Bioavailability of 11 Quinidine Formulations and Pharmacokinetic Variation in Humans

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Abstract □ The bioavailabilities of eight quinidine sulfate, two gluconate, and one polygalacturonate formulations were compared, with one of the sulfate formulations as a reference (R) in a panel of 24 volunteers, according to a design comprising duplicate 6 × 6 Latin squares in two subject groups. Only one gluconate formulation (H) gave a significantly lower ($p < 0.05$) area under the curve from 0 to 30 hr (AUC^{30}), 90% of R, which was not as significant as AUC^{∞} (94% of R). Formulation H also gave a significantly lower peak concentration (C_{max}) and a longer time to peak concentration (t_{max}) and generally exhibited some characteristics of a sustained-release product. In addition, one product (F) gave a significantly higher C_{max} while another formulation (D) gave a longer t_{max}. The wide range of dissolution times obtained with these products with three test conditions was not reflected in the AUC, C_{max}, or t_{max} values obtained, except that Formulation H was consistently the slowest to dissolve. The terminal rate constants, expressed as $t_{1/2}$, of the 24 subjects gave an overall mean of 7.49 ± 0.77 hr and ranged from 6.24 ± 0.28 to 9.49 ± 0.90 hr in individuals. The estimated total body clearance, with the assumption that the oral bioavailability was 70%, gave an overall mean of 4.22 ± 1.05 and ranged from 2.49 ± 0.28 to 6.42 ± 0.70 ml/min/kg in individuals, demonstrating the wide range of quinidine disposition even in healthy subjects; this finding is in agreement with recently published results.

Keyphrases □ Quinidine—bioavailability and pharmacokinetic variations of various quinidine formulations studied in humans □ Bioavailability—quinidine formulations evaluated for variations in drug content, dissolution, absorption, and clearance characteristics in humans □ Pharmacokinetics—quinidine formulations, evaluation for variations in bioavailability, humans

The cinchona alkaloid, quinidine, is an important antiarrhythmic agent, which has been limited in use for maintenance therapy because of difficulties in defining the appropriate dosage schedule for the individual patient (1). Erratic patient response and marked variations in serum quinidine concentrations, in subjects to whom equivalent doses were administered, were observed by many investigators (2). While some variations are attributable to the disease (3–5), some contribution from bioavailability differences was suspected (2). However, few studies have tested this supposition. Other criteria suggesting that quinidine is a prime candidate for bioavailability studies were also reported (2).

One crossover study (6) noted that, while there was no significant difference in bioavailability between solution, capsule, and tablet formulations of quinidine sulfate, their bioavailabilities were all significantly lower than the bioavailability of an intramuscular injection of quinidine gluconate.

An oral solution of quinidine gluconate gave ~70% of the area under the curve (AUC) of an intravenous solution, with the loss attributed to a first-pass effect (7). Another study (8) compared an intramuscular lactate salt formulation and oral sulfate and gluconate formulations with an intravenous dose of lactate. The intramuscular route gave ~87%, the oral sulfate gave ~80%, and the oral gluconate gave 66% of the AUC obtained for the intravenous lactate. Guentert *et al.* (9) also compared intravenous quinidine gluconate and an oral quinidine sulfate solution and found a mean oral bioavailability of 70%.

The bioavailability of chemically equivalent brands of quinidine sulfate tablets was compared; while no significant bioavailability differences were found, there were significant differences among brands in some rate parameters (10). These rate parameters were correlated with disintegration and dissolution (11) parameters.

The present study compares the bioavailabilities of available Canadian oral dose forms of quinidine having similar dosage recommendations and relates the *in vivo* results with dissolution properties.

EXPERIMENTAL

Drugs—Commercial production lots consisting of eight tablet formulations of quinidine sulfate, two of quinidine gluconate, and one of quinidine polygalacturonate were obtained directly from the manufacturers. The label claim of the sulfate was 200 mg (equivalent to 165 mg of anhydrous base), that of the gluconate was 325 mg (equivalent to 203 mg of base), and that of the polygalacturonate was 275 mg (equivalent to 166 mg of base).

***In Vitro* Tests**—Samples were tested for identity and drug content by the USP procedure (12). Dissolution characteristics were determined by the USP procedure (13), by a modification of that procedure in which distilled water was used as the dissolution fluid, and by the paddle flask procedure of Poole (14) with 900 ml of glycine buffer, pH 4.0, stirred at 50 rpm.

Human Study Protocol—Twenty-four healthy volunteers (24–60 years old, 50.8–88.5 kg) were admitted to the study. The pretrial medical assessment included a full history and attention to cardiovascular, renal, hepatic, and GI conditions. Complete blood counts, urinalysis, and liver function tests were assessed before and between administrations. ECGs were assessed before and for 4 hr following a 100-mg test dose of quinidine sulfate before admission to the trial.

Volunteers with a history of sensitivity to any drug or who had suffered from allergy or allergic response were excluded.

The subjects were required to avoid all drugs for 3 weeks preceding and until 4 days after the study, to inform the physician of any emergency drug use required, and to report any adverse effects. Subjects were also asked to abstain from any alcoholic beverage from 24 hr before to 3 days after study completion and to fast from 10 hr before (overnight) to 4 hr after each administration. Written informed consent was obtained.

The subjects were randomly assigned into two groups (Table I). In the first study, the 12 subjects were administered six quinidine sulfate formulations (A–E and the innovator reference R-1) according to two replicate balanced 6 × 6 Latin squares. The second study was similar, with the treatments being three quinidine sulfate formulations (F, G, and the innovator R-2), two quinidine gluconate formulations (H and K), and a polygalacturonate (J). The innovator reference tablets (R-1 and R-2) were taken from the same bottle.

Each overnight-fasted volunteer received a single dose of a different quinidine formulation (165–203 mg of equivalent base) given with 50 ml of water early on each investigational day. No food or drink was taken for 4 hr postadministration with the exception of 150 ml of carbonated noncaffeine-containing beverage 1.5 hr after dosing. There was a 2-week interval between treatments. Blood samples (10 ml) were drawn by

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Table I—Mean of the Terminal Half-Lives[a] and Mean Apparent Total Body Clearance [b] Values for All Subjects

Group I												
Subject	1	2	3	4	5	6[c]	7	8	9	10	11	12
Weight, kg	79.5	71.7	77.2	73.5	84.0	71.7	88.5	70.4	88.5	69.0	68.1	70.4
Age, years	24	27	25	37	36	60	34	35	27	28.	28	37
$t_{1/2}$[a], hr	7.50	7.34	6.66	7.57	7.08	8.09	8.54	7.46	7.19	7.10	6.69	7.60
RSD, %	14.77	1.30	3.72	11.59	2.70	8.44	10.78	11.66	5.69	5.08	9.52	10.46
Cl[d], ml/min	392.7	331.3	366.7	350.6	679.6	455.3	566.4	249.9	449.6	440.2	571.4	433.7
Cl_{tot}[b], ml/min/kg	4.94	4.62	4.75	4.77	8.09	6.35	6.40	3.55	5.08	6.38	8.39	6.16
RSD, %	11.59	16.04	12.49	11.80	9.44	12.12	14.89	11.24	6.54	10.34	7.70	8.82
Cl_{corr}[e], ml/min/kg	3.46	3.23	3.33	3.40	5.66	4.45	4.48	2.49	3.56	4.47	5.87	4.31
Group II[f]												
Subject	13	14	15	16	17	18[c]	19	20	21	22	23[c]	24
Weight, kg	79.5	77.2	84.0	81.7	77.2	50.8	77.2	68.1	68.1	86.3	57.7	77.2
Age, years	32	34	29	25	28	30	29	39	31	39	41	44
$t_{1/2}$[a], hr	7.11	6.76	8.60	8.66	7.79	7.06	9.49	7.14	6.67	8.27	6.24	7.23
RSD, %	5.79	10.25	9.91	5.30	10.32	9.12	9.46	15.43	7.78	11.29	4.49	2.77
Cl[d], ml/min	442.8	433.9	572.0	344.0	549.7	308.9	426.9	597.9	468.5	441.0	526.8	321.2
Cl_{tot}[b], ml/min/kg	5.57	5.62	6.81	4.21	7.12	6.08	5.53	8.78	6.88	5.11	9.13	4.16
RSD, %	10.02	19,58	9.82	8.24	9.26	21.71	7.82	7.21	8.73	14.18	11.00	3.34
Cl_{corr}[e], ml/min/kg	3.90	3.93	4.77	2.95	4.98	4.26	3.87	6.15	4.82	3.58	6.39	2.91

[a] Calculated from $0.693/\beta$, where β = slope of 7–30 hr. [b] Apparent total body clearance = *Cl*/body weight. [c] Female subject. [d] Apparent clearance, which is dose/AUC^{30}. [e] Corrected apparent total body clearance = $0.7 \times Cl_{tot}$, where 0.7 is a correction factor for oral to intravenous (see Ref. 19). [f] Formulation H data were omitted.

venipuncture at 0, 0.5, 1, 2, 3, 5, 7, 24, 26, 28, and 30 hr following each administration. Plasma, separated within 2 hr, was stored at −18° until it was assayed.

Plasma Assay—Aliquots (1 ml) of plasma were assayed in duplicate for each time point by the double-extraction fluorescence technique of Armand and Badinand (15) using a suitable spectrofluorometer[1]. Selected samples were also assayed by a GLC procedure (16) and a novel high-performance liquid chromatographic (HPLC) procedure (17).

Data Analyses—For the statistical treatment, six variables were examined: (*a*) the area under the plasma concentration curve from 0 to 30 hr (AUC^{30}), in which values for each individual treatment were determined using the linear trapezoidal method; (*b*) the area under the plasma concentration curve extrapolated from zero to infinity (AUC^{∞}) calculated for each individual treatment using:

$$AUC^{\infty} = \int_0^7 Cp\,dt + \frac{Ie^{-7\beta}}{\beta} \qquad \text{(Eq. 1)}$$

where *Cp* is the observed plasma concentration, $\int_0^7 Cp\,dt$ is determined using the trapezoidal rule, *I* is the *Cp* intercept using the linear least-squares regression of ln *Cp versus* time over 7–30 hr, and β is the negative slope of the same regression line; (*c*) β as defined in (*b*); (*d*) the maximum observed concentration (C_{max}) for each individual profile; (*e*) the time to C_{max} (t_{max}); and (*f*) the apparent total body clearance (Cl_{tot}), which was calculated by:

$$Cl_{tot} = \frac{\text{apparent clearance}}{\text{body weight}} = \frac{\text{dose}}{AUC^{30} \times \text{body weight}} \qquad \text{(Eq. 2)}$$

In each study, the analysis of variance was conducted on the logarithmic transform of the raw data for the variables AUC^{30}, AUC^{∞}, and C_{max} and on the raw data for the remaining variables. The subject effect, period effect, and formulation effect were taken into account in each analysis. Comparisons between the means of the tested and reference formulations for each variable were also made with the least-significant difference test, which is basically a Student *t* test using the pooled error variance of the analysis of variance. For comparison of β and Cl_{tot} between subjects, however, paired *t* tests were applied.

Absorption rate estimates were obtained by the Wagner–Nelson (18) treatment of the mean plasma concentration values for the formulations. Corrected apparent total body clearance estimates (Cl_{corr}) were adjusted by multiplying by a factor of 0.7 from Cl_{tot} for the difference between oral and intravenous doses (19).

RESULTS AND DISCUSSION

The *in vitro* results are presented in Table II. The drug content ranged from 97.7 to 104.9% and was within limits. The gluconate products presented a 20% larger dose. An assay (20) also was applied to determine the amounts of dihydroquinidine in each formulation; a maximum of 6% was found, well below the 20% USP limit. Only one sulfate formulation (R, the innovator) failed the USP dissolution test, which requires that 90% be dissolved in 30 min (introduced shortly after the study was initiated). One gluconate formulation (H) was outside this limit, which is not official for this salt. Results with the other dissolution tests gave variable results for the different formulations. However, only the gluconate Formulation H gave consistently long dissolution times.

Spectrofluorometric procedures for quinidine analysis in plasma recently were criticized for lack of specificity (19, 21). However, in single-dose studies, the major interfering 3-hydroxy metabolite present with chronic dosing was not detected in the plasma (21). Although the Armand–Badinand (15) procedure may also extract a portion of the recently described *N*-oxide metabolite present in single-dose samples (19), previously reported comparisons (17) of values from the Armand–Badinand procedure with those obtained with a specific HPLC procedure indicated general agreement. While there was some divergence (up to 15%) in the later 24–30-hr samples, with HPLC values being lower, the area under the curve values were not affected markedly, although some pharmacokinetic estimates could be (9, 19). The previously reported comparison of results from the Armand–Badinand determination with those from a GLC procedure (22) tended to support this lack of interference in single-dose bioavailability studies. In that study, some steady-state samples from patients had up to 30% greater values by fluorometric analysis than by GLC analysis, while single-dose data were in excellent agreement.

Agreement was obtained between GLC and spectrofluorometric procedures in a limited comparison with plasma samples from patients maintained on quinidine (23). A reasonable correlation ($r^2 = 0.92$) was obtained in a similar comparison using more samples, although the data indicated that the fluorescent procedure gave higher values for most samples (24). Comparisons of HPLC and fluorescent procedures were described for samples from patients maintained on quinidine (25–27), with reasonable agreement being reported. However, some of these chromatographic procedures, as with fluorescent procedures, may not separate quinidine metabolites (19, 21). The spectrofluorometric method does not differentiate quinidine from the cardioactive congener dihydroquinidine. However, since this impurity was present in amounts averaging <5% in formulations and the difference of randomly selected *AUC* values generated by the fluorometric and specific HPLC procedures was of that order (17), the bioavailability assessment was not affected.

The mean plasma level results, by formulation, are given in Table III with no correction for the actual dose administered. The peak levels of ~0.5 μg/ml occurred at 2–3 hr with all formulations except the gluconate (H). The dose correction was applied in Table IV, which lists the average AUC^{30} and AUC^{∞} values by formulation, and in Table V, in which the average peak concentration and time to peak are presented with estimates of the mean absorption rate parameters. In Group I, there were no significant differences between formulations in either the AUC^{30} comparison (ranging from 98.1 to 107.2% of R) or C_{max}. Formulation D had a significantly longer t_{max} than R (Table V). The overall relative standard deviation of 11.2% for AUC^{30} was reasonable for this size of experiment and could detect a difference of 10%. In this group, the AUC^{∞} results were equivalent to those of AUC^{30}.

In Group II, Formulation H had a significantly lower AUC^{30} (Table IV, 90%), a lower C_{max} (Table V, 72.2%), and a longer t_{max} (Table V, 2.5 hr) than R. The AUC^{∞} at 94% was not significantly lower. The only other

[1] Spectrophotofluorometer model SPF 125 (American Instrument Co., Silver Spring, MD 20910). The excitation and emission wavelengths were 361 and 448 nm, respectively, with a slit width of 2 mm for both.

Table II—Drug Content and Dissolution Data of Quinidine Formulations

Formulation	Salt[a]	Label Strength, mg	Assay, %	Dose as Quinidine Base, mg	Dissolution: USP XIX[b] Percent at 30 min ± *RSD*	Dissolution: USP XIX[b] $\bar{t}_{60}$ min ± *RSD*	Dissolution: USP I[c], $\bar{t}_{60}$ min ± *RSD*	Dissolution: Paddle Flask[d], $\bar{t}_{60}$ min ± *RSD*
R(1 + 2)	Sulfate	200	101.0	166.9	87 ± 10	15 ± 16	38 ± 19	14 ± 15
A	Sulfate	200	100.7	166.4	95 ± 3	13 ± 12	89 ± 9	42 ± 41
B	Sulfate	200	99.3	164.0	101 ± 4	12 ± 17	63 ± 32	55 ± 28
C	Sulfate	200	99.1	163.7	106 ± 4	3 ± 4	8 ± 129	3.6 ± 13
D	Sulfate	200	104.9	173.3	101 ± 4	7.3 ± 33	19 ± 5	24 ± 37
E	Sulfate	200	97.7	161.4	103 ± 4	3.6 ± 34	4.3 ± 16	4.2 ± 8
F	Sulfate	200	99.7	164.7	103 ± 3	10 ± 6	16 ± 6	19 ± 24
G	Sulfate	200	101.1	167.0	103 ± 4	3 ± 6	4.8 ± 28	10 ± 82
H	Gluconate	325	100.0	202.5	28 ± 1	127 ± 3	47[e] ± 4	28[e] ± 4
J	Polygalacturonate	275	104.8	168.0	—	—	8.5[f] ± 10	16 ± 61
K	Gluconate	325	101.1	204.7	98 ± 1	10 ± 22	14 ± 7	18 ± 15

[a] Quinidine sulfate, gluconate, and polygalacturonate contain the equivalent of 82.6, 62.3, and 60.4% anhydrous quinidine, respectively. [b] The USP XIX 4th Supplement procedure requires apparatus I with 0.1 *N* HCl as the medium. The limit is >90% in 30 min. The time, $\bar{t}_{60}$, for 60% is also given. [c] USP apparatus I rotated at 100 rpm with distilled water. [d] Not USP apparatus (see text); pH 4.0 glycine buffer used as dissolution medium. [e] Percent dissolved in 120 min. [f] Percent dissolved in 60 min.

significant difference was a C_{max} of 117.6% for the sulfate formulation (F) (Table V). Again, the overall variation (*RSD* = 12.5%) for AUC^{30} was reasonable for the size of the experiment. The range of mean profiles is illustrated in Fig. 1.

The different methods of calculation of AUC^{30} (linear trapezoidal) and AUC^{∞} (linear, 0–7 hr; exponential, 7 hr to infinity) do not contribute to large differences in the estimate of the means (Table IV). The potential for differences between the "linear" and "exponential" trapezoidal calculation was discussed previously (28), and Guentert *et al.* (9) applied an appropriate correction to quinidine data. The mean AUC^{30}, adjusted for 330 mg of base for comparison with that of Guentert *et al.* (9), was 13.00 (μg hr)/ml for Group I and 12.44 (μg hr)/ml for Group II. These values were less than those of Greenblatt *et al.* (8) and other studies which used less specific procedures and were similar to the means [12.7 (μg hr)/ml] of those single-dose studies considered by Guentert *et al.* (19, 21) to have used specific procedures for measurement of plasma quinidine. The different methods in the *AUC* calculation resulted in different findings for the *AUC* comparison of Formulations H and R. Product H had a late peak (Tables III and V and Fig. 1), which contributed to slight differences in the estimates with the two methods. Thus, the AUC^{30} ratio estimate for H to R had a significantly ($p < 0.05$) lower value of 90%, whereas the AUC^{∞} ratio estimate was 94% and was not significant.

From these comparisons (Tables IV and V), the quinidine sulfate formulations, A–G and R, were acceptable and interchangeable with the polygalacturonate (J) and gluconate (K) formulations.

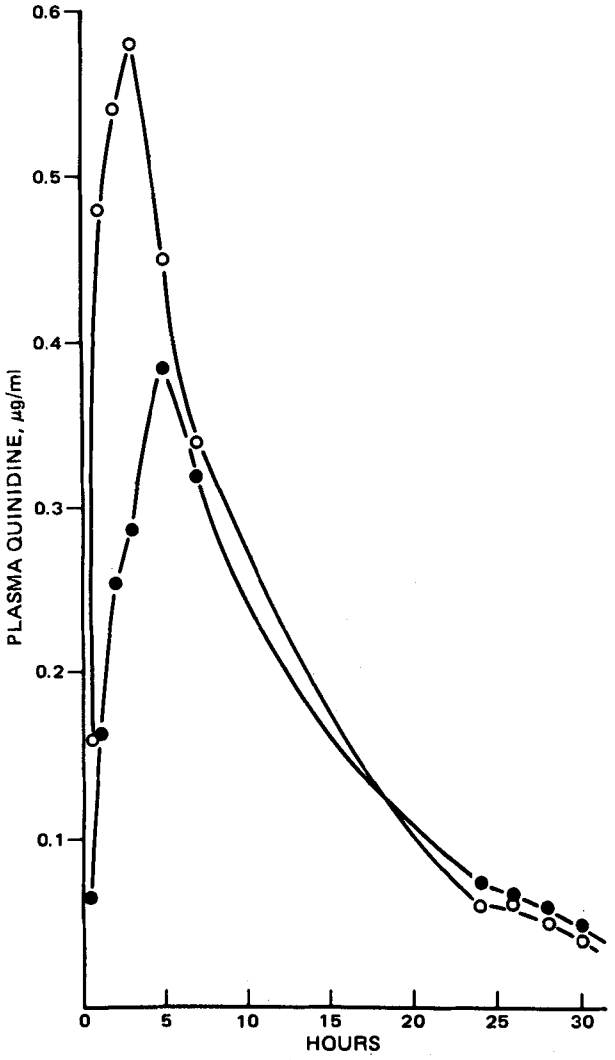

Figure 1—*Mean plasma quinidine concentrations for Formulations F (○) and H (●) corrected for dose.*

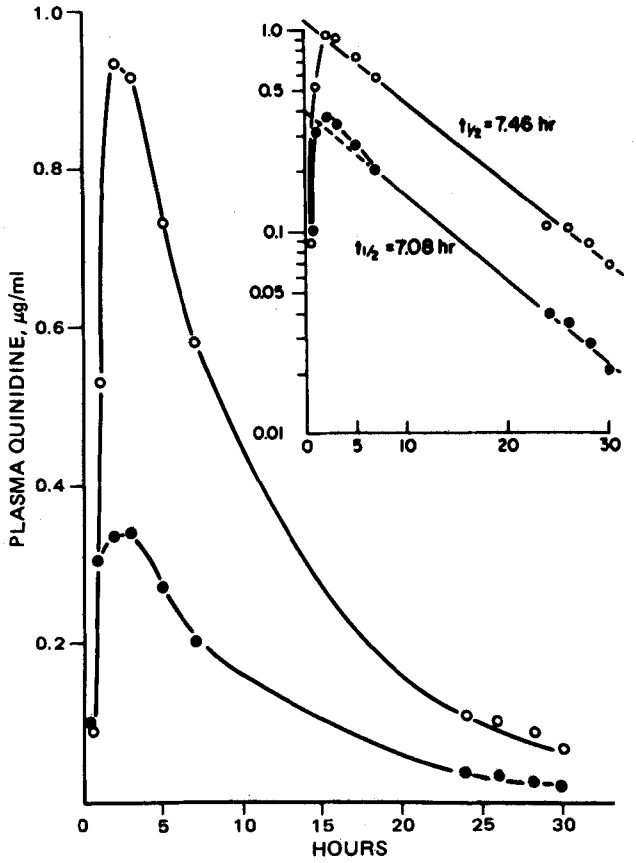

Figure 2—*Mean plasma quinidine concentrations for formulations (n = 6) taken by Subject 5, showing a high clearance (●), and Subject 8, showing a low clearance (○). The insert is a log plasma profile illustrating the similarity of half-lives.*

Table III—Average Plasma Quinidine Concentrations by Formulation, Uncorrected for Quinidine Content

Formulation	Sample Time, hr									
	0.5	1.0	2.0	3.0	5.0	7.0	24	26	28	30
					Group I					
R-1	0.19[a]	0.51	0.56	0.51	0.43	0.34	0.07	0.06	0.05	0.04
	(104.0)[b]	(51.8)	(26.9)	(25.3)	(33.8)	(36.0)	(36.7)	(37.8)	(37.2)	(44.9)
A	0.16	0.46	0.59	0.60	0.47	0.35	0.06	0.06	0.05	0.04
	(56.6)	(33.9)	(34.4)	(47.4)	(37.7)	(37.2)	(31.8)	(32.5)	(32.8)	(33.7)
B	0.19	0.49	0.61	0.53	0.45	0.36	0.07	0.06	0.05	0.04
	(68.1)	(25.5)	(38.0)	(25.9)	(35.8)	(34.1)	(32.3)	(32.3)	(29.5)	(30.0)
C	0.17	0.45	0.52	0.52	0.45	0.34	0.06	0.05	0.04	0.04
	(73.8)	(41.0)	(31.8)	(35.0)	(31.9)	(34.7)	(39.1)	(32.7)	(33.2)	32.2)
D	0.07	0.36	0.52	0.58	0.45	0.37	0.07	0.06	0.06	0.04
	(110.6)	(50.0)	(33.6)	(31.8)	(28.2)	(30.5)	(35.6)	(39.6)	(46.3)	(41.1)
E	0.17	0.39	0.52	0.48	0.41	0.31	0.07	0.06	0.05	0.04
	(83.8)	(34.7)	(23.3)	(25.2)	(27.4)	(29.2)	(45.7)	(46.3)	(45.0)	(39.6)
					Group II					
R-2	0.18	0.36	0.48	0.48	0.38	0.32	0.06	0.05	0.05	0.04
	(94.7)	(49.9)	(21.8)	(22.7)	(26.9)	(27.3)	(32.4)	(37.5)	(38.6)	(36.0)
F	0.16	0.48	0.54	0.58	0.45	0.34	0.06	0.06	0.05	0.04
	(82.6)	(49.4)	(29.5)	(35.0)	(38.4)	(31.8)	(34.2)	(38.5)	(38.6)	(42.1)
G	0.35	0.52	0.53	0.51	0.39	0.32	0.06	0.05	0.05	0.04
	(69.1)	(49.8)	(16.5)	(28.6)	(26.0)	(31.5)	(34.7)	(36.9)	(35.5)	(40.1)
H	0.08	0.20	0.31	0.35	0.47	0.39	0.09	0.08	0.07	0.06
	(98.1)	(50.2)	(27.9)	(29.6)	(29.2)	(29.6)	(30.6)	(34.4)	(27.2)	(28.6)
J	0.19	0.42	0.53	0.54	0.43	0.34	0.07	0.06	0.06	0.05
	(73.0)	(41.7)	(27.1)	(34.3)	(33.9)	(28.8)	(36.4)	(38.8)	(43.4)	(48.6)
K	0.15	0.52	0.66	0.62	0.51	0.40	0.07	0.07	0.06	0.05
	(82.9)	(49.5)	(25.0)	(30.5)	(28.1)	(26.2)	(31.6)	(36.6)	(37.0)	(35.4)

[a] Level in micrograms per milliliter. [b] Relative standard deviation (*RSD*) expressed in percent is in parentheses.

Formulation H, which had different absorption characteristics, also was studied by Greenblatt *et al.* (8) and Ochs *et al.* (29). In comparison with intravenous quinidine, tablet doses of a sulfate formulation and Formulation H gave AUC^{30} ratios of 81 and 71%, respectively; *i.e.*, H was 88% of the oral sulfate formulation and significantly lower (8), which is in excellent agreement with the 90–94% of the present study. Covinsky *et al.* (30) found that this gluconate gave 95% of the *AUC* of a sulfate reference (not significant) with a 52% C_{max} value. In a chronic dose study, Ochs *et al.* (29) found that this 10% difference in serum or plasma levels (H was lower than sulfate) was maintained. Both studies (8, 29) also noted that variability with this formulation was greater than with the oral sulfate. In the current study, although the AUC^{30} of Formulation H was ~10% lower than that of the sulfate, the intersubject variations in AUC^{30} for Formulation H (*RSD* = 27.4%) were no larger than those for other Group II formulations, which ranged from 22 to 30%.

The absorption half-lives ($t_{1/2,abs}$) and the estimated time for 50% to be absorbed (A_{50}) were calculated from the formulation mean plasma concentration *versus* time data with the Wagner–Nelson procedure (18). Although this procedure assumes a one-compartment model [which often is not appropriate for quinidine (9)] since intravenous data were not available for more complex modeling, it allows some estimate of the relative absorption rate of the formulations.

These absorption parameters (Table V) were useful for comparison with the dissolution times in Table II. However, since there were few differences between formulations in the *in vivo* results, only limited information can be derived. Formulation D, which had a longer t_{max} than R, had shorter dissolution times than R in two tests. Formulation F, which had a high C_{max} (118% of R) and apparently a more rapid absorption rate, had a faster dissolution than R in water but not in pH 4 glycine buffer. However, other formulations, such as C and G, gave shorter times than both F and R in those systems with no *in vivo* difference. The only consistent finding was the slow dissolution of Formulation H in all systems. Indeed, although H had dosage recommendations that were similar to the other formulations, it was designed as a slow-release product.

Since all Group I products were similar and only Formulation H in Group II was significantly different, it was possible to examine the inter- and intrasubject variations in some pharmacokinetic parameters. In Group II, with Formulation H, the estimated half-life tended to be longer and the clearance estimate higher, because of the significantly lower AUC^{30}. Therefore, subject comparisons were made without this formulation. Presumably, the terminal slope (β) from 7 to 30 hr is distorted by the extended absorption from this formulation (Table V).

Since several studies indicated that the pharmacokinetics of intravenous quinidine require fitting with different models in different subjects

Table IV—Average Values (Geometric Means) of Bioavailability Parameters of Quinidine Formulations (Corrected per Dose)[a]

Group	Formulation	AUC^{30} [b], (μg hr)/ml	Relative AUC^{30}, %	AUC^{30}, 95% CI[c]	AUC^{∞} [b], (μg hr)/ml	Relative AUC^{∞}, %
I	R-1	6.40	100		6.58	100
	A	6.63	103.6	(94.5, 113.5)	6.82	103.7
	B	6.86	107.2	(97.8, 117.5)	7.01	106.5
	C	6.49	101.4	(92.5, 111.1)	6.55	99.5
	D	6.47	101.1	(92.3, 110.8)	6.66	101.2
	E	6.28	98.1	(89.5, 107.5)	6.43	97.7
	RSD[d]	11.2%				
II	R-2	6.00	100		6.09	100
	F	6.60	109.9	(99.2, 121.8)	6.80	111.7
	G	6.18	102.9	(92.9, 114.0)	6.29	103.3
	H	5.40	90.0[e]	(81.2, 99.7)	5.73	94.0
	J	6.28	104.6	(94.4, 115.9)	6.47	106.2
	K	6.24	104.0	(93.8, 115.2)	6.27	103.0
	RSD	12.5%				

[a] Corrected for equivalent weight of the salt by label claim and drug content in Table II. [b] Area under plasma concentration–time curve from 0 to 30 hr (AUC^{30}) calculated by linear trapezoidal, and area under plasma concentration–time curve from 0 to ∞ (AUC^{∞}) as given in text. [c] The 95% confidence interval. [d] Overall relative standard deviation. [e] Significantly different than R ($p < 0.05$).

Table V—Means of Parameters Reflecting Absorption Rate

Formulation	C_{max}[a], hr	C_{max}[a] Ratio, %	t_{max}[a], hr	$t_{1/2,abs}$[b], hr	A_{50}[c], hr
R-1	0.57	100	2.00	0.32	0.65
A	0.61	106.1	2.25	0.42	0.75
B	0.59	103.6	1.96	0.36	0.72
C	0.60	105.3	2.50	0.40	0.72
D	0.56	97.2	2.75[d]	0.65	1.00
E	0.53	92.2	2.00	0.42	0.75
R-2	0.51	100	2.33	0.60	0.77
F	0.60	117.6[d]	1.92	0.32	0.70
G	0.56	108.6	1.72	0.34	0.42
H	0.37	72.2[d]	4.75[d]	1.50	1.75
J	0.51	100.2	2.00	0.45	0.68
K	0.55	107.2	2.08	0.38	0.75

[a] See text for symbols. [b] Wagner–Nelson estimate from mean plasma concentration by formulation absorption half-life. [c] As in footnote *b*; graphical estimate of time for 50% to be absorbed (A_{50}), which includes any lag time. [d] Significantly different than R ($p < 0.05$).

(8, 9) and often give poor prediction of steady-state levels (9, 31, 32), fitting of the oral curves and derivation of meaningful individual absorption rates (*e.g.*, two- and three-compartment fitting) could not be accomplished. Some data (Fig. 2) appeared to be fitted by one compartment (*e.g.*, Subject 8), while some (*e.g.*, Subject 5) obviously required two-compartment fitting. The terminal half-lives were calculated for each subject from the 7–30-hr data points (Table I) and ranged from 6.66 ± 0.24 (*SD*) to 8.54 ± 0.92 hr in Group I with a mean of 7.42 hr and from 6.24 ± 0.28 to 9.49 ± 0.90 hr in Group II with a mean of 7.49 hr. The extremes are illustrated in Fig. 3. The between-subject variation was greater than the within-subject variation, and many subjects were significantly different from each other. The terminal half-lives of Subjects 3 and 4 in Group I were significantly shorter ($p < 0.05$) than those of all other subjects. In addition, the long terminal half-lives of Subjects 6 and 7 were significantly different ($p < 0.01$) from those of the other subjects, and the terminal half-life of Subject 7 was significantly different ($p < 0.05$) from that of Subject 6. For Group II, Subject 19 was significantly longer ($p < 0.01$) than all other subjects. The values obtained were well within the extremes reported by Mason *et al.* (6) (1.16–15.75 hr) and within the range of mean values reported elsewhere (7–10).

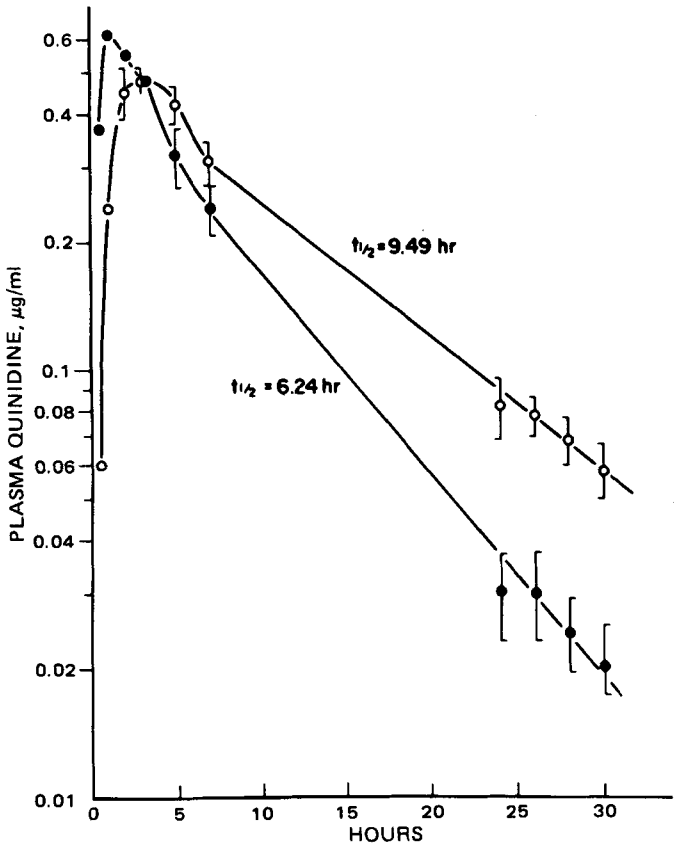

Figure 3—*Mean plasma quinidine concentrations* ±SD *of the volunteers with the shortest (Subject 23, ●) and the longest (Subject 19, ○) terminal half-lives* (n = 5).

The apparent total body clearance of quinidine in this study ranged from 3.55 ± 0.40 to 8.39 ± 0.65 ml/kg/min in Group I and from 4.16 ± 0.14 to 9.13 ± 1.00 ml/min/kg in Group II with means of 5.79 ± 1.44 and 6.25 ± 1.58 ml/min/kg, respectively. As expected, the intersubject variation of ~25% (*RSD*) was much greater than the intrasubject variation of 10% or less. Many subjects were significantly different when compared. For Group I, Subject 8 was significantly lower ($p < 0.05$) than all other subjects; Subjects 5 and 11, with high apparent total body clearance values, were significantly greater ($p < 0.01$) than the other subjects. The apparent total body clearance values for Subjects 20 and 23 in Group II were significantly higher ($p < 0.01$) than those of all other subjects.

Since the oral absorption of quinidine was shown (7–9) to be only 70–80% of intravenous absorption, the estimated corrected total body clearance (Cl_{corr}) is also given for comparison with the literature, using the factor of 0.7 as was suggested by Guentert *et al.* (19) to be the most accurate. The overall mean value for Cl_{corr} was 4.22 ± 1.05 (*SD*) ml/min/kg, close to that (3.85 ± 1.09) of Greenblatt *et al.* (8) and to that (4.26 ± 1.42) of Fremstad *et al.* (33), who also used a spectrofluorometric procedure which was criticized by Guentert *et al.* (9, 19). However, the range of Cl_{corr} values in this present study (Table I) overlapped those of Guentert *et al.* (mean of 4.88 ± 1.56) and also agreed with studies reported by Ueda *et al.*, who found means of 4.7 ± 1.78 (31), 4.95 ± 1.36 (34), and 4.02 ± 1.94 (5) ml/min/kg in three separate studies. Recently, Drayer *et al.* (35), who used HPLC, found a range of quinidine clearances in patients from 3.8 ± 3.9 ml/min for a "low metabolizing" group to 9.0 ± 3.6 ml/min for a group with higher levels of the 3-hydroxy metabolite. These clearances were calculated with an oral absorption factor of 0.87; the values were converted to 3.27 ± 3.36 and 7.76 ± 3.10, using the 0.7 factor of Guentert *et al.* (19) for comparison purposes, rather similar to the range of values found in this study in normal subjects (Table I).

The fluorescence procedure used to estimate plasma quinidine does not differentiate dihydroquinidine; however, this limitation is not expected to influence the clearance since Ueda *et al.* (5) found similar clearance values for this analog (4.17 ± 1.81 *versus* 4.02 ± 1.94 for quinidine) in the same subjects.

The terminal half-life obviously has some influence on clearance. However, recent studies (33, 36) support intersubject differences in protein binding capacity, possibly an α-1-acid glycoprotein or lipoprotein,

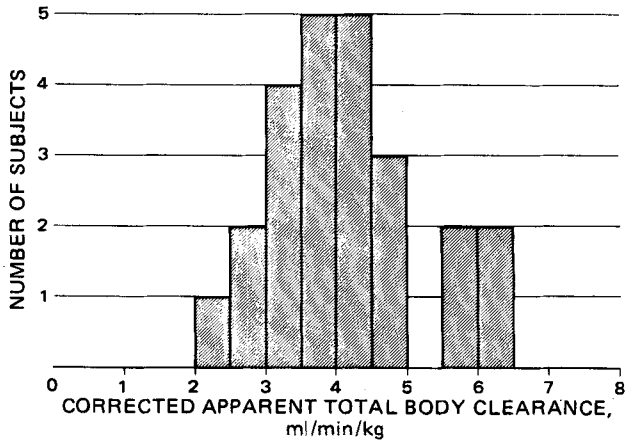

Figure 4—*Frequency distribution of mean corrected total body clearance* (Cl_{corr}) *of quinidine in the 24 subjects.*

as a major influence on clearance and volume of distribution. There was no correlation between the half-life and clearance (Table I), as shown in Fig. 2, and there were major differences in AUC and minor differences in $t_{1/2}$ between subjects.

Drayer *et al.* (35), who measured (3*S*)-3-hydroxyquinidine to quinidine ratios in patients, found evidence to suggest a bimodal distribution in the hydroxylating efficiency, which related reasonably well with quinidine clearance. In the present study of 24 healthy subjects, the frequency distribution of clearance (Fig. 4) appeared to be normal.

In conclusion, the bioavailabilities of eight quinidine sulfate, one gluconate, and one polygalacturonate products were found to be similar from plasma concentration estimates. The bioavailability of one gluconate product was significantly lower ($p < 0.05$) in one estimate, and its plasma concentration showed sustained-release characteristics. There was no meaningful correlation between the absorption parameters and dissolution, except that the slow-dissolving gluconate product had the lowest AUC and C_{max} values and the longest t_{max} value. The pharmacokinetics of quinidine in the 24 subjects in terms of terminal half-life (mean of 7.49 ± 0.76 hr) and total body clearance (mean of 4.22 ± 1.05 ml/min/kg) showed considerable intersubject variation ($RSD \simeq 25\%$) and less intrasubject variation ($RSD \simeq 10\%$).

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