Plasma and Saliva Propafenone Concentrations at Steady State

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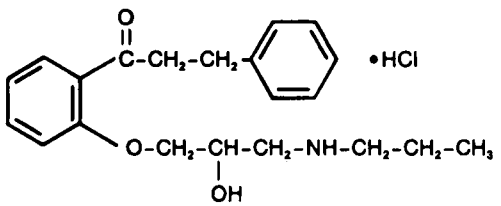
Abstract □ Twenty-four healthy male subjects were administered 300 mg of propafenone every 8 h for 6 d in each of two phases that were separated by 2 d. Plasma samples were collected during the approach to steady state for each phase, and plasma and saliva samples were collected frequently at steady state. Both plasma and saliva propafenone were assayed by a specific HPLC method. Two estimates of elimination half-life ($t_{1/2}$), mean steady-state concentration ($\overline{CP_{ss}}$), time to maximal concentration (t_{max}), and maximal concentration (CP_{max}) were estimated for each subject. Also mean steady-state saliva concentrations ($\overline{CS_{ss}}$), time to maximal saliva concentration (tS_{max}), and maximal saliva concentrations (CS_{max}) were estimated. A large intersubject variance in both $t_{1/2}$ and $\overline{CP_{ss}}$ were observed in the 24 subjects, with the $t_{1/2}$ values ranging from 2.1 to 27.2 h and the $\overline{CP_{ss}}$ values from 0.3 to 3.03 μg/mL. Each subject was quite consistent for the two phases, suggesting a relatively low intrasubject variance for propafenone kinetics. A histogram shows most subjects to have $t_{1/2}$ values between 2 and 10 h, with diminishing numbers of subjects at greater $t_{1/2}$ values rather than a bimodal distribution. Saliva concentrations ranged from 12 to 72% of the corresponding plasma concentrations, being 24.7 ± 11.1% of the simultaneously collected plasma sample overall (mean ± SD). A significant ($p < 0.001$) positive correlation exists between $\overline{CP_{ss}}$ and $\overline{CS_{ss}}$.

Propafenone is a promising new antiarrhythmic drug which has been marketed in several countries and is presently undergoing clinical testing in the USA. Propafenone has been proved effective in suppressing ventricular[1,2] and supraventricular arrhythmias.[3] Both the clinical pharmacology[4] and disposition kinetics[5,6] have been the subject of recent reports. The published reports[4-6] and observations in our laboratories indicate a relatively large interpatient range in plasma concentrations of propafenone for the same daily dosage. Also, the bioavailability and/or systemic clearance[5] of propafenone is reported to be dose dependent. In 11 patients taking 900 mg/d,[4] the steady-state plasma concentrations ranged from 0.482 to 1.812 μg/mL (mean 1.008 μg/mL), with therapeutically effective concentrations between 0.064 and 1.044 μg/mL (mean 0.588 μg/mL). The wide range of plasma concentrations has been associated with a corresponding range of plasma half-lives. For example, Salerno et al.[1] reported steady-state elimination half-lives ranging from 1.8 to 17.2 h, and Siddoway et al.[7] reported a range of 1.8 to 32.3 h.

Propafenone is extensively metabolized, with <1% of an oral dose being recovered in the urine unchanged.[8] Propafenone, like sparteine,[9] phenformin,[10] and debrisoquin[11] may have genetically determined differences in the metabolic pathway. In support of this hypothesis, Siddoway et al.[12,13] used debrisoquin metabolism as a marker to classify patients into "poor" and "extensive" metabolizers of propafenone. These studies suggest as many as 20% of the population may be "poor" metabolizers with half-lives >10 h. Further studies of the distribution of propafenone metabolizers and kinetics of metabolism are needed to evaluate this hypothesis.



Propafenone

The study reported herein was conducted as part of a bioequivalency study with the further objectives of evaluating the inter- and intrasubject variance in steady-state plasma propafenone; the distribution of elimination half-lives for propafenone; and the possible correlation of saliva propafenone concentrations with plasma propafenone concentrations.

Experimental Section

Study Design—Twenty-four nonsmoking, healthy, adult male volunteers between the ages of 19 and 32 years (mean 24.1 years) and weighing between 63.6 and 81.8 kg (mean 72.6 kg) participated in the study. The health of each subject was assessed by a complete medical history, physical exam, a 12-lead electrocardiogram, and clinical laboratory analysis. Those with a history of chronic drug use and those having any drugs within the last two weeks were excluded. Alcohol and caffeine beverages were omitted for 72 h prior to and during the study. All subjects signed an IRB-approved informed consent.

A two-phase design allowed two estimates of elimination half-life and steady-state plasma concentrations in each subject. Each phase consisted of 5 d of dosing with 300 mg of propafenone [a randomized crossover of Rytmol (Lot No. 64-0183, Knoll, USA) and Rytmonorm (Lot No. 0894, Knoll, AG) was used and the two were found bioequivalent] every 8 h (7:00 a.m., 3:00 p.m., and 11:00 p.m.) and a single 300-mg dose at 7:00 a.m. on the sixth day. Phase 2 dosing began 48 h after the last dose of phase 1. Blood samples were collected daily just prior to the 7:00 a.m. and 11:00 p.m. doses (trough concentrations) on days 1–5, and 2 h after the 7:00 a.m. doses on days 3, 4, and 5 of each phase. All subjects fasted 10 h prior to and 2 h after the final dose of each phase, and blood samples were collected prior to dosing and at 0.25, 0.50, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h. Also, saliva was collected over a 10-min interval immediately prior to dosing and at 2, 4, 8, and 12 h after dosing on day 6 of each phase. Plasma was immediately separated from the blood, and all plasma and saliva samples were quickly frozen and maintained frozen until analysis.

Propafenone Assay—Both plasma and saliva propafenone were quantitated using a highly specific HPLC method described previously.[14] As employed in this study, the lower limit for quantitation of propafenone was 0.05 μg/mL in plasma and 0.07 μg/mL in saliva.

Pharmacokinetic Analysis—A noncompartment model approach was employed to describe the plasma propafenone profiles on day 6 of each phase. The highest observed plasma and saliva concentrations (CP_{max} and CS_{max}) and time from dosing to CP_{max} or CS_{max} (tP_{max} and tS_{max}) were recorded for each plasma curve. Linear regression of the natural logarithm of plasma concentration versus time for times greater than $2 \times tP_{max}$ were used to estimate the elimination half-life in plasma. The linear trapezoidal approximation was used to

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estimate the area under the curve (AUC) for plasma and saliva over one dosing interval (i.e., 8 h) on the sixth day of each phase. The AUC for an 8-h dosing interval was divided by 8 h to estimate the mean concentration for both plasma ($\overline{CP_{ss}}$) and saliva ($\overline{CS_{ss}}$).

Results and Discussion

Table I summarizes the plasma propafenone concentrations for both trough (7:00 a.m. and 11:00 p.m.) and 2 h postdosing (9:00 a.m.) samples on days 1–6 of each phase. Plasma concentrations rise steadily over each phase with the concentrations of the second phase being significantly higher than those of the first phase. Trough concentrations on day 6 of the first phase are ~10% higher than on day 5 ($p < 0.05$), while the differences between these two days differ <6% for the second phase. Also, the concentrations of the second phase are higher than those of the first phase for corresponding sample times. These observations suggest a steady state was approached in both phases. As steady state is approached, the 7:00 a.m. concentrations are ~15% higher than the 11:00 p.m. concentrations, suggesting a small diurnal variation.

Of note is the decrease in variance among subjects as the steady state is approached. Coefficients of variation are >200% for the trough concentrations on day 2, and decline to <70% by day 6. Similarly, the 2-h concentrations have coefficients of variation of 87% on day 3 of the first phase, which decline to 42% by day 6. Similar but less dramatic changes are observed during the second phase. This intersubject variance is also observed in the range of concentrations observed in these 24 subjects. For example, as late as the fifth day of the second phase, three subjects have trough concentrations at 11:00 p.m. <0.05 μg/mL, while the highest observed concentration is 2.1 μg/mL.

A comparative view of inter- and intrasubject variance in the mean steady-state plasma concentrations and elimination half-lives for day 6 of each phase is presented in Table II. The subjects are presented in rank order of the mean steady-state plasma concentration which closely parallels the rank order of the half-lives. There is about a 10-fold range in the average plasma concentrations, with the highest at ~3.0 μg/mL and the lowest at 0.30 μg/mL, while the half-lives range from ~2 d to 2 h. Compared with the wide range among subjects, the two observations in each subject differ very little. For 20 of the 24 subjects, the $\overline{CP_{ss}}$ for two observations differs <25%, with the range of the ratios 0.61–1.44. Figure 1 is a histogram of the average half-life (for two observations in each subject) showing 19 subjects with half-lives <8 h and five with half-lives >10 h. This plot shows the greatest

Table II—Mean Steady-State Propafenone Concentration and Half-Life[a]

Subject	Weight, kg	First Phase		Second Phase		Ratio (1st:2nd)	
		Half-Life, h	$\overline{CP_{ss}}$, μg/mL	Half-Life, h	$\overline{CP_{ss}}$, μg/mL	Half-Life	$\overline{CP_{ss}}$
23	71.8	22.44	2.39	12.24	1.92	1.83	1.24
11	65.5	20.44	1.98	14.19	3.03	1.44	0.65
17	78.2	25.73	1.93	28.63	2.07	0.90	0.93
5	75.5	4.31	1.84	8.18	1.71	0.53	1.08
4	73.6	6.36	1.52	6.13	1.42	1.04	1.07
16	78.6	5.47	1.36	5.67	1.30	0.96	1.05
19	79.5	8.94	1.34	11.45	1.60	0.78	0.84
24	64.5	4.83	1.34	8.01	1.36	0.60	0.99
1	78.2	11.26	1.30	11.24	1.29	1.00	1.01
2	81.8	4.43	1.16	6.92	1.27	0.64	0.91
10	73.6	2.38	1.08	3.48	1.28	0.68	0.84
15	73.6	4.32	1.05	5.68	1.17	0.76	0.90
8	75.5	8.19	1.00	2.95	1.39	2.78	0.72
21	66.8	4.08	1.00	4.92	0.94	0.83	1.06
18	71.4	4.08	0.98	4.23	1.03	0.96	0.95
7	63.6	3.52	0.96	3.60	1.13	0.98	0.85
12	68.2	3.87	0.82	3.90	0.57	0.99	1.44
13	68.2	4.03	0.80	2.87	0.81	1.40	0.99
20	68.2	2.77	0.79	3.14	0.83	0.88	0.95
22	78.2	2.52	0.63	3.60	1.03	0.70	0.61
14	73.2	3.35	0.62	1.91	0.57	1.75	1.09
9	75.0	6.93	0.60	2.10	0.66	3.30	0.91
3	64.1	3.47	0.58	3.26	0.58	1.06	1.00
6	64.5	2.16	0.31	2.08	0.30	1.04	1.03

[a] Following 300 mg of propafenone every 8 h for 6 d.

Table I—Plasma Propafenone Concentrations[a]

Day	First Phase[b]					Second Phase				
	Mean	%CV	Median	Low	High	Mean	%CV	Median	Low	High
				7:00 a.m. (Pre-First Dose)						
1	BQL[c]	0	BQL	BQL (24)	BQL	0.05	280	BQL	BQL (21)	0.54
2	0.27	226	BQL	BQL (18)	2.38	0.43	93	0.44	BQL (7)	1.42
3	0.44	161	0.19	BQL (12)	3.06	0.67	73	0.64	BQL (3)	1.81
4	0.63	94	0.52	BQL (4)	2.61	0.78	64	0.69	BQL (1)	2.30
5	0.69	72	0.57	BQL (2)	2.05	0.82	59	0.78	0.08	2.12
6	0.74	58	0.63	BQL (1)	1.74	0.82	59	0.75	0.10	2.19
				9:00 a.m. (2 h after First Dose)						
3	0.95	87	0.84	BQL (2)	4.04	1.15	50	1.06	0.38	2.42
4	1.05	61	0.91	0.32	2.97	1.22	54	1.09	0.22	3.39
5	1.07	53	0.98	BQL (1)	2.44	1.22	50	1.15	0.44	3.19
6	1.24	42	1.14	0.40	2.48	1.28	47	1.19	0.37	3.09
				11:00 p.m. (Prior to Third Daily Dose)						
1	0.17	259	BQL	BQL (20)	1.88	0.19	158	BQL	BQL (16)	0.99
2	0.35	206	BQL	BQL (15)	3.09	0.46	85	0.49	BQL (6)	1.32
3	0.48	144	0.39	BQL (11)	2.87	0.64	75	0.61	BQL (3)	2.09
4	0.57	93	0.46	BQL (5)	2.09	0.65	77	0.63	BQL (3)	2.28
5	0.64	70	0.56	BQL (3)	1.77	0.69	72	0.66	BQL (3)	2.10

[a] During dosing of 300 mg of propafenone every 8 h at 7:00 a.m., 3:00 p.m., and 11:00 p.m.; expressed as μg/mL. [b] One day without dosing between phase 1 and phase 2. [c] Below quantitation limit of 0.05 μg/mL, with (n) the number of subjects <0.05 μg/mL (BQL is treated as 0 in average and SD calculations).

frequency of half-lives between 2 and 4 h, with the frequency decreasing at longer half-lives.

Table III presents a summary of the saliva and plasma parameters for the sixth day of each phase. As the first break in the distribution of half-lives of Figure 1 occurred between 8 and 10 h, the five subjects with half-lives >10 h were separated as "poor" metabolizers, as suggested by the work of Siddoway.[12,13] The statistics in Table III are presented for all subjects together and then for those arbitrarily selected "poor" metabolizers and the remaining 19 "extensive" metabolizers. While the mean $\overline{CP_{ss}}$ and CP_{max} values are slightly higher during the second phase, these differences are not significant ($p < 0.05$), and the power to detect a difference is quite high for the "extensive" metabolizers and all subjects combined. The estimates of the plasma half-lives, while not significantly different by phase, are of lower power[15] due to a greater variance. Overall, the "poor" metabolizers have average plasma concentrations about twice those of the "extensive" metabolizers and constitute ~20% of our 24 subjects.

Saliva concentrations during the second phase are significantly higher than during the first phase, by ~16%, and occur ~1.5 h following dosing rather than 2.83 h. Using a typical volume of 0.75 L/d[16] for saliva and the overall mean concentration of 0.27 μg/mL, one can estimate that ~0.02% of the daily dose was recycled via the saliva and thus should not influence plasma profiles. As shown in Figure 2, a significant correlation exists ($p < 0.0001$) between the 48 paired observations of average saliva concentration and average plasma concentration on the sixth day of each phase, with a correlation coefficient of 0.66346. Correlations for the two phases separately were essentially identical to those of the two phases combined. Some subjects noted a distinct metallic taste which may be explained by the propafenone in the saliva.

Several aspects of propafenone disposition kinetics have been demonstrated in this study of 24, well-controlled, healthy subjects. First, the relatively large intersubject variance in both pre-steady-state and steady-state plasma concentrations are in agreement with observations in patients being treated for arrhythmias. In these 24 subjects, half-lives ranged from 2.1 to 27.2 h, and the average steady-state plasma concentrations ranged from 0.30 to 3.03 μg/mL. These results are consistent with values reported by Connol-

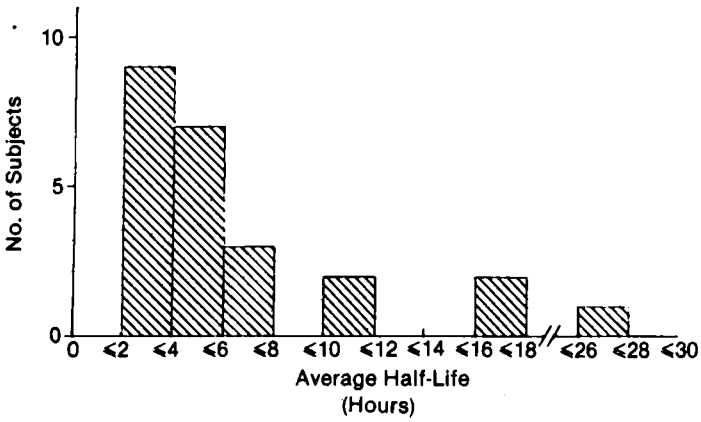

Figure 1—*Mean plasma half-life (two observations) distribution among 24 subjects.*

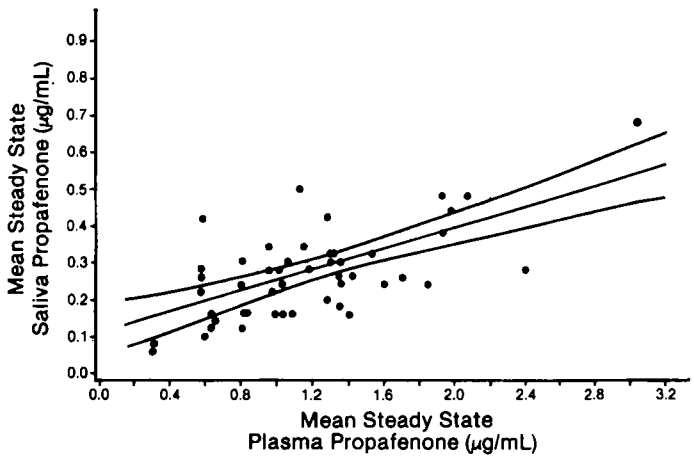

Figure 2—*Mean steady-state saliva propafenone concentration correlation with the mean steady-state plasma propafenone concentration (± 1 SD).*

Table III—Summary Statistics for Plasma and Saliva Propafenone[a]

Parameter	Phase 1 (Mean ± SD)[b]	Phase 2 (Mean ± SD)[b]	ANOVA[c] PR > F	Power to Detect 20% Difference[d]
Plasma				
tP_{max}, h	3.38 ± 1.10	3.58 ± 0.78	0.197	0.987
CP_{max}, μg/mL	1.37 ± 0.54	1.45 ± 0.63	0.202	0.994
Half-Life, h				
"Extensive" metabolizers	4.25 ± 1.59	4.35 ± 1.93	0.875	0.310
"Poor" metabolizers	17.76 ± 7.29	15.55 ± 7.40	0.728	0.025
Combined	7.07 ± 6.53	6.68 ± 5.83	0.574	0.510
$\overline{CP_{ss}}$, μg/mL				
"Extensive" metabolizers	0.97 ± 0.37	1.02 ± 0.37	0.299	0.999
"Poor" metabolizers	1.79 ± 0.46	1.98 ± 0.66	0.759	0.029
Combined	1.14 ± 0.51	1.22 ± 0.59	0.190	0.970
Saliva				
tS_{max}, h	2.83 ± 2.57	1.50 ± 1.06	0.027	Significant[e]
CS_{max}, μg/mL	0.36 ± 0.19	0.44 ± 0.25	0.002	Significant[e]
$\overline{CS_{ss}}$, μg/mL	0.25 ± 0.10	0.29 ± 0.14	0.003	Significant[e]

[a] Six days of dosing at 300 mg every 8 h. [b] Data reports results from 24 subjects including 19 "extensive" metabolizers and 5 "poor" metabolizers; $\overline{CP_{ss}}$ an steady-state plasma propafenone concentration; $\overline{CP_{ss}}$ = mean steady-state saliva propafenone concentration. [c] Analysis of variance by subject, drug, phase with the PR > F for phase. [d] Power ($1 - \beta$) to detect a difference of 20% from the mean of phase 1 (see ref 14). [e] Statistically significant difference ($p < 0.05$).

ly et al.[4] As there is a break in the histogram for half-life between 8 and 10 h in these 24 subjects, the five subjects with half-lives >10 h were arbitrarily separated as "poor" metabolizers as proposed by Siddoway.[12,13] The histogram in Figure 1 does not indicate a bimodal distribution but a distribution in which most subjects have half-lives between 2 to 8 h. Also, those with longer half-lives are in the minority, becoming more rare as the longer half-lives are approached. Mean trough propafenone plasma concentrations of 0.80 μg/mL in these healthy subjects agree favorably with the value of 1.16 μg/mL obtained in 10 elderly (mean age 59 years) patients with ventricular arrhythmias.[17] As steady state is approached, the variance in the plasma concentrations for both trough and 2-h post-dose samples decrease, which is consistent with more precise assay results at higher concentrations and less variance in disposition processes as steady state is approached. While the concentrations 2 h after dosing are less variable than the trough concentrations in this well-controlled study, one may not find this in therapeutic monitoring where the precise times of dosing and sample collection are more difficult to control. Thus, trough concentrations in therapeutic monitoring may be more reliable. Because a relatively low intrasubject variance and a relatively large intersubject variance for plasma propafenone was observed, therapeutic plasma monitoring may be of value as the therapeutic concentration becomes more precisely defined.

Saliva concentrations appear to take longer to reach steady state, but do correlate with plasma propafenone concentrations. Thus, monitoring saliva concentrations may serve as a relatively convenient way to determine compliance and propafenone accumulation during therapy. This possibility requires further testing in patient populations during treatment. Subsequent to this study, 10 subjects rinsed their mouths with a solution of 0.25 μg/mL of propafenone and half of these people experienced a distinct metallic taste. Thus, the metallic taste noted by some patients[4] may be due to propafenone in the saliva.

Conclusions

While this study presents a further clarification of the distribution of elimination half-lives for propafenone and shows healthy subjects in a well-controlled environment to be in agreement with reports on patients, the basis for the differences requires further study. The correlation of Siddoway et al.[12,13] between patients who have longer propafenone half-lives and also have a low capacity for hydroxylation of debrisoquin, suggests a diminished capacity to hydroxylate propafenone in those individuals with long half-lives. In our 24 subjects, five (20.8%) can be classified as "poor" metabolizers. This is consistent with the 21.4% recently reported in patients[13] and also with the 16.6% in a group of 24 normal subjects.[19] Preliminary observations in our laboratories, using an assay method which quantitates 5-hydroxypropafenone, show that the amount of this metabolite is very low or absent in patients with high average plasma propafenone concentrations and relatively high in patients with low plasma propafenone concentrations. How well this explains the distribution of propafenone half-lives and the relationship to other metabolites requires further investigation.

Finally, saliva propafenone concentrations correlate with plasma concentrations of steady state, with concentrations in saliva ~23% of those in the plasma.

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