolism as well as for the metabolism of cyclosporine and nifedipine /2,3/. Initially, it was thought that population nifedipine metabolism exhibited a bimodal distribution and may represent a metabolic polymorphism analogous to debrisoquine /4,5/. Larger studies have demonstrated that, although the intersubject variability in nifedipine metabolism is wide, no true phenotypic polymorphism exists /5/.



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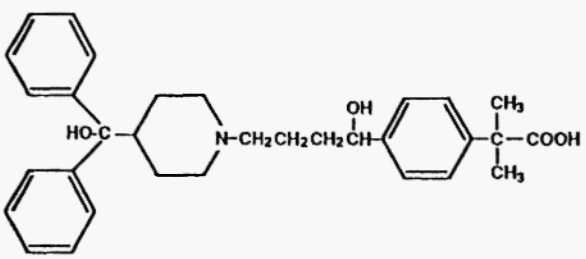

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Fig. 1: Structures of terfenadine (**A**) and its acid metabolite (**B**).

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During the conduction of several drug-drug interaction studies with terfenadine, it was noted that two of the initial 30 subjects evaluated had quantifiable maximum terfenadine concentrations (C_{max} > 5 ng/ml at two consecutive time points) /6/. These volunteers were rechallenged with terfenadine and serial 12-lead ECGs were obtained through the dosing interval. Both subjects again had quantifiable terfenadine concentrations (C_{max} 13 and 8 ng/ml) which were accompanied by quantifiable (QTc change of 25 and 33 msecs) and morphological changes in their T-U wave complexes (Figure 2). These findings were the impetus for the present prospective pharmacokinetic study in which a large cohort was screened for terfenadine metabolism capacity at steady-state after dosing with the recommended dosage of terfenadine.

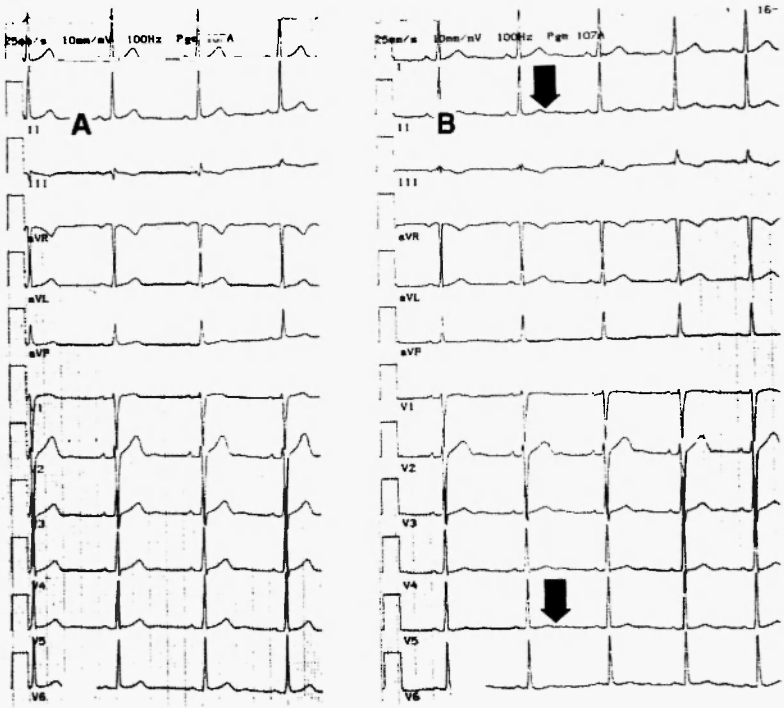

Fig. 2: Electrocardiograms obtained from a healthy male at preterfenadine baseline (**A**) and after one week of terfenadine (**B**). Arrows indicate morphological changes in T-U segments (decreased T wave amplitudes, increased U wave amplitudes and early notching) associated with quantifiable concentrations of unmetabolized terfenadine.

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MATERIALS AND METHODS

Study site

This study was conducted at the clinical research facilities of the Uniformed Services University of the Health Sciences in Bethesda, Maryland.

Subjects

The study was reviewed and approved by the Institutional Review Board of the Uniformed Services University of the Health Sciences. Healthy adults between 18 and 65 were eligible for the study. Health was determined by detailed medical history and physical examination. The presence of any illness or the chronic use of prescription or over-the-counter medication other than oral contraceptives were grounds for exclusion. The use of alcohol, tobacco or medication during the study was prohibited.

Study protocol

A baseline blood sample was obtained prior to beginning dosing with terfenadine (60 mg at 8 AM and 8 PM by mouth for 7 days) to insure that the subjects had no endogenous interfering substances present in their plasma. After 7 days, the 8 AM dose was witnessed and blood was obtained at 2 and 4 hours afterwards to correspond with known C_{max} times of terfenadine /7/.

Terfenadine assays

Plasma was separated from blood cells by centrifugation at 1000 *g* within 30 minutes of phlebotomy and stored frozen at -70°C. A solid phase extraction was used to prepare the samples for quantification by automated high performance liquid chromatography with fluorescence detection /8/. Samples were analyzed within 30 days of collection. The lower limit of quantification in plasma for both parent terfenadine and its acid metabolite was 5 ng/ml. Subjects were only considered to be poor metabolizers if terfenadine concentrations at both time points exceeded quantifiable limits of detection.

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Statistical analyses

Demographic and anthropomorphic information of the subjects was compared using the appropriate categorical (Mantel-Haentzel chi-squared) or parametric (Student's t-test) statistical procedures. A p value of <0.05 was required to reject the null hypothesis.

RESULTS

162 normal volunteers were enrolled. Twelve subjects did not complete the study. Six subjects self-discontinued due to scheduling conflicts and five did not complete the study due to various reasons including painful phlebotomy or onset of acute viral illness or other unrelated concomitant illness. One subject discontinued due to drowsiness after starting terfenadine. 150 completed the study (109 male, 41 female, ages 19-49). More importantly, 11 of the 150 (5 male, 6 female) subjects had quantifiable parent terfenadine concentrations after steady state dosing (Table 1). The C_{max} for terfenadine ranged from 6 to 14 ng/ml. Two additional subjects had isolated maximum concentrations over the limit of quantification and several others had detectable but unquantifiable concentrations. The existence of these subjects in this intermediate area suggests that a wide continuum of capacity to metabolize terfenadine exists in the population.

DISCUSSION

The categorizing of this subset of poor metabolizers most likely represents an artifact of the sensitivity of the HPLC assay and, therefore, a phenotypic pseudopolymorphism. Terfenadine, like nifedipine, is a metabolic oxidative substrate of cytochrome P-4503A4 /2,3/ and, therefore, it is unlikely that a true polymorphism exists for terfenadine in the population. Because of the relatively small cohort of poor metabolizers, no distinguishing demographic or anthropomorphic features other than female gender ($p<0.05$) could be identified as a predictor of poor metabolizer status. Although P-450 metabolic gender differences are found in rodents, gender variability in oxidative metabolic capacity is less well documented in humans /9/. The findings of this study may support the hypothesis that endogenous steroid hormones may compete *in vivo* for available metabolic enzymes /10/.

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TABLE 1
Subject demographics and terfenadine concentrations (ng/ml)
11 poor metabolizers / 3 intermediate metabolizers

Age	Gender	Race	BMI	Terfenadine- 2 hrs	Terfenadine- 4 hrs
32	F	B	23.2	7.5	7.4
22	F	C	21.2	8.7	7.3
43	M	C	25.1	5.6	BLQ
49	F	B	23.4	BLQ	5.6
25	M	C	35.2	5.3	5.5
24	M	B	24.0	14.4	13.3
28	F	C	18.4	BLQ	5.1
22	F	A	22.3	6.3	6.4
26	M	C	21.8	5.8	5.3
22	M	C	25.8	5.6	6.1
23	F	B	19.2	5.6	5.4
23	M	A	25.8	6.0	5.2
41	F	H	25.4	6.6	5.4
24	F	B	20.8	7.8	6.9

RACE: A=Asian, B=Black, C=Caucasian, H=Hispanic
BMI: Body Mass Index=$[lbs/(in)^2]x703$
BLQ: Below limit of quantification ($0<x<5$)

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The presence of these metabolic outliers does, however, have potential important clinical implications. Unmetabolized terfenadine has been demonstrated to be a potent *in vitro* blocker of the myocardial K^+ channel and the presence of unmetabolized terfenadine in the plasma of humans has been associated with altered cardiac repolarization and Torsade de Pointes /7,11,12/. In fact the two index subjects had quantifiable increases in QTc from baseline determinations. While it is known that chronotropic effects in QTc dispersion exist /13/, the repolarization changes in these subjects were accompanied by qualitative alterations in T-U morphology (Figure 2) and were similar, but less pronounced, to those noted in drug interaction studies in which high concentrations of the cardiotoxic parent terfenadine were seen /7/.

No electrocardiograms were performed during this screening study. Future research with such subjects is required to determine whether such abnormal cardiac repolarization is noted in a larger subset of the healthy population receiving recommended doses of terfenadine. It is known that a dose-mean QTc prolongation relationship exists. An analysis of data from 8 clinical studies revealed a mean 6 millisecond increase in the QTc interval at the dose and dosing schedule used in our study /14/. The results of this current study may help to explain the variability of the electrocardiographic pharmacodynamic response in pharmacokinetic terms. Furthermore, it remains to be seen whether these subjects are more susceptible to the inhibition of metabolism of terfenadine by known inhibitors of drug metabolism and therefore at higher risk for the rare adverse cardiac events associated with this drug.

CONCLUSION

Variability in the pre-systemic clearance of terfenadine is wide across the population. Individuals who are found to have circulating concentrations of unmetabolized terfenadine represent a pharmacokinetic outlier population that may be at risk for adverse cardiac events when taking terfenadine.

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REFERENCES

1. Gareiz DA, Hook PA, Walker BJ, Okerholm RA. Pharmacokinetics and biotransformation studies of terfenadine in man. Arzneimittel-Forshung 1982; 32: 1185-1190.
2. Hunt CM, Watkins PB, Saenger P, Stone GM, Barlascini N, Watlington CO, Wright JT, Guzelian PS. Heterogeneity of CYP3A isoforms metabolizing erythromycin and cortiosol. Clin Pharmacol Ther 1992; 51: 18-23.
3. Yun CH, Okerholm RA, Guengerich FP. Oxidation of the antihistaminic drug terfenadine in human liver microsomes. Drug Metab Disp 1993; 21: 403-409.
4. Mahgoub A, Dring LG, Idle JR, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. Lancet 1977; 2: 584.
5. Breimer DD, Schellens JHM, Soons PA. Nifedipine: variability in its kinetics and metabolism in man. Pharmac Ther 1989; 44: 445-454.
6. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Effect of concomitant administration of cimetidine and ranitidine on the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine. Eur J Clin Pharm 1993; 43: 41-46.
7. Honig PK, Worthan DC, Zamani K, Mullin JC, Cantilena LR. The terfenadine-ketaoconazole interaction: pharmacokinetic and cardiac consequences. JAMA 1993; 269: 1513-1518.
8. Coutant JE, Westmark PA, Nardella PA, Walter SM, Okerholm RA. Determination of terfenadine and terfenadine acid metabolite in plasma using solid-phase extraction and high-performance liquid chromatography with fluorescence detection. J Chromatogr 1991; 570: 139-148.
9. Gustafsson JA. Sex steroid induced changes in hepatic enzymes. Ann Rev Physiol 1983; 45: 51-60.
10. Gibson GG, Skett P. Introduction to Drug Metabolism. New York: Chapman and Hall, 1986.
11. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of cardiotoxic actions of terfenadine. JAMA 1993; 269: 1531-1536.
12. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264: 2788-2790.
13. Morganroth J, Brozovich FV, McDonald JT, Jacobs RA. Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. Am J Cardiol 1991; 67: 774-776.
14. Morganroth J, Brown AM, Critz S, Crumb WJ, Kunze DL, Lacerda AE, Lopez H. Variability of the QTc interval: impact on defining drug effect and low-frequency cardiac events. Am J Cardiol 1993; 26B-31B.

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