Pharmacokinetics of Procainamide and N-Acetylprocainamide in Rats

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Abstract ☐ The pharmacokinetics of distribution and elimination of procainamide and its major metabolite, N-acetylprocainamide, were studied in rats. Eight rats were selected randomly, and each received intravenously ^{14}C-labeled procainamide hydrochloride (75 mg/kg) or ^{14}C-labeled N-acetylprocainamide hydrochloride (86 mg/kg) according to a two-way crossover design. Serial blood samples were withdrawn for 8 hr, and cumulative urine and feces were collected for 48 hr. The plasma concentration–time relationships of procainamide and N-acetylprocainamide were characterized by one- and two-compartment open models, respectively. A pseudo-three-compartment model was necessary to characterize the time course of N-acetylprocainamide in plasma formed after administration of procainamide. The biological half-lives of procainamide and N-acetylprocainamide averaged 0.66 and 2.1 hr, respectively. The urinary excretion profiles of these drugs and the ratio of their biological half-lives in rats were similar to those in humans.

Keyphrases ☐ Pharmacokinetics—procainamide and N-acetylprocainamide, rat blood, urine, and feces, compared with human data ☐ Procainamide—and metabolite N-acetylprocainamide, pharmacokinetic study in rat urine, blood, and feces, compared with human data ☐ N-Acetylprocainamide—metabolite of procainamide, pharmacokinetic study in rats, compared with human data ☐ Metabolism—procainamide and N-acetylprocainamide, pharmacokinetics in rats, compared with human data ☐ Models, pharmacokinetic—procainamide and N-acetylprocainamide metabolism in rats, compared with human data

N-Acetylprocainamide (acecainide, II) has been identified as the major metabolite of procainamide (I) in humans (1). It was found to be as potent as I in suppressing chloroform-induced ventricular fibrillation in mice (2). Various investigations have confirmed the antiarrhythmic efficacy of II in isolated tissues (3, 4), animals (4, 5), and humans (6–9). The most significant difference between these two drugs is that patients on chronic I therapy developed lupus erythematosus while those on II did not (8–10). The longer half-life of II offers another advantage over I; the average half-life of I is 3 hr (11), and that of II is 6.0 hr or longer in humans (12, 13).

In humans, ~50% of a I dose was excreted unchanged in urine and 7–34% was acetylated to II (11), whereas II was excreted mainly unchanged (12). In dogs, 50–67% of I was excreted unchanged in urine and no II was found (14, 15). In monkeys, I was extensively metabolized to II and a small portion of the dose (2.1%) was excreted unchanged in urine (15). In rats, 34% of a 50-mg/kg dose of I was excreted unchanged in urine, 38% was converted to II, and the rest was eliminated as unidentified metabolites (16). In the same study, 72% of a 50-mg/kg dose of II was excreted unchanged in urine. The biotransformation of I to II and the elimination of II in rats are qualitatively similar to those in humans.

The purposes of the present investigation were: (a) to study the comparative pharmacokinetics of I and II in the same rat, (b) to develop a pharmacokinetic model that describes the formation and elimination of II after administration of a single dose of I intravenously, and (c) to confirm the suitability of the rat model for pharmacokinetic studies of I and its metabolite II.

EXPERIMENTAL

^{14}C-Labeled procainamide[1] (32.0 μCi/mg) and ^{14}C-labeled N-acetylprocainamide[1] (23.1 μCi/mg) as hydrochloride salts were diluted with unlabeled drugs[2]. The final specific activities of the administered procainamide hydrochloride (I) and N-acetylprocainamide hydrochloride (II) were 0.561 and 0.775 μCi/mg, respectively.

Eight male Charles River CD rats[3], 250–450 g, were randomly selected and kept in the individual metabolism cages during the study. Each animal received I (75 mg/kg) and II (86 mg/kg) intravenously according to a two-way crossover design. Four of the eight rats received I first while the other four received II. One day before drug administration, a cannula was surgically inserted into the jugular vein of each rat under light ether anesthesia. The preparation of the cannulas and the surgical procedure were described previously (17).

The drug solutions were administered intravenously through the jugular cannula after an overnight fast. Water was freely available at all times. Serial blood samples (0.4 ml each) were withdrawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hr after drug administration. After each withdrawal, 0.4–0.5 ml of normal saline containing 1% heparin solution was infused to replace the lost volume. Plasma was separated and frozen immediately. Urine and feces were collected for 48 hr and frozen until they were assayed. Three to 7 days elapsed before the second phase of the study was performed.

Analytical Methods—The total radioactivity in urine was determined directly *via* a liquid scintillation counter[4]. The total radioactivity in the feces was measured after homogenization[5] and combustion in an oxidizer[6]. The I and II concentrations in plasma and urine were determined by a specific high-pressure liquid chromatographic method (18).

Data Analysis—The plasma concentration–time plots of I and II for each rat were fitted to mono- and biexponential equations, respectively, using nonlinear least-squares regression analysis[7]. The time course of formation and elimination of II after I administration was fitted to a pseudo-three-compartment open model (see *Appendix*). In this model, the pharmacokinetics of I are characterized by a one-compartment open model with two routes of elimination, an acetylation route and a nonacetylation route. The elimination of II is described by a two-compartment open model. Convergence was defined as a relative change in the residual sum of squares $<10^{-8}$. Data in all functions were weighed by the reciprocal of the square of each observation. The parameter estimates of each exponential equation were used to calculate rate constants describing the individual model (19) (see *Appendix*).

RESULTS

Table I summarizes the elimination of procainamide (I) and N-acetylprocainamide (II) in urine and feces 48 hr after intravenous administration of either drug. After dosing with I, 84 and 5% of the total administered radioactivity were eliminated in urine and feces, respectively. Of the amount recovered in urine, 49% was unchanged I and 20% was II. As much as 31% was excreted in an unidentified form. After dosing with II, 90.5 and 3.2% of the total administered radioactivity were eliminated in urine and feces, respectively. Of the amount recovered in urine,

[1] New England Nuclear, Boston, Mass.
[2] Arnar-Stone Laboratories, McGaw Park, Ill.
[3] Charles River Breeding Laboratories, Wilmington, Mass.
[4] Model 2425, Packard Instrument Co., Downers Grove, Ill.
[5] Polytron homogenizer, Brinkmann Instruments, Westbury, N.Y.
[6] Model B306, Packard Instrument Co., Downers Grove, Ill.
[7] NLIN procedure, Statistical Analysis System, SAS Institute, Raleigh, N.C.

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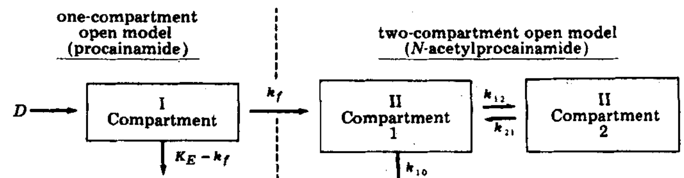
Table I—Elimination of Procainamide (I) and N-Acetylprocainamide (II) in Urine and Feces in 48 hr

	Percent of I Dose				Percent of II Dose		
	Urine			Feces,	Urine		Feces,
Rat	Unchanged I	II	Total Radioactivity	Total Radioactivity	Unchanged II	Total Radioactivity	Total Radioactivity
1	36.8	15.7	77.4	3.4	69.4	91.3	2.2
2	51.4	15.6	82.9	8.5	62.2	71.8	4.2
3	24.5	14.5	71.0	2.9	76.1	90.4	1.1
4	51.2	22.4	98.1	2.4	67.4	94.1	1.3
5	41.8	14.9	89.1	6.7	67.0	92.3	1.9
6	36.4	15.3	83.3	1.9	71.1	95.1	4.0
7	42.5	19.6	93.0	7.3	81.9	90.8	7.7
8	43.5	14.5	78.3	6.0	89.4	98.3	2.8
Mean	41.0	16.6	84.1	4.9	73.1	90.5	3.2
SD	8.7	2.9	8.9	2.5	8.9	8.0	2.2

80% of the dose was unchanged II and the remainder was unidentified. Only traces of I were found in the urine of three rats after II administration.

Figure 1 depicts the time course of the plasma concentrations of I and II following administration of each drug in a representative animal. Table II lists the mean pharmacokinetic parameters and constants that describe the model computer fit for I (one-compartment model), II (two-compartment model), and the N-acetylated metabolite of I (pseudo-three-compartment model). The pseudo-three-compartment model (Scheme I) was derived by combining the pharmacokinetic models used to fit the individual data observed for I and II as unchanged drugs (see *Appendix*).

The metabolite data from seven rats fit quite well (correlation coefficient of ≥0.95) to the proposed model. There were not sufficient data from the eighth animal. On the average, there was excellent agreement between the pharmacokinetic parameters of II obtained by the two-compartment open model after administration of II and by the pseudo-three-compartment model after administration of I. The mean elimination half-life of the N-acetylated metabolite of I was 2.22 hr, which was almost identical to that obtained after administration of II to the same rats. The formation rate constant of II (k_f) from I in seven rats averaged 0.254 hr^{-1}.



Scheme I—Pseudo-three-compartment open model to describe the formation and elimination of the N-*acetylated metabolite of procainamide in the rat.*

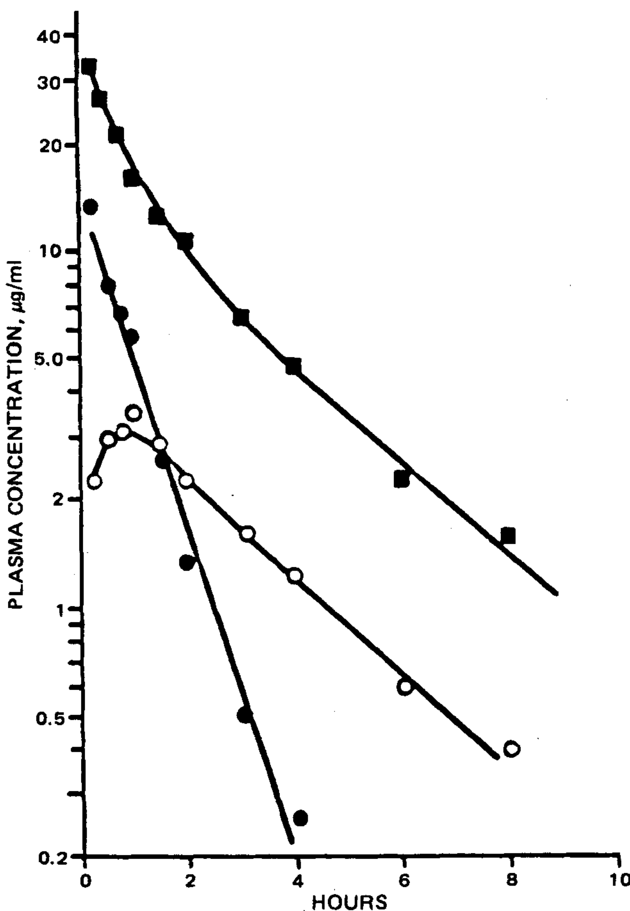


Figure 1—*Typical semilogarithmic plot of plasma concentrations of drugs* versus *time following intravenous administration of procainamide (●) and* N-*acetylprocainamide (■) in one rat. The open circles (○) show the time course of the* N-*acetylated metabolite of procainamide.*

Table III shows the comparative values of the biological half-life, volume of distribution, and renal clearance of I and II in individual rats. The biological half-life of II was 2.13 hr, about three times longer than that of I (0.658 hr). There was little difference in the values of the volume of distribution of either drug. The renal clearance of I was 1.92 liters/hr/kg (32 ml/min/kg), twice as large as that of II, 0.880 liter/hr/kg (14.7 ml/min/kg).

DISCUSSION

There was no appreciable change (>10%) in the hematocrit between the initial samples of the two crossover phases. In addition, there was no difference in the pharmacokinetics of either drug between the two phases

Table II—Parameters Describing the Pharmacokinetics of Procainamide (I) and N-Acetylprocainamide (II) in Rats

		II	
Parameter	I, One-Compartment Open Model ($n = 8$)	Pseudo-Three-Compartment Model[a] ($n = 7$)	Two-Compartment Open Model[b] ($n = 8$)
K_E, hr^{-1}	1.10 (0.05)[c]	—	—
α, hr^{-1}	—	2.70 (0.77)	2.52 (0.38)
β, hr^{-1}	—	0.327 (0.025)	0.333 (0.017)
Half-life, hr	0.66 (0.04)	2.22 (0.20)	2.13 (0.13)
k_{12}, hr^{-1}	—	—	0.983 (0.237)
k_{21}, hr^{-1}	—	—	0.971 (0.134)
k_{10}, hr^{-1}	—	—	0.900 (0.102)
k_{ex}, hr^{-1}	0.448 (0.052)	—	0.657 (0.081)
k_{mu}, hr^{-1}	0.181 (0.020)[d]	—	—
k_f, hr^{-1}	0.248[d]	0.254 (0.044)	—
V_C, liters/kg	—	—	1.46 (0.19)
$V_{d(\beta)}$, liters/kg	4.60 (0.57)	—	3.82 (0.54)
Cl_p, liters/hr/kg	4.84 (0.53)	—	1.24 (0.12)
Cl_r, liters/hr/kg	1.92 (0.17)	0.919 (0.096)	0.880 (0.059)

[a] Data obtained for II formed after administration of I. [b] Data describing the time course of unchanged drug after intravenous administration of II. [c] Data in parentheses show the standard error of the mean. [d] The k_{mu} value represents the excretion of N-acetylated metabolite of I in urine. The k_f value was calculated using a correction factor to account for the amount of II eliminated as metabolites. This factor was obtained from the II data and is 73%.

Table III—Comparisons of Biological Half-Life ($t_{1/2}$), Apparent Volume of Distribution (V_d), and Renal Clearance (Cl_r) of Procainamide (I) and N-Acetylprocainamide (II) in Individual Rats

Rat	$t_{1/2}$, hr			V_d, liters/kg		Cl_r, liters/hr/kg	
	I	II	Ratio	I	II	I	II
1	0.831	2.10	2.53	5.93	3.18	1.82	0.730
2	0.550	2.92	5.31	3.90	7.40	2.53	1.09
3	0.646	1.86	2.88	7.48	3.71	1.97	1.05
4	0.536	1.94	3.62	4.03	4.10	2.67	0.986
5	0.800	2.00	2.50	5.43	3.06	1.97	0.711
6	0.648	2.38	3.67	4.45	3.76	1.74	0.779
7	0.592	2.04	3.45	2.45	2.48	1.22	0.691
8	0.664	1.72	2.59	3.15	2.86	1.43	1.00
Mean	0.658	2.13	3.32	4.60	3.82	1.92	0.919
SD	0.107	0.37	0.94	1.61	1.53	0.48	0.272

of the crossover study. Therefore, it can be assumed that the withdrawal of blood during the first phase did not affect the pharmacokinetics during the second phase.

Procainamide (I) is metabolized partially to N-acetylprocainamide (II) in rats but is excreted mainly unchanged (~50% of the dose) in the urine. On a qualitative basis, there is a similarity in the elimination of I in humans and rats. However, in contrast to the finding in humans, there was no indication of a bimodal distribution of I acetylation in rats. This finding is in agreement with the observation made by Cerna *et al.* (20). N-Acetylprocainamide is excreted primarily unchanged in urine. A fraction of both I and II doses was eliminated in the urine as unidentified polar compounds. No attempt was made to separate or characterize these metabolites, which appear to be unextractable in organic solvents and may consist of congregate forms of the drug.

A small portion (3–5%) of the intravenous dose of both drugs was eliminated in the feces, indicating biliary secretion. If the drugs enter enterohepatic cycling, the magnitude of the biliary excretion should be larger than that indicated by the feces data.

To describe the time course of II formed after I administration in rats, a pseudo-three-compartment open model was derived. This approach was possible by combining the one-compartment open model and two-compartment open model characterizing the pharmacokinetics of I and II, respectively. The link between the two models is k_f, the rate constant for I acetylation in the body. Since there was almost no deacetylation of the metabolite, it was assumed that the k_f represents the rate constant of nonreversible acetylation.

Because a portion of the II dose was eliminated as an unknown metabolite, its urinary excretion rate constant after administration of I probably will be smaller than k_f. This possibility was verified by the value of k_{mu}, which represents the renal excretion of the N-acetylated metabolite but not its formation rate as described by k_f. When the value of k_{mu} (0.181 hr^{-1}) was corrected for the percent of II eliminated as an unidentified metabolite, the rate constant was 0.248 hr^{-1}, which was almost identical to that of k_f (0.254 hr^{-1}). Furthermore, one may calculate that only 73% of the N-acetylated metabolite of I would be eliminated as such in rats. This value is in excellent agreement with the observed value of urinary excretion after administration of II.

A discrepancy between the results of this study and those described previously (16) with respect to the half-life and volume of distribution of II was noted. This difference was addressed previously (21) and was attributed mainly to the use of inadequate blood sampling to characterize the pharmacokinetics of II and the inappropriate method of calculating the volume of distribution.

This investigation of comparative pharmacokinetics in rats showed that the biological half-life of II is about three times longer than that of I in rats. A ratio between 2 and 3 also has been demonstrated in humans. The volume of distribution of these drugs is quite similar. The renal clearance of I (32 ml/min/kg) is twice as large as that for II (15 ml/min/kg). These values are larger than the glomerular filtration rate of 8.0 ml/min/kg (22) in 200-g rats, which indicates that active processes are taking place in urinary excretion of either drug.

In summary, the elimination of I and II when given individually to rats can be described by one- and two-compartment open models. A pseudo-three-compartment model was developed to fit the plasma II concentrations that form following I administration to rats. The results show that the pharmacokinetics and metabolism of I and II are qualitatively similar in both humans and rats. N-Acetylprocainamide has a half-life two or three times longer than that of procainamide in both humans and rats. The percentages of unchanged drug and the metabolites excreted in urine following administration of either drug are qualitatively similar in both species.

APPENDIX

The concentration of N-acetylprocainamide (II) in plasma (C_p) at time t after procainamide (I) administration can be fitted to:

$$C_p = Pe^{-K_E t} + A'e^{-\alpha t} + B'e^{-\beta t} \quad \text{(Eq. A1)}$$

where the parameters P, A', B', K_E, α, and β characterize the three-exponential equation, and:

D = intravenously administered dose
K_E = apparent first-order elimination rate constant for I
k_f = formation rate constant for II
k_{12} and k_{21} = intercompartmental distribution rate constants for II
k_{10} = apparent first-order elimination rate constant from central compartment for II
V_C = apparent volume of central compartment for II

The area under the plasma concentration *versus* time curve (AUC) is given by:

$$AUC = \frac{P}{K_E} + \frac{A'}{\alpha} + \frac{B'}{\beta} \quad \text{(Eq. A2)}$$

The individual pharmacokinetic parameters and constants are defined as follows:

$$P = \frac{K_f D(K_E - k_{21})}{V_C(\beta - K_E)(K_E - \alpha)} \quad \text{(Eq. A3)}$$

$$A' = \frac{k_f D(\alpha - k_{21})}{V_C(\alpha - \beta)(K_E - \alpha)} \quad \text{(Eq. A4)}$$

$$B' = \frac{k_f D(\beta - k_{21})}{V_C(\alpha - \beta)(\beta - K_E)} \quad \text{(Eq. A5)}$$

$$P + A' + B' = 0 \quad \text{(Eq. A6)}$$

$$\alpha + \beta = k_{12} + k_{21} + k_{10} \quad \text{(Eq. A7)}$$

$$\alpha\beta = k_{21}k_{10} \quad \text{(Eq. A8)}$$

$$k_{21} = \frac{B'K_E(\alpha - \beta) + P\beta(\alpha - K_E)}{B'(\alpha - \beta) + P(\alpha - K_E)} \quad \text{(Eq. A9)}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10} \quad \text{(Eq. A10)}$$

$$k_{10} = \frac{\alpha\beta}{k_{21}} \quad \text{(Eq. A11)}$$

$$k_f = \frac{V_C K_E k_{10} AUC}{D} \quad \text{(Eq. A12)}$$

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Electrophoretic Properties of Sulfamethoxazole Microcapsules and Gelatin–Acacia Coacervates

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Abstract □ The electrophoretic properties of sulfamethoxazole microcapsules and the coacervates prepared by gelatin–acacia coacervation were investigated. The effects of the parameters in the microcapsule preparation, such as the coacervation pH, amount of formaldehyde used for hardening, and drying method of the coacervates, on the ζ-potential of the resultant microcapsules were clarified. The Büchner effect was observed in coacervates in an electric field, which indicated that the coacervate wall was flexible. The ζ-potential *versus* pH curves of the coacervates appeared on the upper side of the plain sulfamethoxazole, while those of the microcapsules dried conventionally shifted to the lower side due to denaturation of the gelatin in the microcapsule wall, which occurred during drying. Spray drying increased the denaturation of gelatin, which imparted a negative charge to the spray-dried microcapsules. Formalization of the coacervates refined the electrophoretic behavior of the microcapsules, depending on the amount of formaldehyde used. The ζ-potential of the plain sulfamethoxazole also was measured in the simulated coacervation solution to analyze the mechanism of coacervation electrophoretically.

Keyphrases □ Sulfamethoxazole—microcapsules and coacervates, electrophoretic properties compared □ Gelatin–acacia coacervates—sulfamethoxazole microcapsules and coacervates compared electrophoretically □ Microcapsules, acacia–gelatin—sulfamethoxazole, electrophoretic properties compared □ Coacervation, acacia–gelatin—sulfamethoxazole coacervates and microcapsules compared electrophoretically

Much attention has been paid to the electrophoretic properties of microcapsules because they are decisive parameters in stabilizing suspensions compounded with microcapsules (1). In addition, to prepare a microcapsule containing living cell fluid for use as an artificial cell, it is necessary to simulate the electrophoretic properties of the microcapsule as well as other properties such as elasticity, mechanical strength, and permeability (2).

Measurement of the ζ-potential of microcapsules is one way to assess their electrophoretic properties. The ζ-potential of microcapsules prepared by an interfacial polycondensation method was measured, and the effect of the pH medium on these properties was reported (3). The ζ-potential of gelatin–acacia coacervates, excluding the core material, also was determined (4). However, the electrophoretic properties of gelatin–acacia microcapsules containing the core material were not exhaustively investigated.

In the present study, ζ-potentials of gelatin–acacia coacervates and microcapsules prepared by drying were measured. One aim of the study was to elucidate the parameters that affect the electrophoretic properties of the coacervates and microcapsules. The amount of formaldehyde used for hardening, the coacervation pH, and the drying method of the coacervate droplets were assumed to be the parameters affecting this property. Another purpose was to manifest the coacervation process electrophoretically by measuring the changes in the ζ-potentials of plain sulfamethoxazole particles and gelatin–acacia coacervates during processing.

EXPERIMENTAL

Materials—The test samples used to measure the ζ-potential were micronized sulfamethoxazole[1], gelatin–acacia coacervate droplets, and dried gelatin–acacia microcapsules of sulfamethoxazole. The gelatin–acacia coacervates of sulfamethoxazole were prepared as described earlier (5, 6). The coacervation pH was adjusted to 2.05–4.2. The coacervate droplets were formalized with 0, 30, and 50 ml of formaldehyde.

The conventional method of drying the coacervates (using warm air at 40°) and a spray drying technique were adopted. Spray drying of the slurries containing coacervate droplets was conducted using a centrifugal wheel atomizer driven at 40,000 rpm at 140 ± 10°. The preparation procedures of the microcapsules are shown in Fig. 1.

The microcapsules used for measuring the ζ-potential were characterized by the following micromeritic properties: geometric mean diameter of 8.5–28.5 μm, wall thickness of 0.75–1.31 μm, and particle density of 1.02–1.19 g/cm³ (7).

Dispersion Medium—The dispersion media used to measure the

[1] Micronized to <6 μm by a jet micronizer, Shionogi Pharmaceuticals Co., Osaka, Japan.

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