Population Pharmacokinetics of Terfenadine[1]

Richard L. Lalonde,[2,3] Denis Lessard,[2] and Jacques Gaudreault[2]

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Purpose. After oral administration of terfenadine, plasma concentrations of the parent drug are usually below the limits of quantitation of conventional analytical methods because of extensive first-pass metabolism. Data are usually reported on the carboxylic acid metabolite (M1) but there are no published reports of pharmacokinetic parameters for terfenadine itself. The present study was undertaken to evaluate the population pharmacokinetics of terfenadine.

Methods. Data from 132 healthy male subjects who participated in several different studies were included in this analysis. After an overnight fast, each subject received a single 120 mg oral dose of terfenadine; blood samples were collected for 72 hours. Terfenadine plasma concentrations were measured using HPLC with mass spectrometry detection and M1 plasma concentrations were measured using HPLC with fluorescence detection. A 2-compartment model was fitted to the terfenadine data using NONMEM; terfenadine and M1 data were also analyzed by noncompartmental methods.

Results. Population mean K_a was 2.80 hr^{-1}, T_{lag} was 0.33 hr, Cl/F was 4.42×10^3 l/hr, V_c/F was 89.8×10^3 l, Q/F was 1.85×10^3 l/hr and V_p/F was 29.1×10^3 l. Intersubject CV ranged from 66 to 244% and the residual intrasubject CV was 21%. Based on noncompartmental methods, mean terfenadine C_{max} was 1.54 ng/ml, T_{max} was 1.3 hr, $t_{1/2\,\lambda z}$ was 15.1 hr, Cl/F was 5.48×10^3 l/hr and $V_{\lambda z}/F$ was 119.2×10^3 l. M1 concentrations exceeded terfenadine concentrations by more than 100 fold and showed less intersubject variability.

Conclusions. Terfenadine disposition was characterized by a 2-compartment model with large intersubject variability, consistent with its significant first-pass effect.

KEY WORDS: terfenadine; carboxylic acid terfenadine; population pharmacokinetics; nonlinear mixed effects modeling; NONMEM.

INTRODUCTION

Terfenadine is a histamine H_1-receptor antagonist very widely used for the treatment of histamine-related allergic conditions. In 1991, the manufacturer of terfenadine estimated that over 100 million patients had received the drug since it was approved in the 1980s (1). Surprisingly little is known about its pharmacokinetics because terfenadine is subject to extensive first-pass metabolism after oral administration and consequently plasma concentrations are usually below the limits of quantitation of conventional analytical methods (2–5). Terfenadine pharmacokinetic studies using conventional high performance liquid chromatography (HPLC) assays usually report data for its (major) carboxylic acid metabolite (M1) but no pharmacokinetic parameters such as clearance, volume of distribution or half-life for terfenadine (3–9). An earlier study, using a radioimmunoassay, provided some information on terfenadine disposition after oral administration, but was significantly limited by cross-reactivity with M1 (10,11).

Terfenadine is metabolized by cytochrome P-450 3A4 (and possibly other enzymes) to form a desalkyl- and a hydroxy-metabolite, the latter is further oxidized to form M1 (12). Plasma concentrations of M1 are readily detectable and this metabolite is thought to be responsible for most of the H_1-receptor antagonist effects observed after oral administration of terfenadine (5). However, it may be particularly important to evaluate the disposition of terfenadine itself since, in addition to its H_1-receptor antagonist effects, it also blocks potassium channels and delays repolarization in cardiac tissues (13). Furthermore, administration of terfenadine with inhibitors of P-450 3A4 (*i.e.* ketoconazole, itraconazole, erythromycin) has been associated with accumulation of parent drug, altered cardiac repolarization and a potentially life-threatening cardiac arrhythmia known as torsades de pointes (7,8,14,15).

The objective of this study was to evaluate the population pharmacokinetics of terfenadine using an HPLC/mass spectrometry assay with adequate sensitivity to describe the disposition of terfenadine after oral administration.

MATERIALS AND METHODS

Subjects and Data Collection

A total of 132 subjects participating in different terfenadine pharmacokinetic studies were included in this study. The subjects were healthy non-smoking male volunteers (130 caucasians, 2 blacks) with a mean ± s.d. age of 27.9 ± 6.5 year, weight of 72.6 ± 7.1 kg and height of 174.9 ± 5.9 cm. The studies were approved by an Institutional Review Board and signed informed consent was obtained from each subject. The subjects received no other drug for at least 7 days and abstained from ethanol or xanthine-containing products for at least 48 hours prior to the study. Each subject was administered a single oral 120 mg dose of terfenadine (Seldane®, 2 × 60 mg tablets, Marion Merrell Dow, Kansas City, MO) with 240 ml of water at approximately 08:00h. The subjects were required to fast overnight prior to drug administration and for an additional 4 hr after dosing; standard meals were served 4 and 9 hr after dosing. Blood samples (≈10 ml) were collected in Vacutainer® tubes containing EDTA, prior to, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, 60, and 72 hr after drug administration. Blood samples were cooled in an ice bath, then centrifuged under refrigeration. Plasma was harvested and stored in polypropylene tubes at −80°C pending analysis.

Terfenadine and M1 Acid Metabolite Assay

Terfenadine plasma concentrations were determined by HPLC/mass spectrometry using a method developed in our laboratories (16). The system consisted of an LC-18 reverse phase column and an API III (SCIEX) mass spectrometer. Atmospheric pressure ionization and selected ion monitoring modes were used. The lower limit of quantitation was 50 pg/ml. Between-batch coefficients of variation (CVs) were 14.7,

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[2] Phoenix International Life Sciences Inc., 2350 Cohen Street, Saint-Laurent (Montréal), Québec, Canada H4R 2N6.

[3] To whom correspondence should be addressed.

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6.3, 5.8 and 6.0% and the within-batch CVs were 12.2, 9.7, 5.4, and 3.9% at concentrations of 50.1, 150.3, 751.5, and 3507.0 pg/ml, respectively.

M1 plasma concentrations were measured by HPLC with fluorescence detection. The lower limit of quantitation was 10 ng/ml. Between-batch CVs were 12.3, 6.9, 5.2, and 8.0%, and the within-batch CVs were 5.3, 7.4, 5.6, and 5.5% at concentrations of 10, 25, 250, and 400 ng/ml, respectively.

Data Analysis

Population pharmacokinetic parameters of terfenadine were estimated using nonlinear mixed effects modeling, as implemented in the software package NONMEM (version IV, level 2.1, double precision), and using PREDPP (version III, level 1.1) (17). A total of 1969 terfenadine concentrations from 132 subjects were used in the data analysis. The first-order estimation method was used to estimate population mean parameters, intersubject variability in these parameters and residual intrasubject variability between observed and predicted terfenadine concentrations. Residual variability includes assay error, sampling time error, intrasubject variability in pharmacokinetic parameters over time and model misspecification.

The pharmacostatistical model was developed by initially comparing standard one- and two-compartment models with first-order absorption and elimination. The models were parameterized in terms of clearance and volume of distribution using the NONMEM subroutines ADVAN2 TRANS2 and ADVAN4 TRANS4, for the one- and two-compartment models, respectively. Exponential error models (NONMEM uses a constant CV model as an approximation) were used for both the intersubject and residual intrasubject variability. Parameters were added to the model based on an improvement in residual plots and a decrease in the minimum objective function (MOF), the latter being equal to -2 times the log likelihood of the data. The change in the MOF between two nested models (*i.e.* a full model which can be made equivalent to a reduced model by setting a parameter to a fixed value) is approximately χ^2 distributed with degrees of freedom equal to the number of parameters which are set to a fixed value in the reduced model. Thus, a decrease of 4 units in the MOF was considered statistically significant ($p < 0.05$) for addition of one parameter during the development of the model (18). Once an appropriate full model was developed, each parameter was sequentially tested to determine if it should remain in the final model. A more conservative test ($p < 0.005$) was used because of the multiple comparisons that are made for this final step.

Intersubject and residual variability were modeled as follows:

$$K_{aj} = K_a * e^{\eta_{1j}}$$

$$T_{lag\,j} = T_{lag} * e^{\eta_{2j}}$$

$$Cl_j/F = Cl/F * e^{\eta_{3j}}$$

$$V_{cj}/F = V_c/F * e^{\eta_{4j}}$$

$$Q_j/F = Q/F * e^{\eta_{5j}}$$

$$V_{pj}/F = V_p/F * e^{\eta_{6j}}$$

$$C_{ij} = C * e^{\epsilon_{ij}}$$

where K_a, T_{lag}, Cl/F, V_c/F, Q/F and V_p/F are the population mean estimates for the absorption rate constant, the lag time, the apparent systemic clearance, the apparent volume of distribution of the central compartment, the apparent intercompartmental clearance, and the apparent volume of distribution of the peripheral compartment, respectively. K_{aj}, $T_{lag\,j}$, Cl_j/F, V_{cj}/F, Q_j/F and V_{pj}/F are the corresponding (hypothetical) true parameters for the jth subject. η_1 through η_6 are normally distributed random variables with means zero and whose (intersubject) variances are being estimated, C is the predicted terfenadine plasma concentration at the ith time for the jth subject, C_{ij} is the observed concentration for that subject at that time and ϵ_{ij} is the normally distributed residual intrasubject error with mean zero and whose variance is being estimated. Bayesian estimates of pharmacokinetic parameters for each subject were obtained using the "POSTHOC" option in NONMEM. The importance of different potential covariates (age, weight) was evaluated based on changes in the MOF and inspection of scatterplots of each covariate *versus* the individual Bayesian estimates of pharmacokinetic parameters. For the fixed effects (θ) parameters, the 95% confidence intervals (CI) were calculated as:

$$95\%\ CI = \theta \pm 2 * s.e.$$

where θ is the population parameter and s.e. is the standard error of the estimate. For intersubject and residual intrasubject CVs, the 95% CI were calculated as:

$$95\%\ CI = \sqrt{\text{var} \pm 2 * s.e.} * 100$$

Where var is the estimated variance and s.e. is the standard error of the estimate.

In addition, terfenadine and M1 data were analyzed by standard noncompartmental method (19). The terminal disposition rate constant (λ_z) was determined by linear least-squares regression using the terminal log-linear portion of the plasma concentration *versus* time data and half-life ($t_{1/2\,\lambda z}$) was calculated as $0.693/\lambda_z$. Area under the concentration-time curve (AUC) was calculated using the linear trapezoidal rule and extrapolated to infinity (AUC_{inf}) by adding the ratio of the last measurable plasma concentration to λ_z. Peak Plasma concentrations (C_{max}) and time when C_{max} was reached (T_{max}) were obtained by inspection of each concentration-time profile. The apparent systemic clearance (Cl/F) was calculated as the ratio of Dose to AUC_{inf}, and the apparent volume of distribution ($V_{\lambda z}$/F) as the ratio of Cl/F to λ_z. Results are presented as the geometric mean and the coefficient of variation (CV) calculated as:

$$CV = \sqrt{e^{sd^2} - 1} * 100$$

where sd is the standard deviation of the natural log transformed parameters (20).

RESULTS

Population Analysis

Table I summarizes the steps that produced a statistically significant decrease in the MOF during the development of the pharmacostatistical model. The 2-compartment model with intersubject variability on all the parameters described the data significantly better than the 1-compartment model (decrease in

Table I. Model Building Steps

Model #	Model	Compared with	Decrease in MOF[a]	Inclusion in model
1	2-compartment model with intersubject variability on Cl/F	—	—	—
2	Model 1 with intersubject variability on V_c/F	1	1058.2	yes
3	Model 2 with intersubject variability on K_a	2	322.8	yes
4	Model 3 with intersubject variability on V_p/F	3	254.1	yes
5	Model 4 with intersubject variability on Q/F	4	237.7	yes
6	Model 5 with lag time	5	28.9	yes
7	Model 6 with intersubject variability on lag time	6	27.0	yes
8	Model 7 with covariance between Cl/F and V_c/F	7	40.0	yes
9	Model 8 with weight as covariate for V_c	8	5.5	no[b]
10	Model 8 with additive and exponential residual error	8	42.9	no[c]

[a] A reduction of the MOF of more than 4 units was considered significant ($p < 0.05$).
[b] Removed during testing of full model; see text.
[c] Problems with estimates of fixed and random effects parameters; see text.

the MOF of 549 units, $p < 0.001$), and was selected as the basic pharmacokinetic model. Intersubject variability was added sequentially for Cl/F, V_c/F, K_a, V_p/F and Q/F, and inclusion of all five random effects produced a statistically significant decrease in the MOF. Inclusion of a lag time, followed by addition of a random effect on lag time, decreased the MOF significantly. Covariance between the pharmacokinetic parameters was evaluated and, based on a statistically significant decrease in MOF, covariance between Cl/F and V_c/F was included in the model. Weight was found to be weakly correlated with V_c/F based on a change of 5.5 in the MOF; inclusion of age or weight as a covariate for the other pharmacokinetic parameters did not produce a statistically significant decrease in the MOF. Finally, including an additive error term to the exponential model for residual intrasubject variability resulted in large (1.7 to 2.8 fold) increase in the population parameters of Cl/F, Q/F and V_p/F, and the 95% confidence intervals included 0 for four of the six fixed effects parameters, despite a statistically significant decrease in the MOF. Therefore, the simple exponential model was used for residual intrasubject variability. The full model was tested by sequentially removing each parameter. The MOF increased by at least 38 units in each case, and consequently, all parameters were kept in the final model, with the exception of weight as a covariate of V_c/F, where the change in MOF did not reach the prestated level of statistical significance (see Table I).

Table II presents the population pharmacokinetic parameters while Figure 1 shows the concentration-time data for each subject and the predictions using the population mean parameter estimates. Based on the population mean parameters, the half-life of the early ("alpha") disposition phase was 6.7 hr, $t_{1/2\,\lambda z}$ was 22.8 hr, C_{max} was 1.2 ng/ml and T_{max} was 1.7 hr. Terfenadine absorption was rapid and showed wide intersubject variability (CV of 184% for K_a). Both the apparent systemic clearance and volume of distribution were large, consistent with the extensive first-pass effect and the estimates obtained by noncompartmental methods. Little if any bias was evident in the weighted residuals (Figure 2), although there was residual intrasubject variability of 20.6%.

Noncompartmental Analysis

Mean terfenadine and M1 plasma concentrations are shown in Figure 3 and the noncompartmental analysis results are summarized in Table III. AUC_{inf} for terfenadine was less than 1% of the metabolite AUC_{inf} and was associated with a higher variability (CV of 85% and 26% for terfenadine and M1, respectively). For both analytes, the percent of extrapolation for AUC to infinity was less than 15%. Maximum concentrations of terfenadine were reached earlier (1.3 and 2.5 hr for terfenadine and M1, respectively), and its mean terminal disposition half-life (15.1 hr) was longer than that of M1 (9.5 hr), presumably because of an underestimation of the latter (see below).

DISCUSSION

Previous studies of terfenadine pharmacokinetics have been limited by the sensitivity of conventional HPLC methods. These reports included pharmacokinetic data for M1 but few if any concentrations of terfenadine could be quantitated (3–9). Consequently, parameters such as clearance, volume of distribution and half-life have not been reported for terfenadine. In order to adequately characterize the disposition of terfenadine, an HPLC assay with mass spectrometric detection and a lower limit of quantitation of 50 pg/ml was developed in our labora-

Table II. Population Parameter Estimates for Terfenadine Pharmacokinetics

Fixed effects parameters	Mean	95% CI
K_a (hr^{-1})	2.80	1.91, 3.69
T_{lag} (hr)	0.33	0.22, 0.44
Cl/F ($\times 10^3$ l/hr)	4.42	3.93, 4.91
V_c/F ($\times 10^3$ l)	89.8	77.2, 102.4
Q/F ($\times 10^3$ l/hr)	1.85	0.25, 3.45
V_p/F ($\times 10^3$ l)	29.1	12.6, 45.6
Random effects parameters		
Intersubject variability	**CV%**	**95% CI**
K_a	184.1	99.5, 240.6
T_{lag}	94.2	0, 145.6
Cl/F	65.6	51.4, 77.2
V_c/F	69.8	53.2, 83.1
Q/F	244.3	0, 348.9
V_p/F	194.2	113.6, 250.0
Residual variability	20.6	17.3, 23.4
	Covariance	**95% CI**
Covariance Cl/F and V_c/F (correlation)	0.34 (0.74)	0.21, 0.46

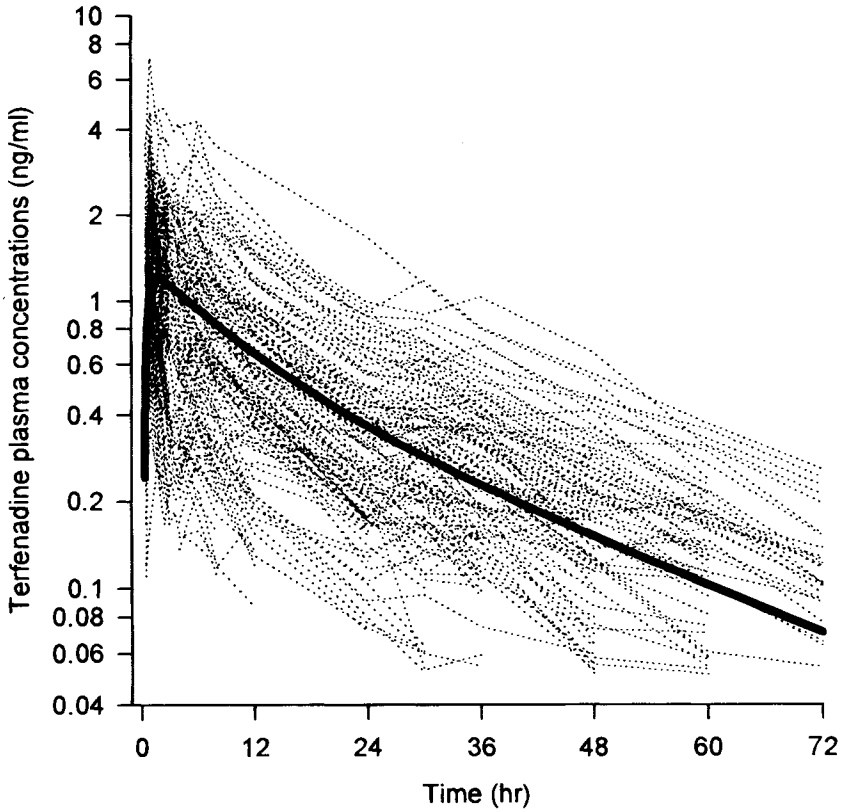

Fig. 1. Concentration-time data for terfenadine after oral administration of a 120 mg dose; the thicker line represents the predictions obtained with the mean population estimates from NONMEM and the dashed lines represent the observed data for each subject.

tories. This study is apparently the first report on the pharmacokinetics of terfenadine in humans using a specific chemical assay.

An earlier study using a radioimmunoassay provided some information on the pharmacokinetics of terfenadine after oral doses of 60 and 180 mg, administered as a suspension to 14 male subjects (11). The authors reported that their radioimmunoassay cross-reacted to the extent of 0.3 ng/ml equivalent of terfenadine at a concentration of 100 ng/ml of M1 (10). Although this cross-reactivity is relatively small, the radioimmunoassay will significantly overestimate terfenadine concentrations since plasma concentrations of M1 exceed those of terfenadine by more than 100-fold (Table III and Figure 3). After adjustment for the difference in doses between studies, the mean C_{max} reported at both doses with the radioimmunoassay was twice the mean C_{max} reported in Table III. The dose-normalized mean AUC with the radioimmunoassay was 1.08 and 1.35 times the value in Table III, for the 60 mg and 180 mg dose, respectively. Although the difference in AUC between studies is relatively small, it should be emphasized that this parameter was measured over only 48 hours in the previous study whereas the values in the current study are extrapolated to infinity. Therefore, the difference in AUC measured over the same time interval should be significantly larger. Inspection of Figure 3 and the parameters in Table III also reveals that the ratio of metabolite to parent drug plasma concentrations decreases after T_{max} and could account for the apparent greater overestimation due to cross-reactivity around C_{max}, compared to AUC which should reflect more of an average value over time. Finally, it should be noted that differences in formulations (marketed tablets *versus* suspension) and study subjects may also have contributed to the apparent differences in the results between these two studies.

M1 dose-adjusted C_{max} and T_{max} were consistent with values reported previously; literature values for mean M1 half-life appear to be more variable and range from 3.4 to 13 hr (4,5,7,21). The shorter half-lives reported for M1 are probably underestimates of the true terminal half-life caused by the limited sampling duration (4–12 hr) used in some studies (7,21). In studies where sampling duration was at least 24 hr, the reported half-life is approximately 13 hr (4,5). Furthermore, after administration of the HCl salt of M1, mean M1 terminal half-life was estimated to be 13.9 hr in a group of 110 subjects with age ranging from 19 to 45 years (22). The somewhat shorter terminal half-life observed in the present study may have been caused by the fact that in some subjects the decline in M1 concentrations appeared mostly monoexponential and only the last two concentrations appeared to be in the terminal disposition phase. Although after administration of terfenadine the true terminal half-life of M1 cannot be shorter than that of the parent compound, this particular phase of disposition may be evident only at very low plasma concentrations. The observed plasma M1 profile after oral administration of terfenadine mainly reflects the relatively large amount of M1 produced during first-pass metabolism and which first enters the systemic circulation as metabolite (*i.e.* metabolite disposition is not limited by disposition of terfenadine) (23).

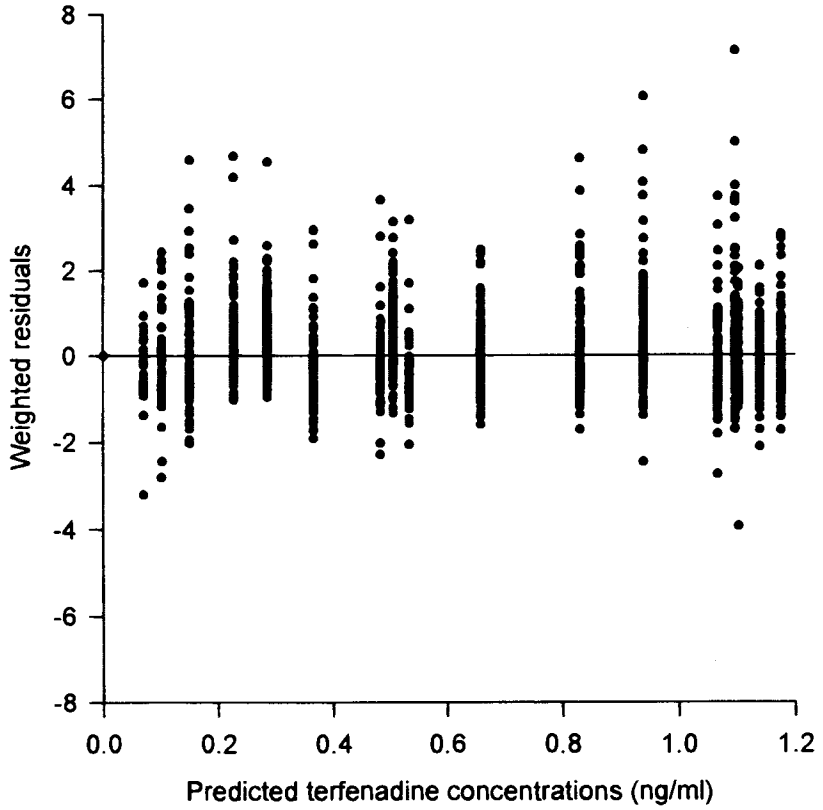

Fig. 2. Weighted residuals *versus* predicted terfenadine concentrations.

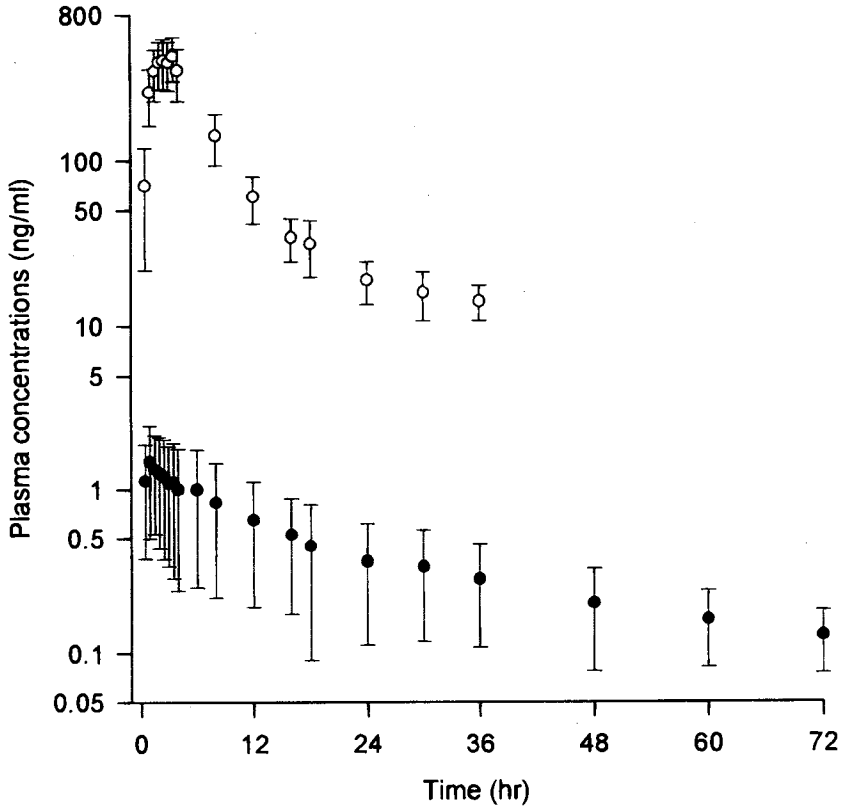

Fig. 3. Concentration-time data for terfenadine (●) and M1 (○) after oral administration of a 120 mg dose; results are presented as the mean ± s.d.

Table III. Noncompartmental Pharmacokinetic Parameters for Terfenadine and M1. Data Are Presented as the Geometric Mean (CV); the Number of Subjects Included Is Indicated in [ ]

Parameter	Terfenadine	M1
AUC_{inf} (ng · hr/ml)	21.89 (85%) [123]	3242 (27%) [125]
C_{max} (ng/ml)	1.54 (60%) [132]	444 (31%) [132]
T_{max} (hr)	1.3 (86%) [132]	2.5 (33%) [132]
λ_z (hr^{-1})	0.0460 (50%) [123]	0.0729 (55%) [125]
$t_{1/2}\lambda_z$ (hr)	15.1 (50%) [123]	9.5 (55%) [125]
Cl/F ($\times 10^3$ l/hr)	5.48 (85%) [123]	—
$V\lambda_z/F$ ($\times 10^3$ l)	119.2 (60%) [123]	—

The results of this study are consistent with those of a previous investigation using radiolabeled terfenadine which reported that over 99% of the terfenadine related material that is absorbed after oral administration undergoes biotransformation (11). In the present study, mean C_{max} and AUC_{inf} for M1 are 288 and 148 times those of terfenadine, respectively (Table III). Maximum concentrations of the metabolite are reached rapidly after the dose of terfenadine suggesting that significant amounts of the former are produced by first-pass metabolism. There is very high variability in terfenadine pharmacokinetic parameters (Tables II and III) which is common for drugs with extensive first-pass metabolism.

Nonlinear mixed effects modeling was used to fit a 2-compartment model to the pooled terfenadine data and directly estimate population pharmacokinetic parameters. Relatively sparse sampling during the absorption phase and the great variability in the terfenadine plasma concentration data made it difficult to fit a similar pharmacokinetic model to individual data and thus precluded a two-stage analysis. Attempts to simultaneously fit the terfenadine and M1 data produced various estimation problems and were not successful. The mixed effects modeling approach allows for the estimation of population mean pharmacokinetic parameters, intersubject variability as well as residual intrasubject variability. No relationship was found between the pharmacokinetic parameters and subjects' weight and age and is most likely due to the narrow range of age and weight of the study subjects. The results obtained using this approach are similar to those obtained by the noncompartmental analysis but it also provided a more complete description of the concentration-time profile in terms of absorption, distribution and elimination. It should be noted that a two-stage analysis, as reported for the noncompartmental approach, confounds intersubject and estimation error and thus the intersubject variability estimated using mixed effects modeling may be more reliable (24). Nevertheless, it should be clear upon review of the data in Tables II and III that there is very significant intersubject variability in the CL/F, V_c/F, AUC_{inf} and C_{max} of terfenadine.

REFERENCES

1. D. R. Mathews, B. McNutt, R. A. Okerholm, M. Flicker, and G. McBride. Torsades de pointes occurring in association with terfenadine use. *JAMA* **266**:2375–2376 (1991).
2. D. McTavish, K. L. Goa, and M. Ferrill. Terfenadine. An updated review of its pharmacological properties and therapeutic efficacy. *Drugs* **39**:552–574 (1990).
3. K. J. Simmons, T. J. Martin, W. T. A. Watson, and F. E. R. Simons. Pharmacokinetics and pharmacodynamics of terfenadine and chlorpheniramine in the elderly. *J. Allergy. Clin. Immunol.* **85**:540–547 (1990).
4. M. G. Eller, B. J. Walker, L. Yuh, K. K. Antony, B. E. McNutt, and R. A. Okerholm. Absence of food effects on the pharmacokinetics of terfenadine. *Biopharm. Drug. Dis.* **13**:171–177 (1992).
5. M. G. Eller, B. J. Walker, P. A. Westmark, S. J. Ruberg, K. K. Antony, B. E. McNutt, and R. A. Okerholm. Pharmacokinetics of terfenadine in healthy elderly subjects. *J. Clin. Pharmacol.* **32**:267–271 (1992).
6. P. K. Honig, D. C. Wortham, K. Zamani, J. C. Mullin, D. P. Conner, and L. R. Cantilena. The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin. Pharmacol. Ther.* **53**:630–636 (1993).
7. P. K. Honig, D. C. Wortham, R. Hull, K. Zamani, J. E. Smith, and L. R. Cantilena. Itraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. *J. Clin. Pharmacol.* **33**:1201–1206 (1993).
8. P. K. Honig, R. L. Woosley, K. Zamani, D. P. Conner, and L. R. Cantilena. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin. Pharmacol. Ther.* **52**:231–238 (1992).
9. P. K. Honig, D. C. Wortham, K. Zamani, D. P. Conner, J. C. Mullin, and L. R. Cantilena. Effect of concomitant administration of cimetidine and ranitidine on the pharmacokinetics and electrocardiographic effects of terfenadine. *Eur. J. Clin. Pharmacol* **45**:41–46 (1993).
10. C. E. Cook, D. L. Williams, M. Myers, C. R. Tallent, G. A. Leeson, R. A. Okerholm, and G. J. Wright. Radioimmunoassay for terfenadine in human plasma. *J. Pharm. Sci.* **69**:1419–1423 (1980).
11. R. A. Okerholm, D. L. Weiner, R. H. Hook, B. J. Walker, G. A. Leeson, S. A. Biedenbach, M. J. Cawein, T. D. Dusebout, G. J. Wright, M. Myers, V. Schindler, and C. E. Cook. Bioavailability of terfenadine in man. *Biopharm. Drug. Dis.* **2**:185–190 (1981).
12. C. H. Yun, R. A. Okerholm, and F. P. Guengerich. Oxidation of the antihistaminic drug terfenadine in human liver microsomes. Role of Cytochrome P-450 3A(4) in N-dealkylation and C-hydroxylation. *Drug. Metab. Dispos.* **21**:403–409 (1993).
13. D. Rampe, B. Wible, A. M. Brown, and R. C. Dage. Effects of terfenadine and its metabolites on a delayed rectifier K^+ channel cloned from the human heart. *Mol. Pharmacol.* **44**:1240–1245 (1993).
14. P. K. Honig, D. C. Wortham, K. Zamani, D. P. Conner, J. C. Mullin, and L. R. Cantilena. Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. *JAMA* **269**:1513–1518 (1993).
15. B. P. Monahan, C. L. Ferguson, E. S. Killeavy, B. K. Lloyd, J. Troy, and L. R. Cantilena. Torsades de pointes occurring in association with terfenadine use. *JAMA* **264**:2788–2790 (1990).
16. D. Lessard, W. Menabo, J. Desrochers, and C. Menard. A high sensitivity HPLC/MS method for the determination of terfenadine in human plasma. *Pharm. Res.* **10**:S394 (1993).
17. S. L. Beal, L. B. Sheiner, A. J. Boeckmann. NONMEM users guide. San Francisco: NONMEM Project Group, University of California, 1993.
18. A. J. Boeckmann, L. B. Sheiner, S. L. Beal. NONMEM users guide Part V. Chapter 5. San Francisco: NONMEM Project Group, University of California, 1992.

19. M. Gibaldi and D. Perrier. Noncompartmental analysis based on statistical moment. In *Pharmacokinetics,* Marcel Dekker, New York, 1982, pp.409–417.
20. G. V. Belle, D. C. Martin. Sample size as a function of coefficient of variation and ratio of means. *Am. Statistician.* **47**:165–167 (1993).
21. S. Surapaneni and S. K. W. Khalil. A preliminary pharmacokinetic study of the enantiomers of the terfenadine acid metabolite in humans. *Chirality* **6**:479–483 (1994).
22. N. Rao, D. R. Weilert, M. G. A. Grace, M. G. Eller, and S. J. Weir. Pharmacokinetics of terfenadine-acid-metabolite, MDL 16,445, in healthy geriatric subjects. *Pharm. Res.* **12**:S-386 (1995).
23. J. B. Houston and G. Taylor. Drug metabolite concentration-time profiles: influence of route of drug administration. *Br. J. Clin. Pharmacol.* **17**:385–394 (1984).
24. L. B. Sheiner and T. M. Ludden. Population pharmacokinetics/ pharmacodynamics. *Annual Review of Pharmacology and Toxicology* **32**:185–209 (1992).