

Prediction of *N*-acetylprocainamide disposition kinetics in rat by combination of gamma variate and physiological pharmacokinetic model¹

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ABSTRACT Clearances and tissue/blood drug concentration ratios of *N*-acetylprocainamide (NAPA) in rats were determined. The clearances of NAPA in rat blood, liver, and kidney were 13.1, 4.88, and 8.24 ml · kg⁻¹ · min⁻¹, respectively. Disposition kinetics of NAPA in rats was predicted with combination of gamma variate and physiological pharmacokinetic model. Equation for estimating the concentration of NAPA in rat blood following iv NAPA 40 mg · kg⁻¹ was $C = 55.06t^{-0.220} \exp(-0.00713t)$. Using r^2 value as a criterion, we found a good agreement between predicted and observed concentrations in blood, lung, small intestine, heart, brain, and skin.

KEY WORDS acetylprocainamide; pharmacokinetics; statistical models

The gamma variate $C = At^{-a} \exp(-bt)$ was suggested as a substitute fitting function for polyexponential series in various applications⁽¹⁻³⁾. Weiss⁽³⁾ suggested the application of gamma variate to fitting pharmacokinetic data and interpreted the parameters with physiological model.

Since Dedrick and Bischoff developed the concept of physiological model, there have been many successful examples of application of this model to describing disposition kinetics of drugs^(4,5). However, there has been no evidence to describe disposition kinetics of drug with combination of gamma variate and physiological pharmacokinetic model.

In this paper, some equations for estimating drug concentration in rat blood and tissues were derived with combination of

gamma variate and physiological model; at same time, we used *N*-acetylprocainamide (NAPA) as a typical compound to further verify the present method. In addition, we tested whether the physiological model developed for NAPA in rat could be used to describe its disposition kinetics in man, in spite of interspecies difference in disposition and distribution.

MATHEMATICAL MODEL

Model In order to describe the kinetics of NAPA in rat, a Bischoff-Dedrick type multicompartment model was developed, which depicts the body as being composed of 11 compartments (Fig 1). The organs with small volume such as spleen were omitted in

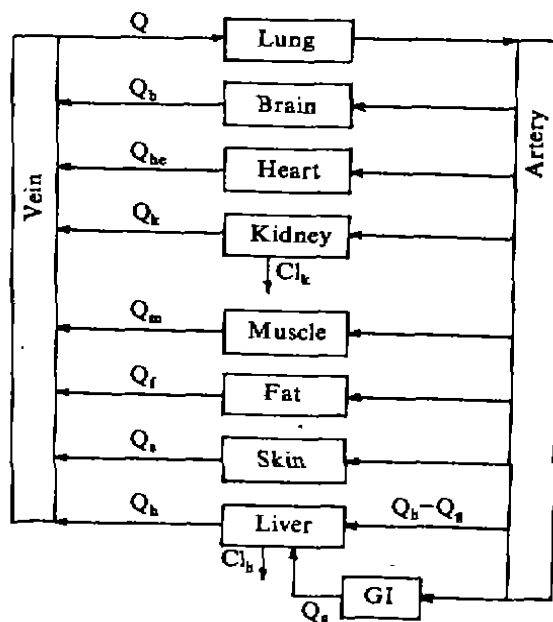


Fig 1. Diagram of physiological pharmacokinetic model developed for NAPA.

Received 1990 Nov 19

Accepted 1991 Nov 29

¹Supported by a grant-in-aid of China Pharmaceutical University.

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the model. A number of assumptions were made in the mathematical analysis of the model. First, intercompartmental transport was assumed to occur *via* blood flow. Second, instantaneous equilibrium is achieved between tissue and blood within the tissue, and drug concentration in the effluent blood is in equilibrium with that in the tissue. Third, all processes are linear. Fourth, elimination of drug occurs only in both kidney and liver.

Events in tissue Probability density function $P_i(t)$ of drug transfer time across the i th tissue may be described by gamma variate.

$$P_i(t) = A_i t^{-a_i} \exp(-b_i t) \quad [1]$$

Relationship between $P_i(t)$ and frequency function $h_i(t)$ of drug transfer time across the i th tissue was given by Weiss⁽⁶⁾

$$h_i(t) = F_i P_i(t) \quad [2]$$

where F_i is availability of drug across the i th tissue and the extraction ratio $E_i = 1 - F_i$.

Basing on statistical moments, we obtained

$$A_i = \frac{b_i^{1+a_i}}{\gamma(1-a_i)} \quad [3]$$

$$\bar{t}_i = (1-a_i) / b_i \quad [4]$$

$$\sigma_i^2 = (1-a_i)^2 / b_i \quad [5]$$

where $\gamma(x) = \int_0^\infty t^{(x-1)} \exp(-t) dt$, \bar{t}_i and σ_i^2 are the mean transfer time and the variance across the i th tissue, respectively.

These parameters are also given as follows^(6,7).

$$F_i = \frac{Q_i}{Q_i + f_u Cl_i} \quad [6]$$

$$\bar{t}_i = \frac{K_i V_i}{Q_i + f_u Cl_i} \quad [7]$$

$$\sigma_i^2 = \bar{t}_i^2 \quad [8]$$

where V_i and Q_i are volume and blood flow of the i th tissue, respectively; K_i is tissue / blood drug concentration ratio; Cl_i is intrinsic clearance in the i th tissue and f_u is free

fraction of drug in blood.

Utilizing eqs(3-8), we got $a_i = 0$, $b_i = \bar{t}_i^{-1}$, $A_i = b_i$, and

$$h_i(t) = F_i \bar{t}_i^{-1} \exp(-\bar{t}_i^{-1} t) \quad [9]$$

The drug concentration $C_i(t)$ in the i th tissue is written⁽⁷⁾.

$$C_i(t) = \int_0^t K_i h_i(t-\tau) C(\tau) d\tau = K_i F_i \bar{t}_i^{-1} \int_0^t \exp[-\bar{t}_i^{-1}(t-\tau)] / C(\tau) d\tau \quad [10]$$

At time t_{j+1} , $t_{j+1} = t_j + k$,

$$C_i(t_{j+1}) = K_i F_i \bar{t}_i^{-1} \exp(-\bar{t}_i^{-1} k) \cdot \int_0^{t_j} \exp[-\bar{t}_i^{-1}(t_j - \tau)] C(\tau) d\tau + K_i F_i \bar{t}_i^{-1} \int_{t_j}^{t_{j+1}} \exp[-\bar{t}_i^{-1}(t_j + k - \tau)] \cdot C(\tau) d\tau \quad [11]$$

The integration from time t_j to t_{j+1} may be estimated with linear trapezoidal rule, thus equation 11 is rewritten.

$$C_i(t_{j+1}) = C_i(t_j) \exp(-\bar{t}_i^{-1} k) + K_i F_i \bar{t}_i^{-1} [C(t_{j+1}) + C(t_j) \exp(-\bar{t}_i^{-1} k)] k / 2 \quad [12]$$

where $C(t)$ is drug concentration in arterial blood and k is step long, and

$$C_i(t_j) = K_i F_i \bar{t}_i^{-1} \int_0^{t_j} \exp[-\bar{t}_i^{-1}(t_j - \tau)] / C(\tau) d\tau$$

But in liver(h)

$$C_h(t_{j+1}) = C_h(t_j) \exp(-\bar{t}_h^{-1} k) + \frac{Q_h - Q_g}{V_h} [C(t_{j+1}) + C(t_j) \exp(-\bar{t}_h^{-1} k)] k / 2 + \frac{Q_g}{K_g V_h} [C_g(t_{j+1}) + C_g(t_j) \exp(-\bar{t}_h^{-1} k)] k / 2 \quad [13]$$

and in lung(p)

$$C_p(t) = K_p C(t) \quad [14]$$

where $C_g(t)$ is drug concentration in small intestine.

Events in the body Probability density function $P(t)$ of residence time in the whole body may be also described with gamma

variate.

$$P(t) = At^{-a} \exp(-bt) \quad [15]$$

The drug concentration $C(t)$ in blood after iv administration of a dose is given as follows:

$$C(t) = \frac{\text{Dose}}{Q} At^{-a} \exp(-bt) \quad [16]$$

where $A = \frac{b^{(1-a)}}{E\gamma(1-a)}$

$$a = 1 - \text{MDRT}^2 / \text{VDRT} \quad [17]$$

$$b = \text{MDRT} / \text{VDRT}$$

Q is cardiac output; E is extraction ratio of drug through circulation. $E = 1 - F$ and $Cl = QE$; MDRT and VDRT represent the mean residence time and the variance, respectively. Estimations of these parameters were given in papers^(6,7).

$$\text{MDRT} = \bar{t}_{\text{cir}} / E \quad [18]$$

$$\text{VDRT} = \sigma_{\text{cir}}^2 / E + \bar{t}_{\text{cir}}^2 F / E^2 \quad [19]$$

$$F = F_p \Sigma(F_i Q_i) / Q \quad [20]$$

$$\bar{t}_{\text{cir}} = \bar{t}_p + \Sigma(F_i Q_i \bar{t}_i) / \Sigma(F_i Q_i) \quad [21]$$

$$\sigma_{\text{cir}}^2 = \sigma_p^2 + \Sigma[F_i Q_i (\bar{t}_i^2 + \sigma_i^2)] / \Sigma(F_i Q_i) - [\Sigma(F_i Q_i \bar{t}_i) / \Sigma(F_i Q_i)]^2 \quad [22]$$

MATERIALS AND METHODS

NAPA was synthesized in our laboratory. Sprague-Dawley rats ($244 \pm s 22$ g) were used.

Urinary recovery of NAPA after iv Rats (3♂ , 4♀) received iv $40 \text{ mg} \cdot \text{kg}^{-1}$ NAPA via tail vein and were housed in the individual metabolic cage during study. The 24 h content of NAPA in urine was then measured.

Disposition kinetics of NAPA in rat after iv Rats (9♂ , 9♀) were divided into 6 groups of 3 rats each. Each rat received iv $40 \text{ mg} \cdot \text{kg}^{-1}$ NAPA via tail vein. The rats were killed by femoral artery bleeding at 5, 15, 30, 60, 120, and 240 min. One ml of blood was used for analysis of NAPA. The rest of blood was centrifuged to obtain plasma. The heart, liver, lung, muscle, kidney, skin, small intestine, brain, and adipose tissue

were immediately removed, sliced, blotted, and weighed. The tissues were homogenized in 1.0 ml of 20% trichloroacetic acid.

Assay procedure NAPA was quantitated by TLC⁽⁸⁾. Briefly, tissue homogenate was centrifuged and supernatant was obtained; the residue was added 1 ml distilled water, mixed and centrifuged. The two supernatants were combined. To the combined solution 1 ml of petroleum ether was added and agitated, the organic layer was removed. NaOH 20% 0.5 ml was added to the aqueous solution, the mixture was extracted with 5 ml chloroform twice. The two chloroform solutions were combined and evaporated to dry, and the residue was used for TLC analysis. Recovery of NAPA in body fluid $87.6 \pm 6.8\%$ (level $10 \mu\text{g} \cdot \text{ml}^{-1}$) and $88.9 \pm 5.5\%$ (level $20 \mu\text{g} \cdot \text{ml}^{-1}$). The correlation coefficient r is >0.99 .

TREATMENT OF DATA

Body clearance Total body clearance Cl was calculated as the ratio of dose divided by the area under the blood drug concentration time curve (AUC_B), ie, $Cl = \text{Dose} / AUC_B$. The AUC_B was calculated with linear trapezoidal rule. Clearance in kidney Cl_k was estimated by equation $Cl_k = f_k Cl$ and clearance in liver $Cl_l = Cl - Cl_k$, where f_k is urinary recovery of NAPA in rat during 24 h.

Determination of tissue / blood drug concentration ratios in rat Tissue / blood drug concentration ratios of NAPA in rat were estimated with area method⁽⁹⁾.

For nonelimination tissues

$$K_i = AUC_i / AUC_B \quad [23]$$

and for liver and kidney

$$K_i = (1 + f_u Cl_i / Q_i) AUC_i / AUC_B \quad [24]$$

where AUC_i is the AUC in the i th tissue.

Simulation of concentration of NAPA in rat tissues The parameters needed to develop a physiological pharmacokinetic model for NAPA disposition kinetics in rat and man were derived as follows. Physiological and

anatomical parameters in 0.25 kg rat and 70 kg man were derived from reported data⁽⁵⁾. Parameters describing metabolism kinetics of NAPA in rat were determined in the experiment and those in man were taken from report of Strong *et al*⁽¹⁰⁾. These parameters were listed in Tab 1.

Using the parameters and the present equations, we can simulate concentration of NAPA in rat and human tissues.

RESULTS

Urinary recovery of NAPA in rat after iv

Urinary recovery of NAPA in 24 h was $62.9 \pm 32.0\%$ of the iv dose $40 \text{ mg} \cdot \text{kg}^{-1}$. The result is in good agreement with that of Pang *et al*⁽¹¹⁾. No procainamide was detected in urine, indicating the absence of a deacety-

lation process.

Body clearance Blood clearance of NAPA in rat was calculated from dose/ AUC_B to be $13.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The estimated clearances in plasma, kidney, and liver were 10.7, 8.24, and $4.88 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively. The estimated plasma clearance was lower than that of Schneck *et al*⁽¹²⁾.

Tissue / blood drug concentration ratios in rat tissues The values of AUC in rat tissues were calculated with linear trapezoidal rules after iv NAPA $40 \text{ mg} \cdot \text{kg}^{-1}$ (Tab 2). Tissue / blood drug concentration ratios in kidney and liver were estimated with equation 24 and those in other tissues were calculated with equation 23. For example, the values of AUC in blood and heart were 3045.3 and

Tab 1. Physiological and biochemical parameters for NAPA in 0.25 kg rat and 70 kg man⁽⁵⁾.

Compartment	Rat of 0.25 kg		Man of 70 kg	
	Volume / ml	Blood flow / $\text{ml} \cdot \text{min}^{-1}$	Volume / ml	Blood flow / $\text{ml} \cdot \text{min}^{-1}$
Brain	1.2	1.1	1500	760
Lung	1.2	44.5	1200	6330
Heart	1.0	4.2	300	240
Liver	11.0	14.7	1500	1580
GI tract	11.1	12.0	2400	1200
Kidney	2.0	11.4	300	1240
Muscle	125.0	6.8	30000	300
Skin	43.5	44.5	7800	1950
Adipose tissue	10.0	1.8	12200	260
Blood				
Artery	6.8		1800	
Vein	13.6		3600	
Recovery in urine		62.9%*		81% ⁽¹⁰⁾
Blood clearance / $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$				
Kidney		8.24		3.13
Liver		4.88		0.74
Total		13.1		3.87**
$f_u \text{Cl}_r$ / $\text{ml} \cdot \text{min}^{-1}$ **				
Kidney		2.51		266.1
Liver		1.33		53.6

* Metabolic parameters of NAPA in rat were determined in the present study. ** Plasma clearance in man derived from Ref 10 was $222 \text{ ml} \cdot \text{min}^{-1}$, total blood clearance was $222 \times 1.22 / 70 = 3.87 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

*** $f_u \text{Cl}_r = \text{Cl}_r / (1 - \text{Cl}_r / Q_r)$.

6648.0 $\mu\text{g} \cdot \text{min} \cdot \text{ml}^{-1}$, respectively, and heart / blood drug concentration ratio was $6648.0 / 3045.3 = 2.18$; AUC in liver was $5418.7 \mu\text{g} \cdot \text{min} \cdot \text{ml}^{-1}$, $f_u \text{Cl}_b'$ was $1.33 \text{ ml} \cdot \text{min}^{-1}$, and blood flow in rat liver was $14.7 \text{ ml} \cdot \text{min}^{-1}$. Thus liver / blood drug concentration ratio was $(1 + 1.33 / 14.7) \times 5418.7 / 3045.3 = 1.94$.

The tissue / blood drug concentration ratios demonstrated that heart, small intestine, kidney, liver, and muscle show greater affinities to NAPA than blood components do (Tab 2). The relatively higher kidney / blood drug concentration ratio and higher kidney clearance are consistent the fact that NAPA is excreted by an active process in rat⁽¹³⁾.

Tab 2. AUC and tissue / blood drug concentration ratios in rat tissues after iv NAPA 40 mg · kg⁻¹.

Compartment	AUC / $\mu\text{g} \cdot \text{min} \cdot \text{ml}^{-1}$ or g^{-1}	K_t / $\text{ml} \cdot \text{g}^{-1}$
Brain	2363.5	0.78
Lung	5451.1	1.79
Heart	6648.0	2.18
Liver	5418.7	1.94
GI tract	6642.5	2.18
Kidney	8114.6	3.25
Muscle	5298.1	1.74
Skin	3846.0	1.26
Adipose tissue	2987.4	0.98
Plasma	3729.2	1.22
Blood	3045.3	

Simulation in rat tissues The F_i , \bar{t}_i , and σ_i^2 in 0.25 kg rat tissues were estimated with equations 6–8 and parameters listed in Tab 1 and Tab 2. These parameters were listed in Tab 3. Using equations 18–22, we got $E = 0.0736$, $\bar{t}_{\text{cir}} = 8.05 \text{ min}$, $\sigma_{\text{cir}}^2 = 313.5 \text{ min}^2$, $\text{MDRT} = 109.4 \text{ min}$ and $\text{VDRT} = 15341.9 \text{ min}^2$. Using equation 17, we obtained $a = 0.220$, $b = 0.00713 \text{ min}^{-1}$, and $A = 0.245$. The equation for estimating concentration of NAPA in 0.25 kg rat blood following iv NAPA 40 mg · kg⁻¹ was $C = 55.06t^{-0.220}$

$\cdot \exp(-0.00713t)$. After prediction of concentration of NAPA in blood, the concentrations in liver and in lung were estimated with equations 13 and 14, respectively, and those in other tissues were simulated with equation 12.

Tab 3. The mean transfer time and the variance of NAPA in rat tissues.

Compartment	\bar{t}_i / min	σ_i^2 / min^2
Brain	0.85	0.722
Lung	0.05	0.002
Heart	0.52	0.270
Liver	1.33	1.769
GI tract	2.02	4.080
Kidney	0.47	0.221
Muscle	31.98	1022.720
Skin	12.18	148.352
Adipose tissue	5.44	29.594

The predicted concentrations of NAPA in rat blood and organs or tissues (brain, heart, lung, small intestine, liver, kidney, muscle, skin, and adipose tissue) were shown in Fig 2 and compared with observed ones after iv NAPA 40 mg · kg⁻¹. Using r^2 values as a criterion⁽¹⁴⁾, we found a good agreement

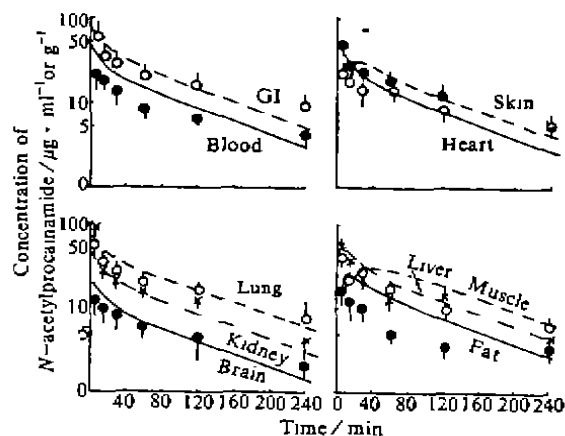


Fig 2. Predicted (line) and observed (point) NAPA concentrations in blood and tissues of 0.25 kg rat after iv NAPA 40 mg · kg⁻¹. Each point and vertical represents $\bar{x} \pm s$ of 3 rats.

($r > 0.80$) between predicted and observed values in blood, brain, liver, skin, lung, and small intestine. There was an underestimation in kidney and an overestimation in adipose tissue. The simulated curves for muscle, skin, and adipose tissue (which were poorly perfused) showed that NAPA concentrations in these tissues increased to a peak over a period about 40, 25, and 10 min, respectively, while our observed data showed that NAPA uptakes in these tissues were extremely rapid. The reason for this discrepancy was not known.

Simulation in man Using physiological parameters of man listed in Tab 1 and tissue/blood drug concentration ratios obtained in rat, we obtained $E = 0.0428$, $t_{cir} = 14.2$ min, $\sigma_{cir}^2 = 3015.8$ min², MDRT = 331.8 min², VDRT = 175826.5 min², $a = 0.374$, $b = 0.00189$ min⁻¹, and $A = 0.3524$. The concentration of NAPA in plasma of man was predicted. The closeness of fitness between the simulated curve, based on the perfused model, and that observed in plasma⁽¹⁵⁾ (Fig 3) was noted.

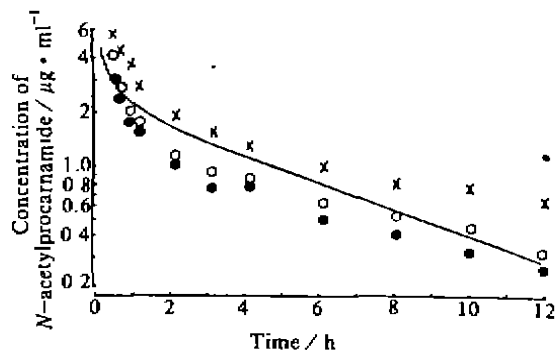


Fig 3. Predicted and observed NAPA concentrations in plasma of man. Observed data of 3 normal men after iv NAPA 250 mg were taken from Fig 2 of Ref 15. Body weights of 3 men were 83 (○), 54 (×), and 77 (●) kg, respectively.

DISCUSSION

We proposed a method for simulating disposition kinetics of drugs in animal using combination of gamma variate and physiological pharmacokinetic model. The present method demands that all processes be linear. We selected NAPA as a model drug and predicted concentrations of NAPA in rat tissues following iv 40 mg · kg⁻¹ of NAPA. A good agreement between prediction and observation was noted in most of the tissues. This indicated that the present method can be used to describe disposition kinetics of NAPA in rat.

When scale-up from rodents to man is attempted, the most difficult problem is how to estimate the tissue/blood drug concentration ratios in man. There are two ways of dealing with this problem. One is to apply the tissue/blood drug concentration ratios obtained in the laboratory animal to other species without any manipulation. In order to describe disposition kinetics of NAPA in man, we presumed values of tissue/blood concentration ratios of NAPA in man to be the same as those in rat, as being determined in the study. The results showed that values of tissue/blood ratios of NAPA obtained in rat can be successfully applied to human being.

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① γ 变量与生理模型结合预报乙酰普鲁卡因胺在大鼠体内处置动力学

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摘要 测定了乙酰普鲁卡因胺(NAPA)在大鼠中清除率和组织/血液药物浓度比。NAPA 在大鼠血, 肝和肾的清除率分别为 13.1, 4.88 和 8.24 ml · kg⁻¹ · min⁻¹。用 γ 变量与生理模型结合预报 NAPA 在大鼠体内处置动力学。iv 40 mg · kg⁻¹ NAPA 后, 估算血药浓度方程为 $C = 55.06t^{-1.220} \exp(-0.00713t)$ 。用 r^2 值为判别标准, 发现在血, 肺, 小肠, 心, 脑和皮肤中预报值与观察值吻合好。

关键词 乙酰普鲁卡因酰胺; 药物动力学; 统计学模型

