Pharmacokinetics of Pirmenol Enantiomers and Pharmacodynamics of Pirmenol Racemate in Patients with Premature Ventricular Contractions

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The pharmacokinetics and pharmacodynamics of pirmenol were investigated in 12 patients with premature ventricular contractions (PVCs) after oral administration of racemic pirmenol, 100 mg and 200 mg every 12 hours. Holter monitoring was performed and serial blood samples were collected after the seventh doses. Plasma concentrations of pirmenol enantiomer were determined using a stereospecific liquid chromatographic assay. Clearance of total (−)-pirmenol was 20% higher than that of total (+)-pirmenol, and the difference in unbound clearance was 45% between enantiomers. Total pirmenol showed a smaller difference because of stereoselective protein binding, with 25% (100-mg dose) or 27% (200-mg dose) higher fraction unbound for (+)-pirmenol than for (−)-pirmenol. Distribution volume was similar for both enantiomers. Dose-dependent clearance was observed for unbound pirmenol enantiomers, as both enantiomers showed 20% lower unbound clearance at the higher dose. Antiarrhythmic effect (% reduction in PVCs from baseline) was correlated with plasma concentrations of pirmenol using a sigmoid maximum drug effect model, and patients showed a large variability in their antiarrhythmic response to plasma concentrations of pirmenol. The median value for minimum effective plasma concentration of racemic pirmenol was 1.5 μg/mL.

Pirmenol is a chiral compound that is being investigated as an antiarrhythmic agent in the racemic form. Pharmacokinetics and pharmacodynamics of pirmenol have been studied after its administration as a racemic mixture. Analytical methods used for these studies quantified pirmenol as a racemate without distinguishing between enantiomers. Studies in healthy individuals and patients with premature ventricular contractions (PVCs) demonstrated that pirmenol is well absorbed, with a bioavailability of 85%.[1–3] Pirmenol is extensively metabolized, as 20% to 30% of an administered dose is excreted unchanged in urine.[1–7] Because unbound renal clearance exceeds glomerular filtration rate, however, the renal clearance of pirmenol also includes a secretory process. Pirmenol is 80% to 90% bound to human plasma proteins at therapeutic plasma concentrations, and the extent of protein binding of pirmenol is highly correlated with α_1-acid glycoprotein concentration in human plasma. Based on substantial metabolism, secretory renal clearance component, and extensive plasma protein binding of pirmenol, possibilities exist for stereoselective pharmacokinetics after administration of racemic drug. In this study, pharmacokinetic differences between enantiomers were evaluated in patients with PVCs after

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repeated oral administration of racemic pirmenol at two different doses. In addition, the effect of racemic pirmenol on suppression of PVCs was investigated. Because individual enantiomers of pirmenol are not yet approved for administration to humans, only the racemate could be studied.

PATIENTS AND METHODS

Patients

Twelve patients with PVCs participated in this multiple-, rising-dose study of pirmenol. Patients were included if a 24-hour baseline Holter monitor (Del Mar Avionics, Irvine, CA) demonstrated at least 720 ectopic beats per 24 hours and if a repeat 24-hour baseline reading showed a PVC frequency that was 40% to 160% of the initial reading. All patients previously receiving antiarrhythmic therapy, including β-adrenergic blockers and calcium channel blockers, were withdrawn from these medications before baseline Holter monitoring. Concurrent medications taken during the study were limited to drugs that do not interfere with drug metabolism and were required to be taken at least 2 hours before or 4 hours after pirmenol on the days of blood sampling. Age of patients ranged from 26 to 79 years, and weight ranged from 66.4 kg to 96.4 kg. There were nine men and three women in the study, and two of the patients were smokers. The protocol and consent form were approved by the Institutional Review Board of the Millard Fillmore Hospital (Buffalo, NY). The study was conducted at the Clinical Pharmacokinetics Laboratory of the Millard Fillmore Hospital. Written informed consent was obtained from each patient.

Study Design

Racemic pirmenol was administered orally at 100 mg or 200 mg every 12 hours with a 3-day washout period between treatments. The 100-mg regimen was administered on days 1 to 4, and the 200-mg regimen was administered on days 8 to 11 of the study; a total of seven doses were given at each dose level. Blood samples were collected before the morning dose for blank plasma on day 1 and for trough plasma concentration determinations on days 3 and 10. Holter monitoring was performed and serial blood samples were collected after the seventh dose (days 4 and 11). Blood samples (5 mL) were obtained from an indwelling intravenous catheter into evacuated collection tubes containing heparin before administration and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours after dose. Plasma was harvested and stored frozen at −20°C until analysis.

Electrocardiograms were obtained 2 hours after the morning dose on days 1, 3, 8, and 10. Holter monitor (24-hour) readings were obtained immediately after the morning dose on days 3, 4, 10, and 11. Additional 24-hour Holter monitor readings were obtained on days 5 and 12. Clinical laboratory measurements (hematology, clinical chemistry, and urinalysis) were taken on days 1 and 13, and vital signs were measured on days 1, 8, and 13.

Plasma Assay

Plasma concentrations of pirmenol enantiomer were determined using a stereospecific liquid chromatographic assay,[8] which was modified for the analysis of human plasma to eliminate an interfering peak in the chromatogram. Briefly, racemic pirmenol and internal standard ((+)-propranolol) were isolated from human plasma by a three-step extraction procedure using toluene, pH 4.5 citrate-phosphate buffer, and hexane, in that order. Pirmenol enantiomers and internal standard were separated using a cellulose-bonded chiral analytical column (Chiralcel OJ; Daicel, Tokyo, Japan) and mobile phase consisting of hexane:isopropanol:diethylamine (98.9:1.0:0.1), with ultraviolet detection at 262 nm. Linear calibration curves were obtained in the concentration range of 0.0200 μg/mL to 5.00 μg/mL for each enantiomer. Validation of the method in dog plasma using nine replicate sets of calibration standards and quality controls resulted in a precision of 7.1% or less and a bias of ±2.2% for both enantiomers. Assay validation was repeated in human plasma (n = 4), and precision and bias results were 13.4% or less and ±3.3%, respectively, for (+)-pirmenol, and 14.7% or less and ±6.0%, respectively, for (−)-pirmenol.

Protein Binding

Unbound concentrations were determined in each study sample using equilibrium dialysis. Plasma containing pirmenol (0.75 mL) was dialyzed against an equal volume of isotonic pH 7.4 phosphate buffer in a 37°C shaking water bath for 16 hours (equilibration was reached, as indicated by preliminary experiments). Plasma and buffer were placed quantitatively in and removed from dialysis cells using 1.0-mL disposable syringes. Samples were assayed for concentrations of pirmenol enantiomer using the liquid chromatographic method described previously.

Bound concentrations were corrected for volume shift[9] using the following equations:

$$Cb' = Cp' - Cf' \quad (1)$$

$$Cb'' = Cb' \left(\frac{Vp'}{Vp}\right) \quad (2)$$

where Cp′ is the concentration of pirmenol in plasma after dialysis; Cf′ is the concentration of pirmenol in buffer after dialysis (unbound or free concentration); Cb′ is the concentration of pirmenol bound in plasma after dialysis; Cb″ is the concentration of pirmenol bound in plasma after dialysis, corrected for volume shift; Vp′ is the volume of plasma after dialysis; and Vp is the volume of plasma before dialysis.

Linear or nonlinear binding was assessed from a plot of Cb″ as a function of Cf′. For nonlinear binding, a single Langmuir equation best described the Cb″-versus-Cf′ data:

$$Cb'' = \frac{P(1) \cdot Cf'}{P(2) + Cf'} \quad (3)$$

where P(1) and P(2) are capacity and dissociation constants, respectively. Nonlinear regression was performed using the program MINSQ II (Version 1.02, MicroMath Scientific Software, Salt Lake City, UT) and a weighting factor of unity. Goodness of fit criteria included standard deviation of the parameter estimates, coefficient of determination (r^2), and visual inspection of the residuals. Because equation 3 describes bound concentration as a function of unbound (free) concentration, total concentration before dialysis (Cp, the sum of bound [Cb] and unbound [Cf] concentrations before dialysis) can be expressed as

$$Cp = \frac{P(1) \cdot Cf}{P(2) + Cf} + Cf \quad (4)$$

Rearrangement of equation 4 results in quadratic equation 5, which is solved for unbound concentration (Cf) using the total concentration in the original plasma sample (Cp) and estimates of P(1) and P(2):

$$Cf^2 + (P(1) + P(2) - Cp) \cdot Cf - Cp \cdot P(2) = 0 \quad (5)$$

The unbound fraction (f_u) in the original sample before dialysis is:

$$f_u = \frac{C_f}{C_p} \quad (6)$$

Similarly, for linear binding, f_u was calculated using the following equation:

$$f_u = \frac{Cf'}{Cf' + Cb''} \quad (7)$$

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated at steady state for each enantiomer (days 4 and 11) using noncompartmental methods. Maximum plasma concentration (C_{max}; μg/mL) and time to reach C_{max} (t_{max}; hours) were determined from visual inspection of the plasma concentration–time data. Half-life ($t_{1/2}$; hours) was calculated as $0.693/\lambda_z$, where λ_z (hr^{-1}) was determined as the negative slope of the log-linear terminal phase of the plasma concentration–time profile. Area under the plasma concentration–time curve from 0 to 12 hours (AUC_{0-12}; μg·hr/mL) and area under the first moment curve ($AUMC_{0-12}$; μg·hr^2/mL) were calculated using a combination of the linear and log trapezoidal rules. Mean residence time (MRT; hours) was determined by dividing the sum of $AUMC_{0-12}$ and $T \cdot AUC_{T-\infty}$ by AUC_{0-12}, where T represents the administration interval (12 hours) and $T \cdot AUC_{T-\infty}$ is the AUMC from T extrapolated to infinity.[10] Apparent plasma clearance (Cl/F; mL/min) was calculated as Dose/AUC_{0-12}, and apparent volume of distribution (Vd/F; L) as $Cl/F \div \lambda_z$. The time-averaged f_u was estimated as AUC_{0-12} of unbound pirmenol divided by AUC_{0-12} of total pirmenol. Statistical differences among the four treatments (100-mg dose for (+)- and (−)-pirmenol and 200-mg dose for (+)- and (−)-pirmenol) were evaluated using analysis of variance, and a P value of ≤ 0.05 was considered significant. Multiple treatment comparisons were evaluated using Tukey's test. C_{max} and AUC_{0-12} values were normalized to a 100-mg dose (NC_{max} [μg/mL] and $NAUC_{0-12}$ [μg·hr/mL]) for statistical comparison of parameters at different doses.

Pharmacodynamic Analysis

Effect–concentration profiles for racemic pirmenol during the 12-hour administration interval after the final 100-mg and 200-mg doses were combined and fitted to a sigmoid E_{max} equation:

$$E = \frac{E_{max} \cdot C^s}{EC_{50}{}^s + C^s} \quad (8)$$

where E is the percent reduction in PVCs from baseline; E_{max} is the maximum drug effect; C is the average plasma pirmenol concentration (μg/mL); EC_{50} is the plasma concentration at 50% of E_{max} (μg/mL); and S is a constant that reflects the sigmoid shape of the effect–concentration curve. Effect data were averaged over 4-hour intervals as PVC frequency was highly variable. Corresponding average plasma concentrations of pirmenol were calculated as AUC_{0-4}, AUC_{4-8}, and AUC_{8-12}, each divided by the time interval (4 hours). Baseline PVCs were determined as the prestudy average number of PVCs per hour from 8:00 AM to 8:00 PM, representing the time of day during which PVCs after the final dose of pirmenol were analyzed. Both initial and repeat Holter monitor read-

ings (during subject selection) were included in the calculation of baseline PVCs. E_{max} was held constant at 100%, and EC_{50} and S values were estimated using nonlinear least-squares regression with the program MINSQ II and a weighting factor of unity. Effective therapeutic concentration, expressed as the concentration at which PVC reduction was 90% (EC_{90}; μg/mL), was calculated using the parameter estimates and a rearrangement of equation 8, such that $EC_{90} = EC_{50}/0.111^{1/S}$

RESULTS

Pharmacokinetics of Enantiomers of Pirmenol

Pharmacokinetic parameters for total and unbound enantiomers of pirmenol and results of statistical comparisons among enantiomers and between doses are given in Table I. Total plasma concentrations of (+)-pirmenol exceeded those of total (−)-pirmenol (Figure 1), with $NAUC_{0-12}$ values that were 13% and 19% higher for total (+)-pirmenol after the 100-mg and 200-mg doses, respectively. Differences in total $NAUC_{0-12}$ were statistically significant. Total C_{max} and t_{max} of pirmenol were not significantly different (NS) for (+)- and (−)-pirmenol. Cl/F of total (+)-pirmenol was 15% lower (significant) at 100 mg and 18% lower (significant) at 200 mg compared with total (−)-pirmenol, whereas Vd/F based on total drug was nearly identical for both enantiomers. As a result, $t_{1/2}$ was 13% (significant) and 17% (significant) longer for total (+)-pirmenol than for total (−)-pirmenol after 100-mg and 200-mg doses, respectively. MRT was approximately 20% longer (significant) for (+)-pirmenol at both doses. No statistically significant differences were observed between doses for the pharmacokinetic parameters of total pirmenol enantiomers.

Plasma concentrations of unbound (+)-pirmenol also exceeded those of unbound (−)-pirmenol (Figure 2). Unbound pirmenol showed 33% (NS) and 35% (significant) higher C_{max} values for (+)-pirmenol at 100 mg and 200 mg, respectively, than (−)-pirmenol, with similar t_{max} values for both enantiomers. Differences in AUC_{0-12} between unbound enantiomers were even greater than for total drug, with 44% (significant) and 53% (significant) higher AUC_{0-12} values for unbound (+)-pirmenol than for unbound (−)-pirmenol after 100-mg and 200-mg doses, respectively. Apparent plasma clearance of unbound (−)-pirmenol (Cl_u/F) was 42% greater (significant) at 100 mg and 49% greater (significant) at 200 mg compared with (+)-pirmenol. Unbound volumes of distribution (Vd_u/F) differed by 10% to 20% (NS) between enantiomers, with Vd_u/F greater for (−)-pirmenol than for (+)-pirmenol. The $t_{1/2}$ values were 31% (significant) and 22% (significant) longer for unbound (+)-pirmenol at 100 mg and 200 mg, respectively. MRT was approximately 20% longer (NS) for (+)-pirmenol at both doses. Protein binding in plasma was stereoselective, as observed by the 25% (significant; 100 mg) and 27% (significant; 200 mg) higher f_u for (+)-pirmenol than for (−)-pirmenol.

Pharmacodynamics of Racemic Pirmenol

Individual effect–concentration profiles are shown for three patients in Figure 3. These profiles represent three different general appearances that were observed: 1) effect data distributed over a wide range of effect (patient no. 4); 2) effect data mostly at or near full suppression of PVCs (patient no. 10); and 3) effect–concentration data displaying possible hysteresis (patient no. 2). Of the 12 patients, 5 showed a wide range of effect, 5 had extensive suppression of PVCs (>80%) for the administration interval, and 2 showed possible hysteresis. Two of the 12 patients showed 100% suppression of PVCs during the entire administration interval. Therefore, fitting of the effect–concentration data was performed only for the remaining 10 patients.

Pharmacodynamic parameter estimates are listed in Tables II and III for total and unbound pirmenol, respectively. Estimates of EC_{50} ranged from 0.080 μg/mL to 1.58 μg/mL (20-fold) with a mean value of 0.73 μg/mL, and S values ranged from approximately 1 to 5 (mean 3.01) for total racemic pirmenol. EC_{90} values for total racemic pirmenol ranged from 0.40 μg/mL to 11.3 μg/mL (mean, 2.29 μg/mL). Because patient no. 12 showed an unusually high EC_{90} value, a mean EC_{90} was also calculated in the absence of this patient (1.29 μg/mL). For unbound racemic pirmenol, EC_{50} estimates ranged from 0.0041 μg/mL to 0.25 μg/mL (61-fold) with a mean value of 0.12 μg/mL, and S values ranged from approximately 1 to 4 (mean, 2.55). EC_{90} values for unbound racemic pirmenol ranged from 0.045 μg/mL to 1.62 μg/mL (mean, 0.38 μg/mL) and from 0.045 μg/mL to 0.57 μg/mL (mean, 0.25 μg/mL) without patient no. 12.

DISCUSSION

Small but significant differences were observed between plasma concentrations of pirmenol enantiomers based on total drug. Cl/F was significantly lower and $t_{1/2}$ was significantly longer for (+)-pirmenol than for (−)-pirmenol, although these differences were 21% or less. When these pharmacokinetic parameters were based on unbound drug, however, a much larger difference between enantiomers was ob-

TABLE I

Pharmacokinetic Parameters of Pirmenol Enantiomers in Patients with Premature Ventricular Contractions (n = 12) after Repeated Oral Administration of 100-mg or 200-mg Racemic Pirmenol Every 12 Hours

Parameter	100 mg		200 mg		Significance		
	(+)	(−)	(+)	(−)	Between Enantiomers (for same dose)	Between Doses (for same enantiomer)	P Value*
Total pirmenol							
NC_{max} (μg/mL)	0.77 (0.26)	0.73 (0.26)	0.81 (0.19)	0.74 (0.19)	NS	NS	0.133
t_{max} (hr)	1.8 (0.5)	1.8 (0.4)	1.8 (0.5)	1.7 (0.5)	NS	NS	0.898
$t_{1/2}$ (hr)	10.5 (3.5)	9.25 (2.67)	10.9 (2.9)	9.25 (2.50)	*S*, (+) > (−)	NS	0.0006
$NAUC_{0-12}$ (μg · hr/mL)	6.29 (2.44)	5.57 (2.36)	6.41 (1.80)	5.39 (1.63)	*S*, (+) > (−)	NS	0.0005
MRT (hr)	15.1 (4.3)	12.9 (3.3)	15.2 (4.8)	12.7 (4.1)	*S*, (+) > (−)	NS	0.0004
Cl/F (mL/min)	151 (57)	178 (81)	141 (44)	171 (61)	*S*, (−) > (+)	NS	0.0004
Vd/F (L)	127 (33)	132 (44)	126 (27)	128 (26)	NS	NS	0.773
Unbound pirmenol							
NC_{max} (μg/mL)	0.16 (0.07)	0.12 (0.05)	0.23 (0.11)	0.17 (0.08)	*S*, (+) > (−) at 200 mg	*S*, (200 mg > 100 mg)	0.0001
t_{max} (hr)	1.8 (0.5)	1.7 (0.5)	1.8 (0.5)	1.7 (0.5)	NS	NS	0.942
$t_{1/2}$ (hr)	8.85 (2.97)	6.77 (1.75)	8.53 (3.38)	6.98 (3.17)	*S*, (+) > (−)	NS	0.0007
$NAUC_{0-12}$ (μg · hr/mL)	1.16 (0.48)	0.808 (0.331)	1.48 (0.60)	0.969 (0.353)	*S*, (+) > (−)	*S*, (200 mg > 100 mg) for (+)	0.0001
MRT (hr)	13.2 (3.8)	11.1 (1.7)	12.1 (4.6)	10.0 (4.1)	NS	NS	0.0053
Cl_u/F (mL/min)	862 (404)	1220 (561)	677 (324)	1010 (467)	*S*, (−) > (+)	*S*, (100 mg > 200 mg)	0.0001
Vd_u/F (L)	593 (166)	652 (172)	464 (227)	558 (249)	NS	*S*, (100 mg > 200 mg) for (+)	0.0002
f_u	0.185 (0.044)	0.148 (0.032)	0.229 (0.066)	0.181 (0.050)	*S*, (+) > (−)	*S*, (200 mg > 100 mg)	0.0001

* *For ANOVA and not for pairwise comparison.*

Values are presented as the mean (± standard deviation). NC_{max}, maximum concentration normalized to a 100-mg dose; t_{max}, time to reach C_{max}; $t_{1/2}$, half-life; $NAUC_{0-12}$, area under the concentration–time curve from time 0 to 12 hours normalized to a 100-mg dose; MRT, mean residence time; Cl/F, apparent plasma clearance; Vd/F, apparent volume of distribution; Cl_u/F, Cl of unbound drug; Vd_u/F, Vd of unbound drug; f_u, time-averaged fraction unbound in plasma; NS, not significant.

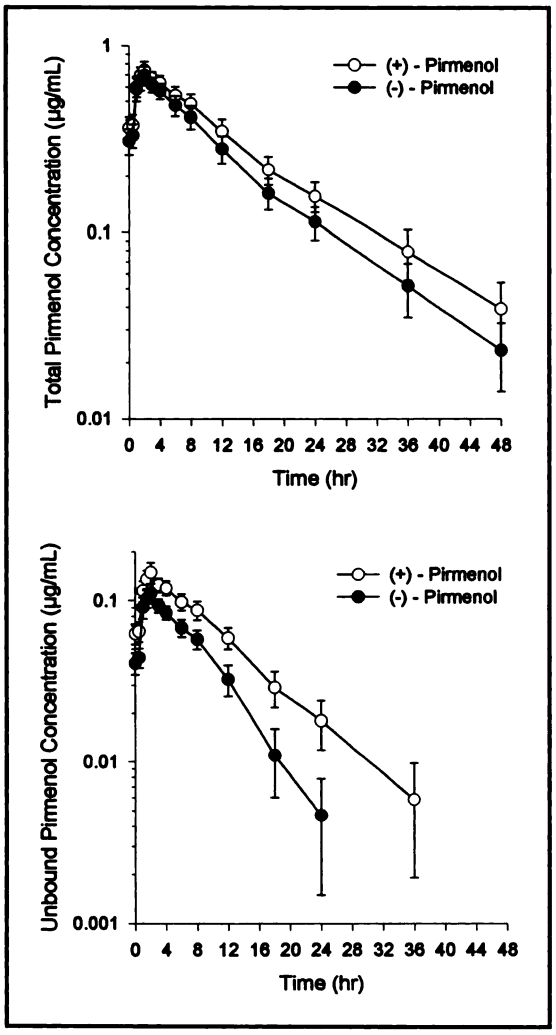

Figure 1. Mean (±SE) plasma concentrations of total and unbound pirmenol enantiomers after repeated oral administration of 100 mg of racemic pirmenol every 12 hours on days 1 through 4 to patients with PVCs (n = 12). Data are from the day 4 dose.

served (≤49%). The more rapidly cleared unbound (−)-pirmenol also had a lower f_u in plasma. Consequently, stereoselective protein binding was in the opposite direction to that of intrinsic clearance, thus minimizing differences in the Cl/F of pirmenol based on total drug.

Disopyramide, which has a chemical structure similar to pirmenol, showed a lack of stereoselectivity in total drug clearance with a significant difference between the enantiomers in clearance of unbound drug.[11–14] Like pirmenol, the enantiomer with higher unbound clearance (i.e., *S*(+)-disopyramide) was also the enantiomer with lower f_u in plasma. Stereoselective plasma clearances have been reported for other antiarrhythmic agents such as tocainide[15–17] (higher clearance for *R*(−)-enantiomer), mexiletine[18] (higher clearance for *R*(−)-enantiomer), flecainide[19] (higher clearance for *S*(+)-enantiomer in poor metabolizers), encainide[20] (higher clearance for (−)-enantiomer in extensive metabolizers), propafenone[21,22] (higher clearance for *S*(+)-enantiomer), propranolol[23–26] (higher clearance for *R*(+)-enantiomer), verapamil[27–29] (higher clearance for *S*(−)-enantiomer), and nitrendipine[30,31] (higher clearance for *R*(+)-enantiomer).

Higher clearance of (−)-pirmenol is not likely a result of stereoselective first-pass metabolism in the liver as pirmenol is not a high extraction ratio drug. Nonrenal blood clearance of pirmenol was reported as 100 mL/min in patients with PVCs.[1] When this

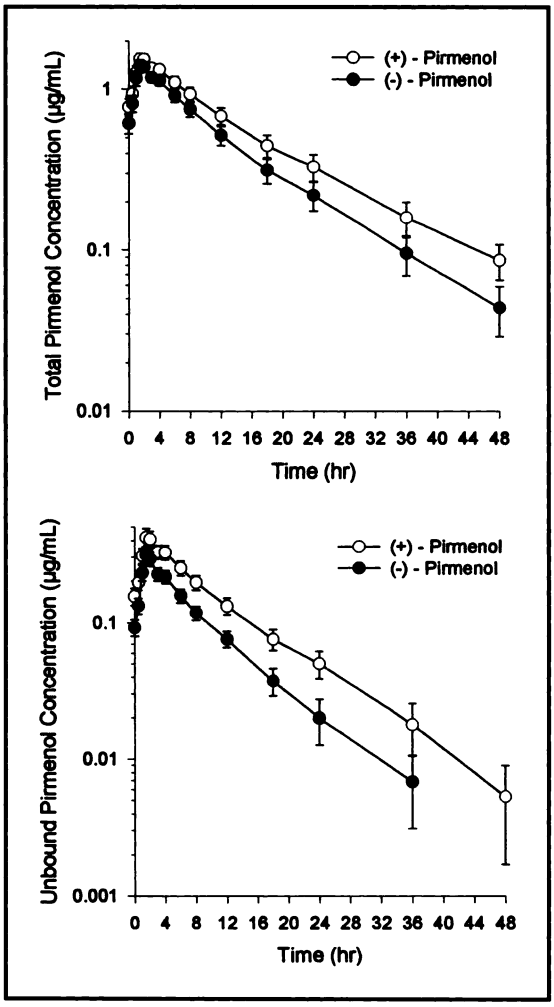

Figure 2. Mean (±SE) plasma concentrations of total and unbound pirmenol enantiomers after repeated oral administration of 200 mg of racemic pirmenol every 12 hours on days 8 through 11 to patients with PVCs (n = 12). Data are from the day 11 dose.

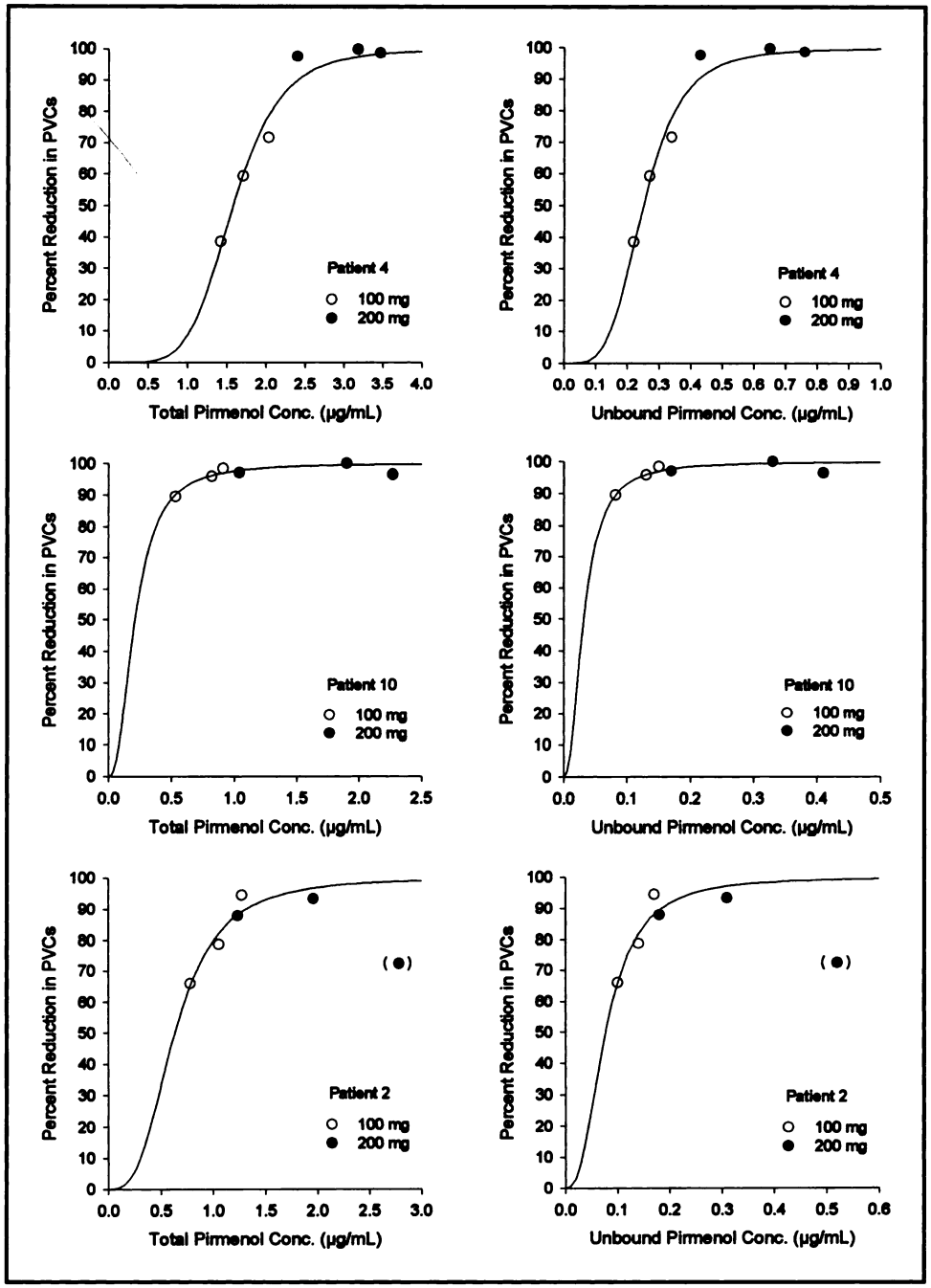

Figure 3. Effect–concentration profiles for total and unbound pirmenol in representative patients after the combined final 100-mg and 200-mg doses of repeated oral administration of racemic pirmenol every 12 hours to patients with PVCs. Data in parentheses were not used in determining the computer-fitted parameters.

value is compared with an average value of 1,350 mL/min for liver blood flow, pirmenol is estimated to have a low hepatic extraction (<10%). In addition, the apparent $t_{1/2}$ of (+)-pirmenol was significantly longer than (−)-pirmenol, which is more suggestive of an enantiomer difference in systemic elimination.

Difference in intrinsic (unbound) clearance between (+)- and (−)-pirmenol may be a result of stereoselective metabolic clearance, renal clearance, or both. (−)-Pirmenol may be preferentially metabolized compared with (+)-pirmenol. Also, if the secretion component of renal excretion is stereoselective, (−)-pirmenol may be excreted more efficiently than (+)-pirmenol. Although metabolic clearance is the

TABLE II

Pharmacodynamic Parameters for Total Pirmenol in Patients with Premature Ventricular Contractions after the Final Dose of Repeated Oral Administration of Racemic Pirmenol at 100 mg and 200 mg Every 12 Hours

Patient	Baseline* PVCs/hr	EC_{50}		S		r^2	EC_{90}
		Estimate	SD	Estimate	SD		
1†	4	—	—	—	—	—	<1.06
2	915	0.63	0.06	2.99	0.65	0.906	1.31
3	681	0.65	0.04	5.32	1.34	0.923	0.98
4	976	1.58	0.05	5.19	0.87	0.963	2.41
5	125	0.90	0.12	3.10	1.41	0.725	1.83
6	120	0.81	0.01	3.31	0.17	0.997	1.57
7	301	0.080	0.048	1.36	0.34	0.878	0.40
8	917	0.35	0.09	2.59	0.95	0.842	0.82
9†	74	—	—	—	—	—	<1.42
10	837	0.21	0.07	2.38	0.71	0.807	0.53
11	237	0.79	0.09	2.82	0.98	0.842	1.72
12	536	1.28	0.26	1.01	0.32	0.754	11.3
Mean		0.73		3.01			2.29
SD		0.46		1.40			3.23
Without patient 12							
Mean							1.29
SD							0.66

* *Based on an 8 AM to 8 PM time interval (12 hours) whereas baseline PVCs/hr for entry into the study were determined during an 8 AM to 8 AM time interval (24 hours).*

† *Subjects 1 and 9 showed 100% PVC suppression during the entire administration interval; estimated EC_{90} values were not included in calculation of mean values.*

PVC, premature ventricular contraction; EC_{50}, plasma drug concentration at 50% of E_{max} (μg/mL); EC_{90}, plasma drug concentration at 90% of E_{max} (μg/mL).

major route of elimination for pirmenol, it can not be assumed that the stereoselective difference in intrinsic clearance is only due to metabolism. As renal clearance was not determined in this study, however, the relative contribution of metabolism and renal excretion to the total clearance of each enantiomer is not known.

Pharmacokinetics of pirmenol appear to be dose proportional from 100 mg to 200 mg when total pirmenol is measured. However, dose-dependent clearance was observed for unbound pirmenol, with a 20% reduction in apparent plasma clearance at the higher dose for both enantiomers. This would suggest that metabolism or final clearance of pirmenol may be saturable; however, unbound clearance should be studied over a wider range of doses to evaluate dose dependence. The dose proportionality observed for total pirmenol may be a result of similar but opposite effects on the f_u and intrinsic (unbound) clearance. Average f_u was approximately 25% higher at the higher dose for both enantiomers (Table I). Higher f_u at the 200-mg dose compared with the 100-mg dose probably contributed to higher concentrations of unbound drug at the higher dose than would have been observed if binding was linear. These unbound drug concentrations may have resulted in a reduced intrinsic (unbound) clearance of pirmenol at the higher dose; thus, the apparent plasma clearance of the enantiomers of total pirmenol appeared independent of dose.

The time course of drug effect is shown in Figure 4; suppression of PVCs is generally highest in the first 4-hour interval after administration, followed by a gradual return of PVCs as drug concentrations decrease. Two patients (nos. 2 and 6) showed an apparent hysteresis in their effect–concentration profile, suggesting an equilibration delay in drug response. Because only 2 of the 12 patients displayed this effect, the apparent preequilibration data were omitted from pharmacodynamic modeling for these patients.

Pharmacodynamic analysis of racemic pirmenol showed good correlation between antiarrhythmic effect and plasma concentrations of pirmenol, with r^2 values ranging from 0.725 to 0.997 for total pirmenol and from 0.727 to 0.999 for unbound pirmenol (Ta-

TABLE III

Pharmacodynamic Parameters for Unbound Pirmenol in Patients with Premature Ventricular Contractions after the Final Dose of Repeated Oral Administration of Racemic Pirmenol at 100 mg and 200 mg Every 12 Hours

Patient	Baseline* PVCs/hr	EC_{50}		S		r^2	EC_{90}
		Estimate	SD	Estimate	SD		
1†	4	—	—	—	—	—	<0.16
2	915	0.077	0.010	2.52	0.63	0.879	0.18
3	681	0.12	0.01	4.42	1.12	0.923	0.20
4	976	0.25	0.01	4.12	0.66	0.969	0.43
5	125	0.13	0.02	2.64	1.22	0.727	0.30
6	120	0.14	0.002	2.77	0.10	0.999	0.31
7	301	0.0041	0.0036	0.92	0.23	0.891	0.045
8	917	0.047	0.014	2.56	1.09	0.802	0.11
9†	74	—	—	—	—	—	<0.21
10	837	0.031	0.010	2.21	0.65	0.810	0.084
11	237	0.23	0.03	2.41	0.84	0.850	0.57
12	536	0.16	0.04	0.95	0.32	0.729	1.62
Mean		0.12		2.55			0.38
SD		0.08		1.12			0.46
Without patient 12							
Mean							0.25
SD							0.17

* *Based on an 8 AM to 8 PM time interval (12 hours) whereas baseline PVCs/hr for entry into the study were determined during an 8 AM to 8 AM time interval (24 hours).*

† *Subjects 1 and 9 showed 100% PVC suppression during the entire administration interval; estimated EC_{90} values were not included in calculation of mean values.*

PVC, premature ventricular contraction; EC_{50}, plasma drug concentration at 50% of E_{max} (μg/mL); EC_{90}, plasma drug concentration at 90% of E_{max} (μg/mL).

bles II and III). Spontaneous variability in PVCs, which has been documented in other studies,[32–35] was reduced by averaging the effect–concentration data over 4-hour intervals. Holazo et al[36] showed that 6-hour averaged data sets adequately described the antiarrhythmic effect profile for cibenzoline and improved correlation compared with using hourly intervals.

Individual antiarrhythmic response to plasma concentrations of pirmenol was highly variable, as shown by the representative effect–concentration plots in Figure 3. The overall effect–concentration relationship (using mean EC_{50} and S values) with individual data superimposed on the curve is shown in Figure 5. This figure demonstrates that individual data are reasonably well represented by the mean parameter estimates.

The plasma concentration of pirmenol required for EC_{90} was selected to represent the minimum effective concentration as at least 70% to 80% reduction from baseline of PVCs is generally accepted as the criterion for antiarrhythmic drug efficacy.[37] The mean (±SD) EC_{90} value of 1.29 ± 0.66 μg/mL (without patient no. 12) for total pirmenol was consistent with the previously reported average minimum effective concentration of approximately 1 μg/mL, which was determined from observation of the pirmenol concentration corresponding to 70% to 90% reduction in PVCs.[1,4,6,7,38–44] Minimum effective concentrations for an individual patient ranged from 0.2 μg/mL to 2.75 μg/mL in these literature reports and are similar to the estimated EC_{90} values of 0.40 μg/mL to 2.41 μg/mL in this study (except for patient no. 12 who had an EC_{90} value of 11.3 μg/mL). Mean (±SD) effective concentration of unbound pirmenol (EC_{90}) in this study was 0.25 ± 0.17 μg/mL (without patient no. 12); values have not been reported for effective concentration of unbound pirmenol in earlier studies.

Based on total drug, clearance of (−)-pirmenol is 20% higher than clearance of (+)-pirmenol, whereas clearance based on unbound drug reveals a larger difference (≤49%) between enantiomers. Both of these differences were statistically significant. Smaller difference in clearance based on total drug may, in part, reflect protein binding differences, as

the more rapidly cleared unbound (−)-pirmenol is also more extensively bound to plasma proteins than is (+)-pirmenol. Pirmenol enantiomers are distributed to tissues to a similar extent.

Pharmacokinetics of pirmenol appear to be dose proportional from 100 mg to 200 mg when total pirmenol is measured. However, unbound pirmenol shows a dose-dependent clearance with 20% slower clearance at the higher dose for both enantiomers. Because protein binding was saturable for most patients, f_u increased at the 200-mg dose (in the opposite direction of unbound clearance), resulting in apparent linearity of pharmacokinetics of total pirmenol.

Antiarrhythmic effect can be correlated with plasma concentrations of pirmenol using a sigmoid E_{max} model. Patients show a large variability in their antiarrhythmic response to plasma concentrations of pirmenol (total or unbound). The median value for EC_{90} of racemic pirmenol was approximately 1.5 μg/mL.

Although unbound clearance of (−)-pirmenol was significantly higher (42% to 49%) than its antipode,

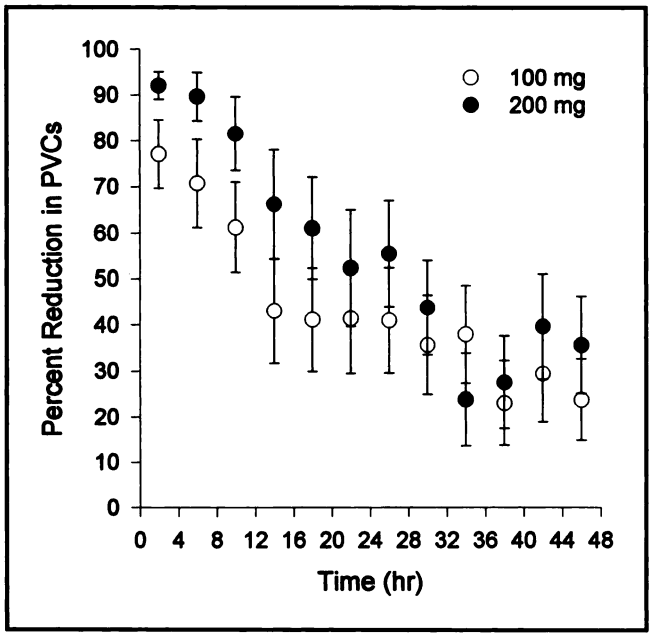

Figure 4. Mean (±SE) effect–time profile after the final 100-mg or 200-mg doses of repeated administration of racemic pirmenol every 12 hours to patients with PVCs. Data are plotted at the midpoint of each 4-hour interval in which average PVC reduction was calculated. Baseline values (PVCs per hour) used to calculate PVC reduction in this figure were determined separately for day (8:00 AM to 8:00 PM) and night (8:00 PM to 8:00 AM) periods to prevent bias in PVC reduction, which could occur if a subject had diurnal variation in baseline PVCs.

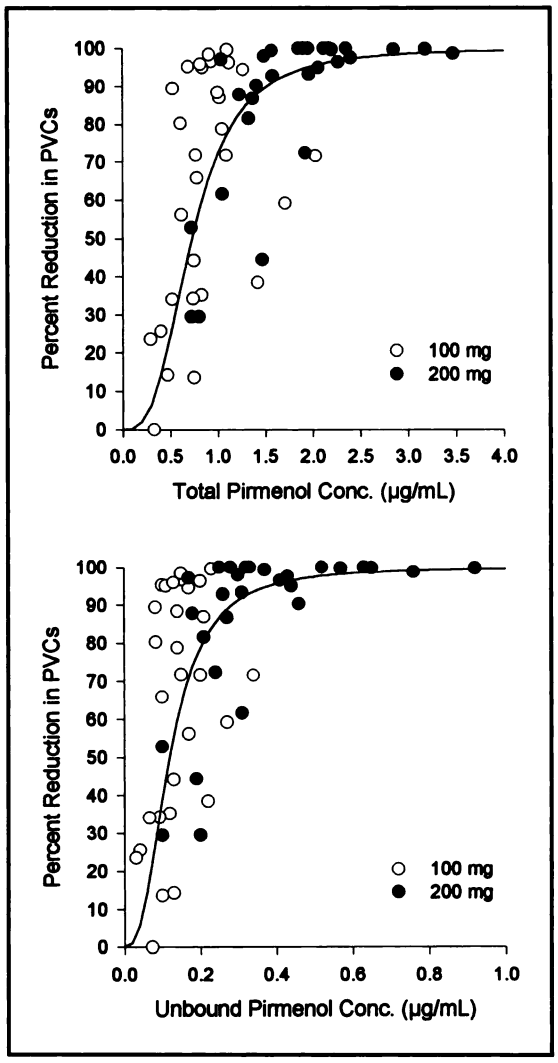

Figure 5. Total and unbound effect–concentration profiles of pirmenol in patients with PVCs after the combined final 100-mg and 200-mg doses of repeated oral administration of racemic pirmenol. The solid line represents the hypothetical effect–concentration curve based on mean EC_{50} and S values as displayed in Tables II and III. Individual data are superimposed on this curve.

the clinical significance of this difference (in terms of dynamics) cannot be determined as it is uncertain whether pirmenol enantiomers will have similar antiarrhythmic activities in humans. In the absence of regulatory agency approval for administration of individual enantiomer to humans, only the racemate has been studied to date.

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