Absorption Kinetics of Procainamide in Humans

CARL V. MANION ˣ, DAVID LALKA *,
DENISE T. BAER, and MELVIN B. MEYER

Abstract □ Plasma procainamide concentrations following the administration of 500 mg of procainamide hydrochloride *via* intravenous infusion, conventional capsules, and sustained-release tablets were compared in 11 healthy male volunteers. Two-compartment open modeling of the plasma levels from the intravenous infusion experiments yielded mean K_{el}, k_{12}, and k_{21} values of 0.0162, 0.0542, and 0.0233 min^{-1}, respectively. The bioavailability of the oral preparations (*versus* intravenous) averaged 83% for the capsule and 79% for the sustained-release tablet. Calculations using a previously reported method suggested that absorption was a first-order process with mean k_a's of 0.0336 and 0.0039 min^{-1} for the capsule and sustained-release tablet, respectively. The sustained-release formulation exhibited delayed release and adequate bioavailability.

Keyphrases □ Procainamide—bioavailability of intravenous infusion, capsules, and sustained-release tablets, absorption of oral forms compared, humans □ Bioavailability—procainamide, intravenous infusion, capsules, and sustained-release tablets compared, humans □ Absorption, GI—procainamide, capsules and sustained-release tablets compared, humans □ Antiarrhythmic agents—procainamide, bioavailability of intravenous infusion, capsules, and sustained-release tablets, absorption of oral forms compared, humans

Procainamide, a widely used antiarrhythmic agent, has a log-linear phase plasma disappearance half-life of about 3 hr (1). This short half-life can lead to subtherapeutic plasma levels 4 hr after oral administration of conventional formulations. Therefore, a 3-hr dosing interval was recommended for maintenance of a therapeutic plasma concentration (2).

More recently, several attempts to prolong the apparent half-life of plasma procainamide utilized formulation techniques to produce sustained release (3–5). Studies with these formulations generally suggested some advantages. The present study was undertaken to measure the absorption rate and bioavailability of an experimental sustained-release tablet and to document its plasma concentration–time curve.

EXPERIMENTAL

Subjects and Dosing—Eleven male subjects participated after giving written informed consent. They were healthy as judged by history, physical examination, and laboratory tests. Their ages ranged between 21 and 28 years with a mean of 21.8, and their weights ranged between 73.6 and 94 kg (Table I).

Procainamide hydrochloride for intravenous use[1] was administered by intravenous infusion over 16 min at a constant rate of 27.1 mg of base/min. Each of the other two dosage forms, the capsule[2] or sustained-release tablet[3], was given with 100 ml of water after an overnight fast. The schedule of administration of dosage forms was randomly determined for each volunteer. Each dosage form was administered at intervals of 1 week or more.

Sample Collection—Blood specimens were collected at −0.25, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hr for both oral preparations. Blood specimens were collected during and after the intravenous infusion at −5, 3.5, 7, 10.5, 14, 17.5, 20, 24, 28, 32, 38, 44, 50, and 60 min and 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hr. A pretreatment urine sample as well as 0–8- and 8–24-hr specimens was collected for drug determination. For the first eight single studies, 24–48-hr urine specimens were collected.

Analysis of Procainamide and Apparent *N*-Acetylprocainamide in Plasma and Urine—Plasma procainamide levels were measured spectrophotometrically by the method of Mark *et al.* (6) as modified by Sitar *et al.* (7). In some studies, conjugates of procainamide (presumably *N*-acetylprocainamide) were approximated by the same method after acid hydrolysis of the methylene chloride extract (evaporated to dryness, dissolved in 1 *N* hydrochloric acid, and heated to 100° for 1 hr) of the plasma specimen. Urine samples were assayed as described but were also analyzed by a modification of a reported GLC procedure (8), again with and without hydrolysis.

The sensitivity of the spectrophotometric method was approximately 0.10 μg/ml with a concentration-independent recovery of 98% during this study; the sensitivity of the GLC method was 1–5 μg/ml with a recovery of 97% over a similar concentration range (urine contained an interfering peak). The coefficient of variation for the spectrophotometric method throughout this study was 3% as measured by quality control specimens run daily. The GLC method yielded an 8% coefficient of variation measured from deviation of slopes of the standard curves. These measurements were similar to previous estimates of precision, sensitivity, and recovery (1, 6–9).

Plasma specimens were frozen to −20° and stored at that temperature until the analysis was performed, except as noted below. Since artifactual procainamide could be generated from *N*-acetylprocainamide (a known metabolite) by hydrolysis, a blank plasma sample to which *N*-acetylprocainamide (10 μg/ml) had been added was also carried through the assay procedure. Furthermore, several sets of samples were assayed within 48 hr or less of the time they were drawn or received and were reanalyzed 6–8 weeks later. These studies were all performed in an effort to ensure that the procainamide plasma and urine levels were not artifactual.

Pharmacokinetics—Plasma concentrations, C_p, following intravenous infusion declined biexponentially in accordance with:

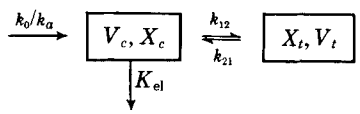
$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

The values of A and B were corrected by the method of Loo and Riegelman (10) for the infusion time of 16 min using:

$$A_i = \frac{k_i \tau}{(1 - e^{-k_i \tau})} A_i' \qquad \text{(Eq. 2)}$$

where τ is the duration of the constant-rate infusion, the A_i's are the $t = \tau$ intercepts of the two exponential phases, and the k_i's are the disposition slope constants (*i.e.*, α and β). The data were fitted to a two-compartment open model (Scheme I), and the values for K_{el}, k_{12}, k_{21}, and V_c were estimated by utilizing the nonlinear least-squares regression analysis program NONLIN (11) on a time-share computer. Each plasma concentration was weighted as its reciprocal.

The computer fit values for K_{el}, k_{12}, k_{21}, and V_c from each individual were then further utilized for the calculation of the apparent absorption rate constant, k_a, by the method of Loo and Riegelman (12). Percent unabsorbed estimations were made at various times, and least-squares



Scheme I—Representation of transfer and elimination in a two-compartment open model; k_{12} *and* k_{21} *are first-order transfer rate constants between the central and peripheral compartments as indicated;* K_{el} *is the first-order elimination rate constant from the central compartment;* k_0 *is a zero-order infusion rate constant;* k_a *is the first-order rate constant for drug absorption;* V_c *and* V_t *are the apparent volumes of the central and tissue compartments, respectively; and* X_c *and* X_t *are the masses of drug contained in these compartments.*

[1] Lot 4J825, Squibb.
[2] Lot 4D302, Squibb.
[3] Lot H7426-5, Hässle.

Table I—Characteristics of Volunteers

Subject	Age, years	Weight, kg	Dose, mg/kg
G.B.	28	78.6	6.36
P.Gt.	21	73.6	6.79
L.D.	22	85.0	5.88
F.N.	21	77.2	6.47
P.Ga.	21	76.3	6.55
B.M.	21	88.6	5.64
P.R.	21	74.0	6.75
S.R.	21	75.0	6.67
C.H.	21	81.8	6.11
C.F.	21	77.2	6.47
T.C.	22	94.0	5.31
Mean ± *SD*	21.8	80.1 ± 6.5	6.27 ± .48

fits were performed to estimate k_a. Plasma level simulations from mean data were performed by the method of superposition as described by Westlake (13). Individual curves were described by:

$$C_p = \frac{k_a DF}{V_c}\left[\frac{(\alpha - k_{21})}{(\alpha - \beta)(k_a - \alpha)}e^{-\alpha t} + \frac{(k_{21} - \beta)}{(\alpha - \beta)(k_a - \beta)}e^{-\beta t} - \frac{(k_a - k_{21})}{(k_a - \alpha)(k_a - \beta)}e^{-k_a t}\right] \quad \text{(Eq. 3)}$$

RESULTS

Intravenous Infusion Experiments—After a brief infusion of procainamide, the plasma concentration declined biexponentially with a $t_{1/2\alpha}$ = 8.8 ± 1.2 min and a $t_{1/2\beta}$ = 204 ± 14 min (Table II). Fitting of these data to a two-compartment open model (Scheme I) yielded mean K_{el}, k_{12}, and k_{21} values of 0.0162, 0.0542, and 0.0233 min^{-1}, respectively (Table III). The apparent volume of the immediately equilibrating space, V_c, was 0.79 liter/kg, and $V_{d\beta}$ was 2.74 liters/kg. Renal clearance, Cl_R, and total body clearance, Cl_B, averaged 400 and 749 ml/min, respectively.

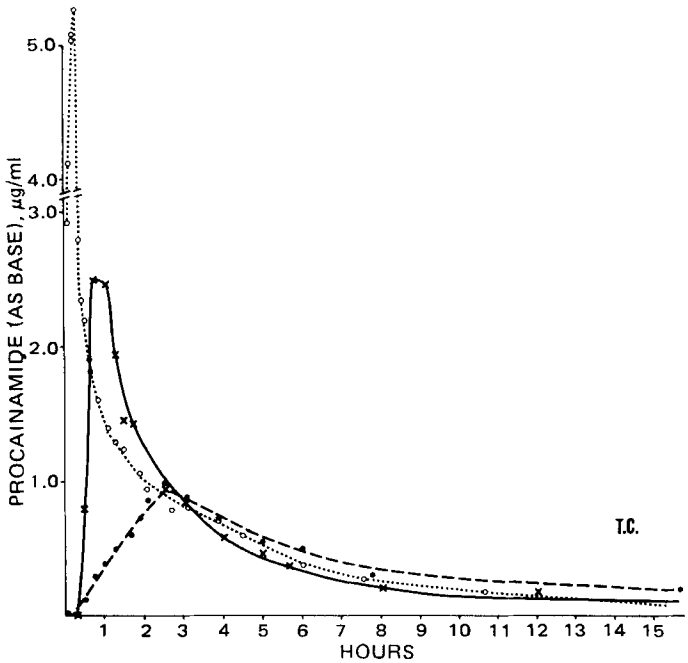


Figure 1—*Plasma concentration–time curves in Subject T.C. following the administration of 500 mg of procainamide hydrochloride as a 16-min constant-rate intravenous infusion (○), a sustained-release tablet (●), and a conventional capsule (×).*

Oral Dose Experiments—The plasma concentration–time curves observed following the administration of an intravenous infusion, a sustained-release tablet, and a conventional capsule to a volunteer who exhibited nearly equal areas under the curve (*AUC*) values following

Table II—Coefficients of the Biexponential Equation Describing the Decline of Plasma Concentration following the Intravenous Administration of 500 mg of Procainamide Hydrochloride to Normal Volunteers[a]

Subject	A, μ/ml	α, min^{-1}	$t_{1/2\alpha}$, min	B, μg/ml	β, min^{-1}	$t_{1/2\beta}$, min
G.B.	5.1	0.066	10.5	1.8	0.0034	204
P.Gt.	2.8	0.031	22.4	1.5	0.0029	239
L.D.	4.6	0.097	7.1	1.8	0.0037	187
F.N.	9.8	0.106	6.5	1.3	0.0044	158
P.Ga.	5.6	0.094	7.4	1.9	0.0042	165
B.M.	5.7	0.073	9.5	0.8	0.0032	217
P.R.	1.6	0.114	6.1	2.1	0.0045	154
S.R.	5.4	0.116	6.0	2.0	0.0043	161
C.H.	16.4	0.138	5.0	1.3	0.0025	277
C.F.	9.0	0.067	10.3	1.0	0.0025	277
T.C.	8.0	0.084	8.3	1.3	0.0033	210
Mean	6.7	0.090	8.8	1.5	0.0035	204
SEM	1.2	0.009	1.2	0.13	0.0002	14

[a] Infusion data corrected to instantaneous input by method of Loo and Riegelman (10).

Table III—Derived Pharmacokinetic Parameters for Procainamide in Normal Volunteers: Constants Characterizing the Two-Compartment Open Model

Subject	k_{12}[a], min^{-1}	k_{21}[a], min^{-1}	K_{el}[a], min^{-1}	V_c[a], liters/kg	$V_{d\beta}$[b], liters/kg	Cl_R[c], ml/min	Cl_B[d], ml/min
G.B.	0.0382	0.0194	0.0116	0.81	2.32	314 (380)[e]	619
P.Gt.	0.0133	0.0128	0.0079	1.35	2.98	407 (349)	635
L.D.	0.0588	0.0301	0.0117	0.79	2.01	297 (303)	633
F.N.	0.0660	0.0161	0.0281	0.51	3.00	464 (548)	1020
P.Ga.	0.0562	0.0272	0.0149	0.76	2.35	533 (537)	752
B.M.	0.0463	0.0135	0.0160	0.73	3.32	214 (457)	942
P.R.	0.0435	0.0670	0.0075	1.57	2.06	393 (485)	687
S.R.	0.0718	0.0345	0.0139	0.78	1.99	320 (406)	641
C.H.	0.0982	0.0123	0.0303	0.30	3.82	458 (433)	781
C.F.	0.0429	0.0087	0.0173	0.56	3.64	541 (447)	702
T.C.	0.0613	0.0145	0.0194	0.49	2.66	454 (269)	825
Mean	0.0542	0.0233	0.0162	0.79	2.74	400 (419)	749
±*SEM*	0.0065	0.0050	0.0022	0.11	0.20	31 (27)	40

[a] Defined in Scheme I. [b] Calculated from $V_{d\beta}$ = dose/$\beta(AUC)$. [c] Calculated from $Cl_R = PA_u^{24hr}/\int_0^{24hr} C_p\,dt$. [d] Calculated from $Cl_B = dose_{iv}/\int_0^{\infty} C_p\,dt$. [e] Numbers in parentheses are the mean renal clearance values for the three experiments in each volunteer; the numbers outside the parentheses are the renal clearances observed from the intravenous experiments.

Table IV—Procainamide Bioavailability in Normal Volunteers

Subject	Bioavailability[a]			
	Conventional Capsule		Sustained-Release Tablet	
	$AUC_{po}^{\alpha}/AUC_{iv}^{\alpha}$	$PA_{u,po}^{\alpha}/PA_{u,iv}^{\alpha}$	$AUC_{po}^{\alpha}/AUC_{iv}^{\alpha}$	$PA_{u,po}^{\alpha}/PA_{u,iv}^{\alpha}$
P.Gt.	71	86	69	25
P.Ga.	113	—	94	96
G.B.	83	77	54	93
L.D.	84	99	70	62
F.N.	73	120	91	82
B.M.	69	207[b]	86	210[b]
P.R.	91	108	65	99
S.R.	66	112	73	81
C.H.	66	69	84	67
C.F.	107	82	86	61
T.C.	88	20	94	52
Mean ± *SEM*	83 ± 4.9	86 ± 5.1	79 ± 4.0	71 ± 18

[a] All ratios ×100. [b] This value was excluded from bioavailability calculations because it is believed that the volunteer lost some urine containing drug following his intravenous dose.

administration of the two oral preparations are shown in Fig. 1. The plasma procainamide levels following the conventional capsule were higher during the first 3 hr of the experiment; at later time points, the sustained-release tablet yielded higher levels.

Bioavailability was estimated by two methods: the ratio of the areas under the plasma concentration–time curves ($AUC_{po}^{24hr}/AUC_{iv}^{24hr}$) and the ratio of the total urinary excretion of procainamide ($PA_{u,po}^{24hr}/PA_{u,iv}^{24hr}$). The *AUC* estimates suggest that the two preparations (conventional capsule and sustained-release tablet) possess nearly equal bioavailability, while the urinary excretion data indicate that procainamide is absorbed more completely from the conventional capsule (86.0 *versus* 71.0%, Table IV).

The plasma levels from each subject were further analyzed by the method of Loo and Riegelman (12) to estimate the apparent absorption rate constant from each formulation (Fig. 2). The results of these estimations for all subjects (assuming first-order absorption) as well as the Loo–Riegelman approximation of the known intravenous infusion rate are shown in Table V. The k_a for the sustained-release tablet averaged almost an order of magnitude slower than the k_a of procainamide from the conventional capsule.

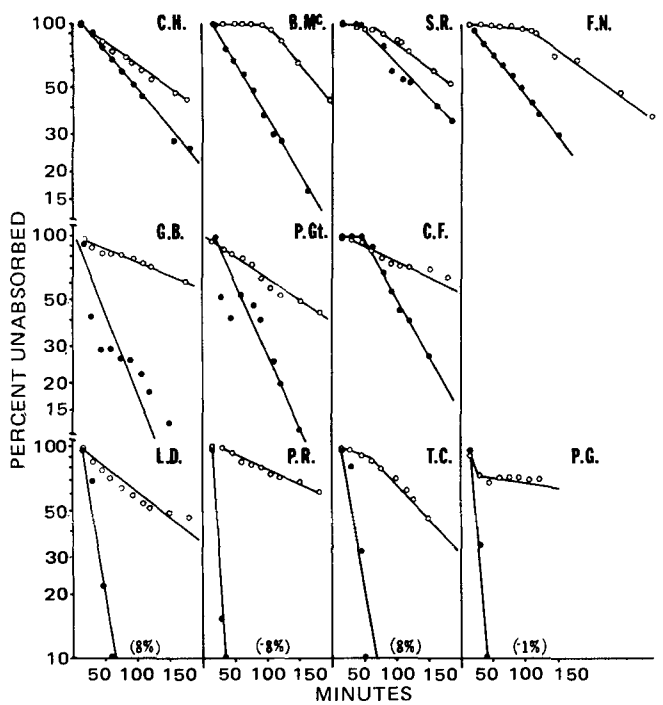


Figure 2—*Loo–Riegelman plots of percent unabsorbed* versus *time following the administration of 500 mg of procainamide hydrochloride as a sustained-release tablet (○) and a conventional capsule (●) for volunteers.*

DISCUSSION

Intravenous Studies—A two-compartment open model adequately described the plasma levels following intravenous infusion of procainamide. The value of V_c was 0.79 ± 0.11 liter/kg, substantially greater than a previously reported value (5). That report (5), however, contained a fixed recording error of elapsed time for the intravenous procainamide doses, which, if corrected, yields a V_c of 0.48 liter/kg[4]. The V_{dB} (2.74 liters/kg) was approximately equal to the previous literature value (5). Other differences in pharmacokinetic constants are, therefore, explained by this correction in V_c.

Concern in this study regarding the potential hydrolysis of *N*-acetylprocainamide to procainamide as a general source of error appears answered by the small coefficient of variation observed for the assay, the absence of hydrolysis as measured under the assay conditions utilized, and the relative agreement of infusion rate prediction (Loo–Riegelman) with the known infusion rate. These observations are supported by a recent report suggesting that the various procainamide assay procedures yield similar results (13). If any method is subject to interference from *N*-acetylprocainamide, it appears to be the fluorometric procedure (14).

Bioavailability—The sustained-release preparation, whose characteristics this study was to determine, appears to have satisfactory bioavailability. First-pass metabolic effect considerations (15) suggest that the bioavailability of both oral preparations approaches the maximum possible for procainamide in humans if nonrenal clearance ($Cl_{NR} = Cl_B - Cl_R$) is presumed to represent hepatic clearance. The difference in the ($PA_{u,po}^{24hr}/PA_{u,iv}^{24hr}$) bioavailability calculation suggests that the sustained-release tablet is less available than the conventional capsule. However, the urinary procainamide excretion from any administration is subject to the problem of the completeness of urine collection, and the urinary recovery ratio method may be less reliable (footnote *a*, Table IV). Indeed, incomplete urinary recovery from Subject B.M. following his intravenous dose is perhaps the most plausible explanation for his high bioavailability when calculated from urinary excretion data. The overall variability in the urinary excretion data is sufficiently great to limit the capacity to suggest a bioavailability difference.

Absorption Rate—A principal objective of this study was to compare the absorption rate of procainamide from a sustained-release tablet to that from a conventional capsule. The calculation of an absorption rate constant further requires that the individual percent unabsorbed *versus* time data points be fitted to an equation. This approach assumes that oral absorption can be adequately described as a simple function of time (which is not necessarily accurate). Since the Loo–Riegelman plots did show good linearity on semilogarithmic coordinates when the initial "lag time" and the postabsorptive phase were ignored, it seems that apparent first-order kinetics were operative. Furthermore, the relative agreement of the known intravenous infusion rate with that calculated by the method of Loo and Riegelman supports this approach for the approximation of the k_a's (at least for the study of procainamide in humans). Based on these data, a substantial alteration has been achieved in k_a that may be clinically meaningful (16).

[4] C. Graffner, A. B. Hässle, Mölndal, Sweden, personal communication.

Table V—Apparent Absorption Rate of Procainamide in Normal Volunteers

Subject	K_a, Capsule, min^{-1}	K_a, Sustained Release, min^{-1}	k_0, Intravenous Infusion, mg/min
S.R.	0.0045	0.0034	29.3
C.H.	0.0077	0.0046	37.6
B.M.	0.0107	0.0058	33.1
F.N.	0.0092	0.0045	29.9
P.Gt.	0.0198	0.0040	42.0
C.F.	0.0173	0.0036	31.1
G.B.	0.0116	0.0022	60.1[a]
P.R.	0.0866	0.0027	28.6
T.C.	0.0693	0.0051	30.8
P.Ga.	0.0866	0.0026	42
L.D.	0.0462	0.0041	27.0
Mean	0.0336	0.0039	33.1
SEM	0.0098	0.0003	1.7

[a] This value was not used in the calculation of the mean k_0 since when it was deleted it fell more than 5 *SD* above the mean.

CONCLUSIONS

1. It seems to be possible to delay the *in vivo* absorption rate of procainamide in humans at least an order of magnitude and still achieve satisfactory bioavailability.
2. The method of Loo and Riegelman seems to be satisfactory for the estimation of absorption rate constants for procainamide in humans.
3. Plasma procainamide levels following a brief intravenous infusion were well described by a biexponential equation.
4. Therapeutic blood levels may be achieved with the sustained-release tablet with doses of approximately 1–2 g (four tablets) every 6–8 hr.

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* Present address: Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY, 14214.

[x] To whom inquiries should be directed.

Liposomal Entrapment of Floxuridine

STEPHEN P. SIMMONS and PAUL A. KRAMER [x]

Abstract □ Floxuridine was found to have an apparent initial entrapment within negatively charged sphingomyelin liposomes about three times higher than its parent, fluorouracil. The drug also diffused out of the liposomes at a much lower rate than fluorouracil. Substitution of lecithin for sphingomyelin destroyed the effect. Liposomal entrapment may provide enhanced stability and decreased toxicity of floxuridine, permitting wider therapeutic utilization of pyrimidine nucleosides.

Keyphrases □ Floxuridine—entrapment within sphingomyelin and lecithin liposomes, compared to fluorouracil □ Liposomes, sphingomyelin and lecithin—entrapment of floxuridine, compared to fluorouracil □ Antitumor agents—floxuridine, entrapment within sphingomyelin and lecithin liposomes, compared to fluorouracil

The actual inhibitor of thymidylate synthetase and, hence, DNA biosynthesis in tumor growth inhibition by fluorouracil (I) is 2′-deoxy-5-fluorouridine 5′-monophosphate (II) (1). Floxuridine (2′-deoxy-5-fluorouridine) (III) is a better precursor of II than I, as evidenced by the fact that it is 10^3 times as effective in inhibiting DNA thymine synthesis in Ehrlich ascites cells *in vitro* (2) and is a more effective carcinostatic agent against both Ehrlich ascites and Sarcoma-180 *in vivo* (3). This increased intrinsic activity is not translated into increased effectiveness in humans, because III is degraded to its constituent pyrimidine and sugar moieties by nucleoside phosphorylases in serum and tissues (4). Attempts at stabilization have included chemical modification of the drug itself as well as the addition of deoxyribose donors and enzyme inhibitors to suppress the degradation reaction (5, 6).

One might expect the encapsulation of III within the aqueous compartments of phospholipid vesicles (liposomes) to be of utility in this regard. The protective lipid sheath might prevent enzymatic degradation in serum and reduce the toxicity of the drug by excluding it from regions such as the GI tract. Previous workers reported difficulty