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Metabolism of Piromidic Acid, a New Antibacterial Agent. IV.[1] Pharmacokinetics of Piromidic Acid in Rats

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The pharmacokinetic studies of piromidic acid (PA, 5,8-dihydro-8-ethyl-5-oxo-2-pyrrolidinopyrido[2,3-*d*]pyrimidine-6-carboxylic acid) were performed in rats after intravenous administration. Two compartment model, the central and peripheral compartment was adopted and the central compartment was connected to four metabolite compartments in branched metabolic pathways, totaling eleven parameters involved. Each parameter was determined by conjunction of graphical and mathematical methods using the experimental data on blood levels along with urinary and biliary excretions in rats receiving PA or each metabolite. Calculated blood levels of PA or its metabolites thus obtained were found to be reasonable. The peripheral compartment is ascribed to enterohepatic circulation of PA. This pharmacokinetic model may possibly applied on human subjects, since urinary metabolic patterns were similar in rats and human subjects receiving PA.

The previous papers[1,3] revealed that piromidic acid (PA, 5,8-dihydro-8-ethyl-5-oxo-2-pyrrolidinopyrido[2,3-*d*]pyrimidine-6-carboxylic acid), a new antibacterial agent, was extensively metabolized in rats and human subjects according to the following metabolic pathway (Chart 1). The antibacterial activities are varied with metabolites that unconjugated metabolites retaining pyrrolidine ring exhibited potentiated activities as compared with PA, whereas those without retaining pyrrolidine ring exhibited markedly decreased activities and all their glucuronides abolished activities. Therefore, a detailed study of the pharmacokinetic profile of PA and its metabolites is relevant to better understanding of the chemotherapeutic effect of PA.

This paper deals with determination of each kinetic parameter for the complete pharmacokinetic description of PA in rats, based on evaluation of blood levels, and urinary and biliary excretion data in rats receiving intravenous PA or each metabolite.

Pharmacokinetic Model

The previous works[3] on the metabolic pathway of PA together with time course of blood levels of PA and its metabolites led to a pharmacokinetic model as shown in Chart 1, which can be assumed to simulate the behaviour of PA in a body after intravenous administration. In the model, compartments 1, 3, 4, 5 and 6 can be assumed to be blood and other fluid or tissues in which each substance rapidly equilibrates. On the contrary, compartment 2 can be assumed to be a peripheral compartment since blood level of PA in rats after intravenous administration was found to be biphasic,[1] therefore a so-called two-compartment model was expected as a description of unchanged PA in a body. Compartment 6 contains both of M-III and M-VI (see the legend in Chart 1), since M-VI is chemically unstable and rapidly converted to M-III. PA, M-II, M-III and M-V (see the legend in Chart 1) were assumed to be excreted exclusively into urine in the model, whereas M-IV was found to be excreted into both urine and bile without reabsorption from intestinal tracts.[1]

1) Part III: Y. Sekine, M. Miyamoto, M. Hashimoto, and K. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **24**, 1433 (1976).
2) Location: *33–94 Enoki-cho, Suita, Osaka, 564, Japan.*
3) *a*) Y. Sekine, M. Miyamoto, M. Hashomoto, and K. Nakamura, *Xenobiotica*, **6**, 185 (1976); *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), 24, 437 (1976).

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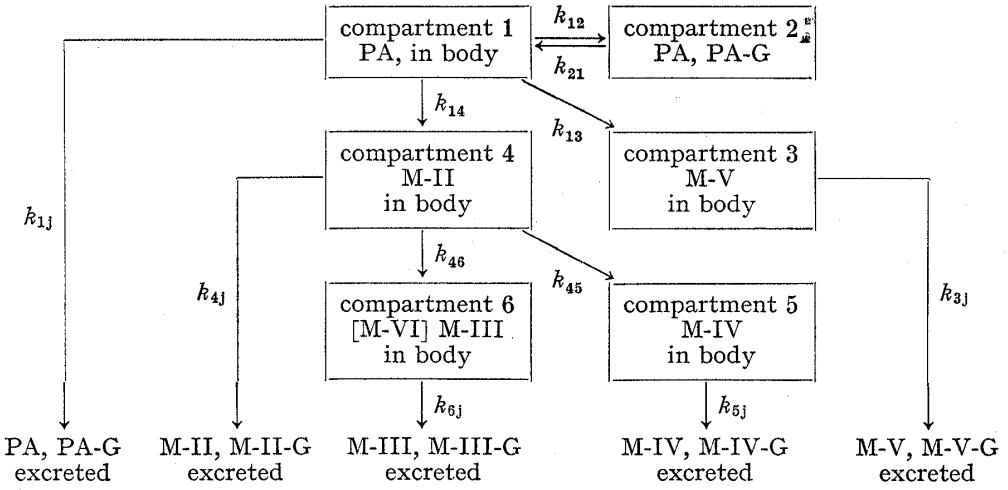

Chart 1. Schematic Representation of PA and Its Metabolites in Body as Linear Compartment Model in Rats after Intravenous Administration

M-II: 2-(2-hydroxypyrrolidino)-PPA
M-III: 2-amino-PPA
M-IV: 2-(3-hydroxycarbonylpropylamino)-PPA
M-V: 2-(3-hydroxypyrrolidino)-PPA
G: glucuronide
PPA: 5,8-dihydro-8-ethyl-5-oxo-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid

Experimental

Materials and Animal Experiments——Materials, animals and procedures used in this study were the same as those described in the previous papers,[1,3] except following.

M-II, M-III, M-IV, or M-V dissolved in a 0.01 N NaOH (5 mg/ml) was administered to rats (*ca.* 200 g) at a dose of 25 mg/kg. Blood samples were drawn from a group of three animals at 5, 10, 15, 20, 30, 40, 50, 60, or 90 min post dosing.

Determination of PA and Its Metabolites——Determination was performed utilizing thin-layer chromatographic separation followed by ultraviolet spectroscopic method as described in the previous paper,[1] except followings.

Blood levels of unchanged M-III, M-IV, or M-V in rats receiving each metabolite were determined as follows: To 1 ml of whole blood in a 40 ml glass-stoppered centrifuge tube, 3 ml of a buffer solution (pH 4.0, 1/5 M Na_2HPO_4–1/10 M citric acid) and 8 ml of $CHCl_3$ were added, the mixture was shaken vigorously for 15 min on a conventional shaker and centrifuged at 3000 rpm for 10 min. The absorbance in the chloroform phase at a given wavelength was measured (M-III at 254 nm, M-IV at 270 nm and M-V at 280 nm, respectively). Blood levels of M-III, M-IV and M-V were determined with calibration curves prepared beforehand. Blood levels of unchanged M-II in rats receiving intravenous M-II were separately determined in the similar way to that for PA and its metabolites described in the previous paper.[1]

Calculations——Determination of Elimination Rate Constants k_{3j}, $(k_{45}+k_{46}+k_{4j})$, k_{5j} and k_{6j}: The elimination rate constants k_{3j}, $(k_{45}+k_{46}+k_{4j})$, k_{5j} and k_{6j} were estimated from the least squares fit for observed blood levels of rats receiving intravenous each metabolite, since one-compartment model was expected for the simulation of the behaviour of each substance in a body.

Two-Compartment Model: According to the model shown in Chart 1, blood levels of unchanged PA (c) versus time (t) may be interpreted in terms of a two-compartment model which is given in the following biexponential equation:[4]

$$c/c_0 = Ae^{-\alpha t} + Be^{-\beta t} \tag{1}$$

$$A + B = 1 \tag{2}$$

where c_0 is the concentration of a drug in blood at zero time, α and β are the hybrid rate constants derived from the slopes of the curve, A and B are the ordinate axis intercepts. A, B, α and β were obtained by the usual graphical analysis method.[5] Therefore, the rate constants k_{12}, k_{21}, and $(k_{13}+k_{14}+k_{1j})$ are given with A, B, α and β as follows:[4]

$$k_{12} = A(1-A)(\alpha-\beta)^2/\{\alpha-A(\alpha-\beta)\} \tag{3}$$

4) S. Riegelman, J.C.K. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117 (1968).
5) H. Nogami, M. Hanano, S. Awazu, and T. Iga, *Chem. Pharm. Bull.* (Tokyo), **18**, 228 (1970).

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$$k_{21} = \alpha - A(\alpha-\beta) \tag{4}$$

$$k_{13} + k_{14} + k_{1j} = \alpha\beta/\{\alpha - A(\alpha-\beta)\} \tag{5}$$

α and β are, therefore, written as in Eq. (6) and (7):

$$\alpha\beta = k_{21}(k_{13}+k_{14}+k_{1j}) \tag{6}$$

$$\alpha + \beta = k_{12} + k_{21} + k_{13} + k_{14} + k_{1j} \tag{7}$$

Analysis of Pharmacokinetic Model——In the model, the amounts of drug in each compartment at any time t after intraverous administration are given as X_1, X_2,$\cdots X_i$,$\cdots$ and X_6, respectively. The apparent volumes of distribution (V_i) are designated as $V_1=V_2=\cdots=V_6$ for six compartments. k_{ij} indicates the rate constant from the compartment i to j. Therefore, k_{ij} equals zero at i=j. All the rate processes are assumed to be first-order. The variation of the amount X_i of drug in the compartment i can be written as the following equation:

$$dX_i/dt = \sum_{j=1}^{n}(k_{ji}X_j) - (\sum_{j=1}^{n}k_{ij})X_i \tag{8}$$

$$i,\ j = 1,\ 2,\ \cdots\ 6$$

Laplace transformation of Eq. (8) lead to Eq. (9) to (14) as follows:

$$X_1/x_0 = (\alpha-k_{21})\exp(-\alpha t)/(\alpha-\beta) + (k_{21}-\beta)\exp(-\beta t)/(\alpha-\beta) \tag{9}$$

$$X_2/x_0 = k_{12}\exp(-\alpha t)/(\beta-\alpha) + k_{12}\exp(-\beta t)/(\alpha-\beta) \tag{10}$$

$$\begin{aligned} X_3/x_0 = {} & k_{13}(k_{21}-k_{3j})\exp(-k_{3j}t)/(\alpha-k_{3j})(\beta-k_{3j}) \\ & + k_{13}(k_{21}-\alpha)\exp(-\alpha t)/(k_{3j}-\alpha)(\beta-\alpha) \\ & + k_{13}(k_{21}-\beta)\exp(-\beta t)/(\alpha-\beta)(k_{3j}-\beta) \end{aligned} \tag{11}$$

$$\begin{aligned} X_4/x_0 = {} & k_{14}(k_{21}-k')\exp(-k't)/(\alpha-k')(\beta-k') \\ & + k_{14}(k_{21}-\alpha)\exp(-\alpha t)/(k'-\alpha)(\beta-\alpha) \\ & + k_{14}(k_{21}-\beta)\exp(-\beta t)/(k'-\beta)(\alpha-\beta) \end{aligned} \tag{12}$$

$$\begin{aligned} X_5/x_0 = {} & k_{14}k_{45}(k_{21}-k')\exp(-k't)/(k_{5j}-k')(\alpha-k')(\beta-k') \\ & + k_{14}k_{45}(k_{21}-k_{5j})\exp(-k_{5j}t)/(k'-k_{5j})(\alpha-k_{5j})(\beta-k_{5j}) \\ & + k_{14}k_{45}(k_{21}-\alpha)\exp(-\alpha t)/(k'-\alpha))k_{5j}-\alpha)(\beta-\alpha) \\ & + k_{14}k_{45}(k_{21}-\beta)\exp(-\beta t)/(k'-\beta)(k_{5j}-\beta)(\alpha-\beta) \end{aligned} \tag{13}$$

$$\begin{aligned} X_6/x_0 = {} & k_{14}k_{46}(k_{21}-k')\exp(-k't)/(k_{6j}-k')(\alpha-k')(\beta-k') \\ & + k_{14}k_{46}(k_{21}-k_{6j})\exp(-k_{6j}t)/(k'-k_{6j})(\alpha-k_{6j})(\beta-k_{6j}) \\ & + k_{14}k_{46}(k_{21}-\alpha)\exp(-\alpha t)/(k'-\alpha)(k_{6j}-\alpha)(\beta-\alpha) \\ & + k_{14}k_{46}(k_{21}-\beta)\exp(-\beta t)/(k'-\beta)(k_{6j}-\beta)(\alpha-\beta) \end{aligned} \tag{14}$$

where x_0 is the amounts of PA in the compartment 1 at time zero, and k' is given in Eq. (15):

$$k' = k_{45} + k_{46} + k_{4j} \tag{15}$$

The constant k_{1j} can be calculated from α, β, k_{21} and Eq. (16) since PA and PA-glucuronide were completely excreted into 24-hr urine of rats after intravenous administration.

$$\begin{aligned} X_u/x_0 = {} & k_{1j}k_{21}/\alpha\beta - k_{1j}(k_{21}-\alpha)\exp(-\alpha t)/\alpha(\beta-\alpha) \\ & - k_{1j}(k_{21}-\beta)\exp(-\beta t)/\beta(\alpha-\beta) \end{aligned} \tag{16}$$

where X_u is the amount of PA and PA-glucuronide excreted into urine.

The constant k_{13} can be calculated from Eq. (11) using the data for blood levels of M-V. Similarly, k_{14} can be calculated. If the constants k_{13}, k_{14}, and k_{1j} calculated from Eq. (11), (12), and (16) are poorly satisfied with Eq. (5), each constant must be corrected as follows: (a) $(k_{13}+k_{14}+k_{1j})$ are first calculated. (b) α and β are re-calculated from Eq. (6) and (7) using $(k_{13}+k_{14}+k_{1j})$ calculated above. (c) A and B are corrected for the new constants α, β, and k_{21} from Eq. (1) and (9). (d) The constants k_{12}, k_{21}, and $(k_{13}+k_{14}+k_{1j})$ are re-calculated with α, β, A and B corrected. (e) The constants k_{13}, k_{14}, and k_{1j} are re-calculated by the same way as described above. (f) The corrections are made until the summation of squares of the differences between the calculated and observed values of PA, M-II, and M-V is minimized by a trial and error procedure.

The constant k_{45} can be calculated by the same estimation as that of k_{13}, whereas k_{46} can not be calculated from Eq. (14) since blood level of M-III is too low to be determined by our method. The ratio of k_{46}

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to $(k_{45}+k_{46}+k_{4j})$ can be assumed to be equal to the ratio of urinary and biliary excretion as given by Eq. (17):[6]

$$k_{46}/(k_{45}+k_{46}+k_{4j}) = E_{M-III}/(E_{M-IV}+E_{M-III}+E_{M-II}) \quad (17)$$

where E_{M-II}, E_{M-III}, and E_{M-IV} are the amounts of M-II, M-III, and M-IV excreted into urine and bile of rats receiving intravenous PA, respectively. Therefore, the constant k_{46} may be calculated from Eq. (17).

Results

I. Blood Levels of Unchanged PA and Its Metabolites in Rats receiving Intravenous PA

Blood levels of unchanged PA and its metabolites were determined after a single intravenous administration to rats (25 mg/kg). The results are shown in Table I. This indicates that PA was rapidly metabolized to M-II and M-IV.

Table I. Blood Levels of PA and Its Metabolites in Rats[a] receiving Intravenous PA at a Dose of 25 mg/kg

Time (min)	Blood level[b] (μg/ml)				
	PA	M-II	M-V	M-IV	M-III
5	23.3	12.8	1.20	1.21	0
10	13.2	23.5	2.26	2.93	0
15	6.87	19.8	2.54	4.80	trace
20	4.48	15.5	1.89	4.06	trace
30	2.01	9.91	1.15	3.19	trace
40	1.14	9.88	1.19	3.47	0
50	0.98	7.38	1.15	2.46	0
60	0.68	4.36	0.84	1.76	0
90	0.35	2.23	0.64	1.20	0

a) Wistar, male, body wt. 200—220 g
b) mean of three animals

The data of urinary and biliary excretion of PA and its metabolites in rats receiving intravenous PA were reported in the previous paper.[1] These levels of PA and its metabolites in blood and urine were found almost entirely to be unconjugated (more than 95%), whereas those in bile total amounts of unconjugated and glucuronides were nearly equal, with a marked predominance of PA-glucuronide.

II. Kinetics of Unchanged PA in Blood of Rats after Intravenous Administration

The blood level *versus* time relation can be interpreted in terms of a two-compartment model as given in Eq. (1) and (2), since the semilogarithmic plots of PA had two linear phases. The constants α, β, A and B in Eq. (1) were determined by the graphical analysis method as given in Eq. (18) and the constants k_{12}, k_{21} and $(k_{13}+k_{14}+k_{1j})$ are calculated from Eq. (3), (4) and (5). The results are shown in Table II.

$$c/48.05 = 0.9361e^{-0.1472t} + 0.0639e^{-0.0242t} \quad (18)$$

Table II. Rate Constants k_{12}, k_{21} and $(k_{13}+k_{14}+k_{1j})$ calculated with Eq. (3), (4) and (5)

Rate constant	k(min^{-1})
k_{12}	2.82×10^{-2}
k_{21}	3.20×10^{-2}
$k_{13}+k_{14}+k_{1j}$	1.11×10^{-1}

6) M. Hanano, "Iyakuhin Kaihatsu Kiso Koza," Vol. 15, Chijinshokan, Tokyo, 1971, p. 356.

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III. Blood Levels of Unchanged Drug in Rats receiving Intravenous M-II, M-III, M-IV or M-V

Blood levels of unchanged M-II were determined after an intravenous dosing of M-II to rats (25 mg/kg). The semilogarithmic plots of blood level of M-II are shown in Fig. 1. Likewise, Fig. 2, 3 and 4 illustrate blood levels of unchanged M-III, M-IV and M-V, respectively, in rats receiving intravenously each drug. As can be seen from these figures, blood level-time curves may be represented monoexponential equations. The pharmacokinetic parameters

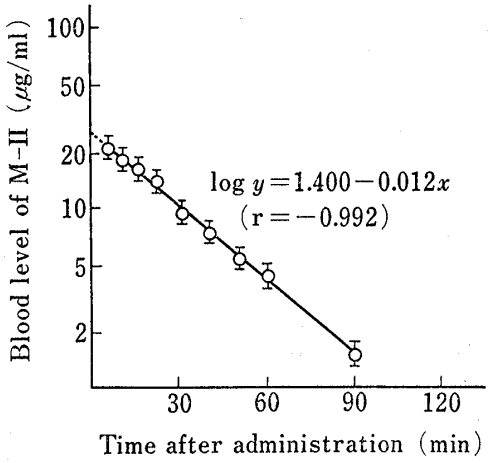

Fig. 1. Semilogarithmic Plots of Blood Level of M-II after Intravenous Administration of M-II at a Dose of 25mg/kg

animal: rats (Wistar, male, body wt. *ca.* 200 g)
plotting: mean ±S.E. (n=3)
y: blood level (μg/ml), x: time (min),
r: correlation coefficient

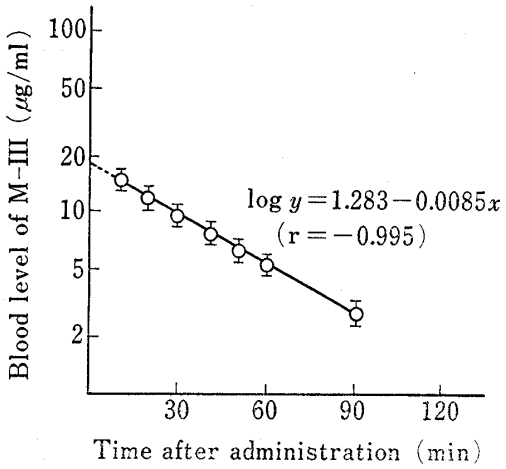

Fig. 2. Semilogarithmic Plots of Blood Level of M-III after Intravenous Administration of M-III at a Dose of 25 mg/kg

animal: rats (Wistar, male, body wt. *ca.* 200 g)
plotting: mean ±S.E. (n=3)
y: blood level (μg/ml), x: time (min),
r: correlation coefficient

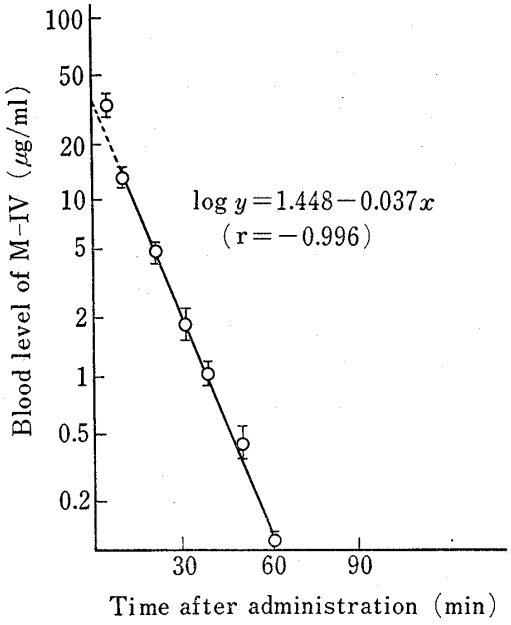

Fig. 3. Semilogarithmic Plots of Blood Level of M-IV after Intravenous Administration of M-IV at a Dose of 25 mg/kg

animal: rats (Wistar, male, body wt. *ca.* 200 g)
plotting: mean ±S.E. (n=3)
y: blood level (μg/ml), x: time (min),
r: correlation coefficient

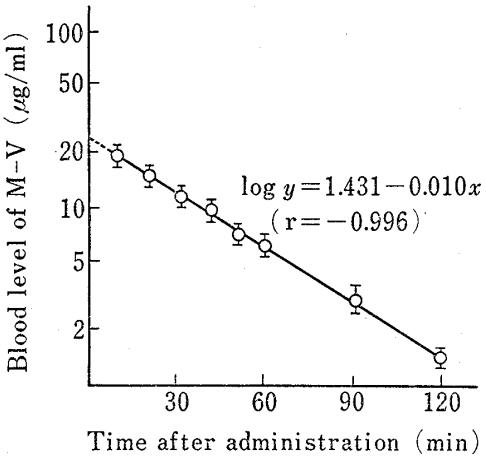

Fig. 4. Semilogarithmic Plots of Blood Level of M-V after Intravenous Administration of M-V at a Dose of 25 mg/kg

animal: rats (Wistar, male, body wt. *ca.* 200 g)
plotting: mean ±S.E. (n=3)
y: blood level (μg/ml), x: time (min),
r: correlation coefficient

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TABLE III. Kinetic Parameters for M-II, M-III, M-IV and M-V in Rats

Metabolite	k(min^{-1})	k(hr^{-1})	$t_{1/2}$(hr)	V(ml)
M-II	2.86×10^{-2}	1.71	0.41	189
M-III	1.96×10^{-2}	1.18	0.59	261
M-IV	8.48×10^{-2}	5.09	0.14	204
M-V	2.33×10^{-2}	1.40	0.50	186

k: elimination rate constant
$t_{1/2}$: biological half-life
V: apparent volume of distribution

TABLE IV. Rate Constants in Kinetic Model of PA in Chart 1

Rate constant	k (min^{-1})	Rate constant	k (min^{-1})
k_{12}	2.81×10^{-2}	k_{6j}	1.96×10^{-2}
k_{21}	3.20×10^{-2}	k_{45}	2.54×10^{-2}
k_{13}	1.51×10^{-2}	k_{46}	2.29×10^{-3}
k_{14}	1.36×10^{-1}	k_{4j}	8.70×10^{-4}
k_{1j}	7.80×10^{-4}		
k_{3j}	2.33×10^{-2}	α	1.62×10^{-1}
k_{5j}	8.48×10^{-2}	β	2.51×10^{-2}

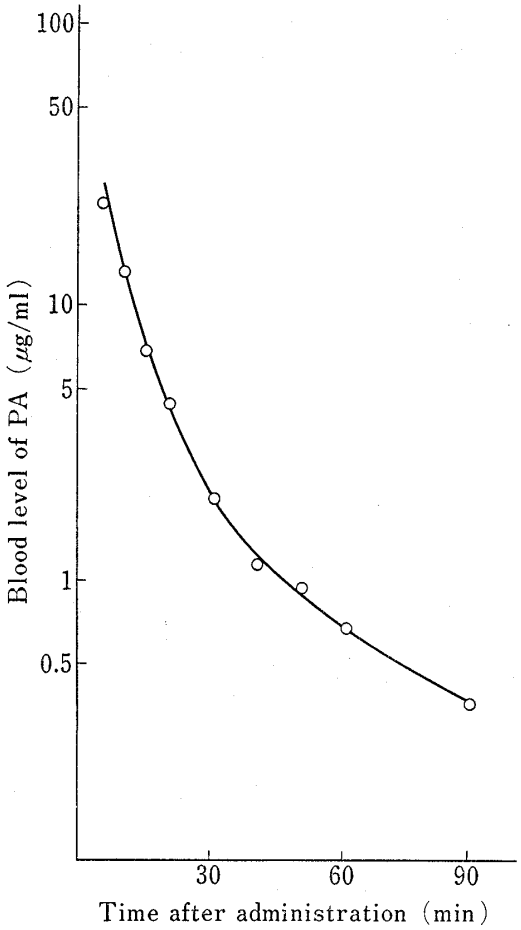

Fig. 5. PA Blood Level Plots and Its Calculated Curve in Rats receiving Intravenous PA at a Dose of 25 mg/kg

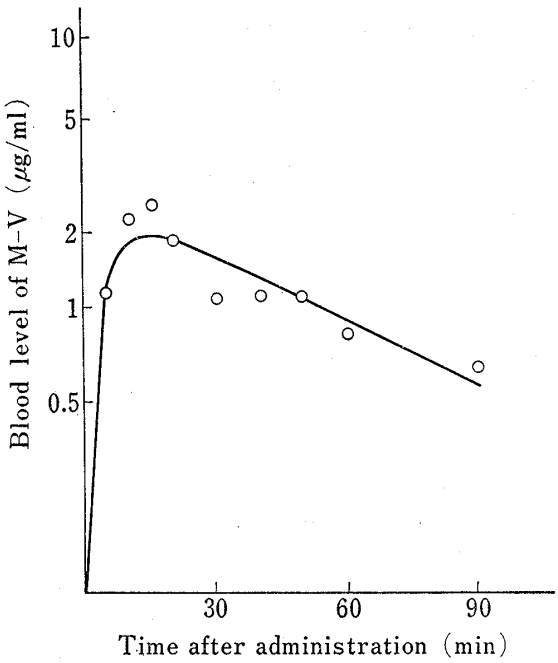

Fig. 6. M-V Blood Level Plots and Its Calculated Curve in Rats receiving Intravenous PA at a dose of 25 mg/kg

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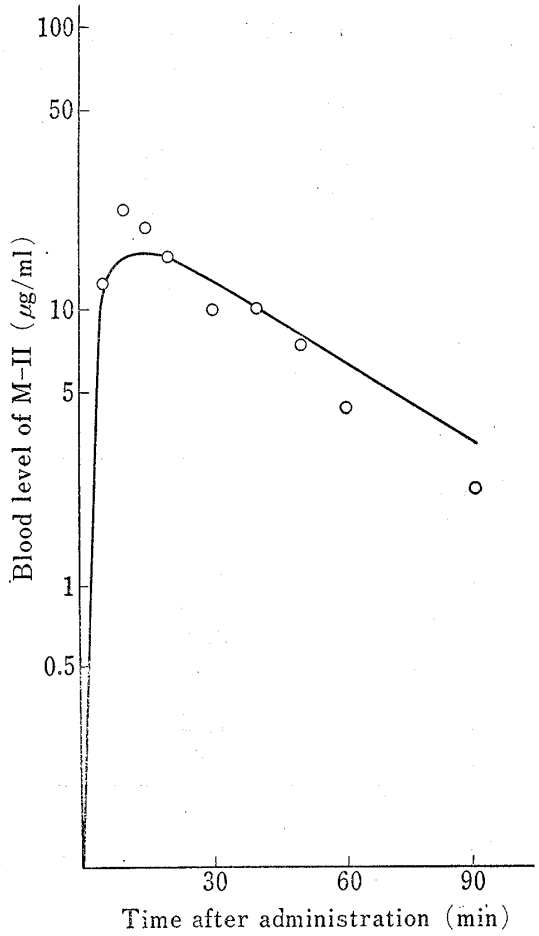

Fig. 7. M-II Blood Level Plots and Its Calculated Curve in Rats receiving PA at a Dose of 25 mg/kg

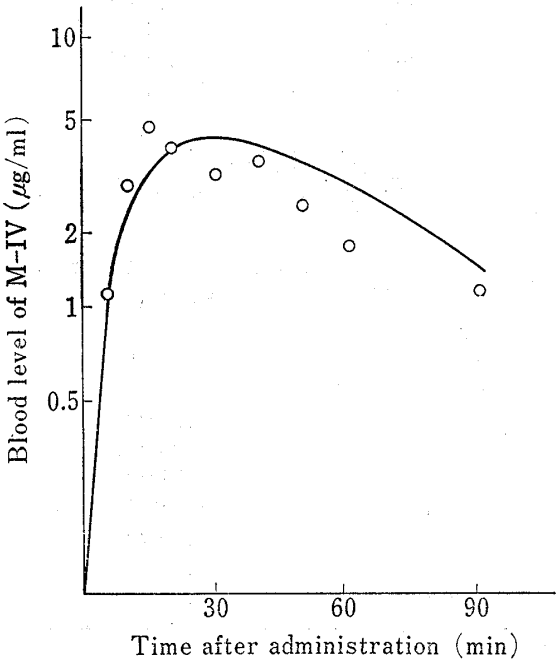

Fig. 8. M-IV Blood Level Plots and Its Calculated Curve in Rats receiving Intravenous PA at a Dose of 25 mg/kg

obtained for M-II, M-III, M-IV and M-V are shown in Table III. There found marked differences in the elimination rate constants between M-IV and M-II, M-III or M-V.

IV. Pharmacokinetic Study

The eleven rate constants in the pharmacokinetic model of PA in Chart 1, together with hybrid rate constants, α and β, were calculated from the observed data on blood levels and biliary and urinary excretions of PA and its metabolites after intravenous dosing of PA, along with blood levels of each metabolite after its intravenous dosing. The parameters obtained are listed in Table IV.

Substitutions of these parameters in Eq. (9), (11), (12) and (13) afford blood level-time curves of PA, M-V, M-II and M-IV, respectively, in rats receiving intravenous PA. These calculated blood level-time curves, together with observed blood levels are depicted in Fig. 5, 6, 7 and 8. Fitness is good for unchanged PA (Fig. 5) and is reasonable for its first step metabolites, M-V (Fig. 6) and M-II (Fig. 7). However, a further converted metabolite is not in good fitness, though rate constant in the elimination phase seems to be similar between observed and calculated ones (Fig. 8), suggesting that individual differences of animals in the metabolic rates are reflected more profound on calculated blood levels of a secondary metabolite involved in the extensive metabolism.

Discussion

The pharmacokinetic model shown in Chart 1 was found to be a useful and simplified description of PA metabolism in rats after intravenous administration. Compartment 2

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in the model can be assumed to be a peripheral compartment which contains biliary excretion of PA and PA-glucuronide from the following evidences. (a) Unchanged PA and PA-glucuronide were found to be excreted into 24 hr bile of rats receiving intravenous PA, accounting for about 16% of the dose.[1] (b) The biliary excretion of PA and PA-glucuronide in rats receiving intravenous PA was nearly equal to the calculated amount of PA distributed in compartment 2 in the model. (c) PA was found *in vitro* and *in vivo* to be well-absorbed from intestinal tract.[7] (d) PA-glucuronide excreted into bile is highly likely to be hydrolized enzymatically to PA as well as many other glucuronides in the intestinal tract[8] and the resulting PA is probably reabsorbed. Therefore, biphasic elimination of unchanged PA in blood is likely to depend on the enterohepatic circulation of PA as shown in Chart 2.

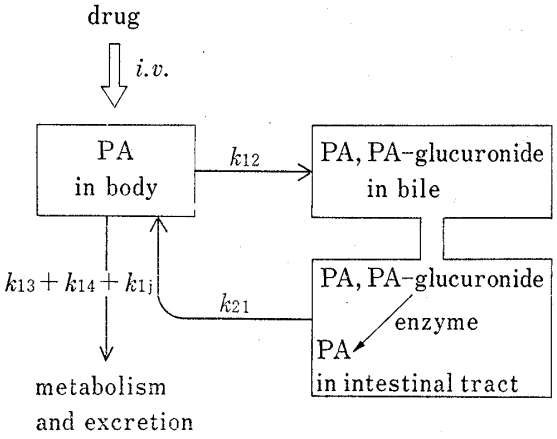

Chart 2. Pharmacokinetic Model for Unchanged PA in Rats after Intravenous Administration

Table V. Calculated and Observed Values of PA and Its Metabolites in 24-hr Urine of Rats after Intravenous Administration at a Dose of 25 mg/kg

Metabolite[a]	Urinary excretion[b] (μg)	
	Calculated	Observed
PA	41.7	42.0
M-II	222	214
M-III	584	731
M-IV	6479	1452
M-V	807	636

a) Each contains a small amount of its glucuronide (up to 5%).
b) expressed as PA equivalents

The metabolic rate constants of 2-hydroxypyrrolidine (M-II) and 3-hydroxypyrrolidine (M-V) derivative formation, involved in the first step of PA metabolism, were 8.16 hr^{-1} and 0.906 hr^{-1}, respectively. The ratio of the rate constants 8.16 hr^{-1}/0.906 hr^{-1}, was found to be nearly equal to the ratio (9:1) of M-II and M-V formed on *in vitro* incubation of PA as described previously.[3b] The elimination rate constant of M-II was found to be nearly equal to that of M-V in rats (Table III). However, M-V was excreted without successive oxidation, whereas M-II was further metabolized by about 89% to M-IV and by about 8% to M-III via M-VI. Only 3% of M-II was excreted as an intact form. Therefore, the main route of M-II disappearing from the compartment was found to be biotransformation to M-IV. The metabolic rate of M-II to M-III in rats was also found to be slow (0.137 hr^{-1}) as compared with the elimination rate of M-III (1.18 hr^{-1}). This indicates that the blood level of M-III in rats receiving PA may be too low to be determined.

Provided that all metabolites are entirely excreted into urine, total urinary excretions of PA and each metabolite are calculated according to the model and results are shown in Table V. These calculated excretions were found to coincide nearly with 24-hr urinary excretions observed for PA, M-II, M-III and M-V, with exception of M-IV. These results indicate that PA, M-II, M-III and M-V were finally excreted into urine of rats after intravenous administration, whereas M-IV is likely to be excreted into both of urine and feces. Fecal excretion of M-IV was confirmed by the following evidences. (a) After an intravenous 25 mg/kg dose of PA to rats, M-IV was a major metabolite in 24 hr bile, accounting for 29% of the

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dose.[1] (b) Following 50 mg/kg dose of M-IV intravenously administered to rats, M-IV in 24-hr urine and bile accounted for 17% and 80% of the dose, respectively.[9] (c) After 100 mg/kg oral M-IV, it was poorly absorbed to give undetectable blood levels and a small 24-hr urinary excretion amounting up to 0.7% of the dose.[9]

The kinetic pathway of PA in rats receiving intravenous PA are summarized in Chart 3. After intravenous administration to rats, PA was found to be rapidly converted to M-V and M-II, with rates of 0.906 hr^{-1} and 8.16 hr^{-1}, both of them exhibiting potentiated antibacterial activity as compared with PA.[3a] The former excreted into urine with a minor portion in

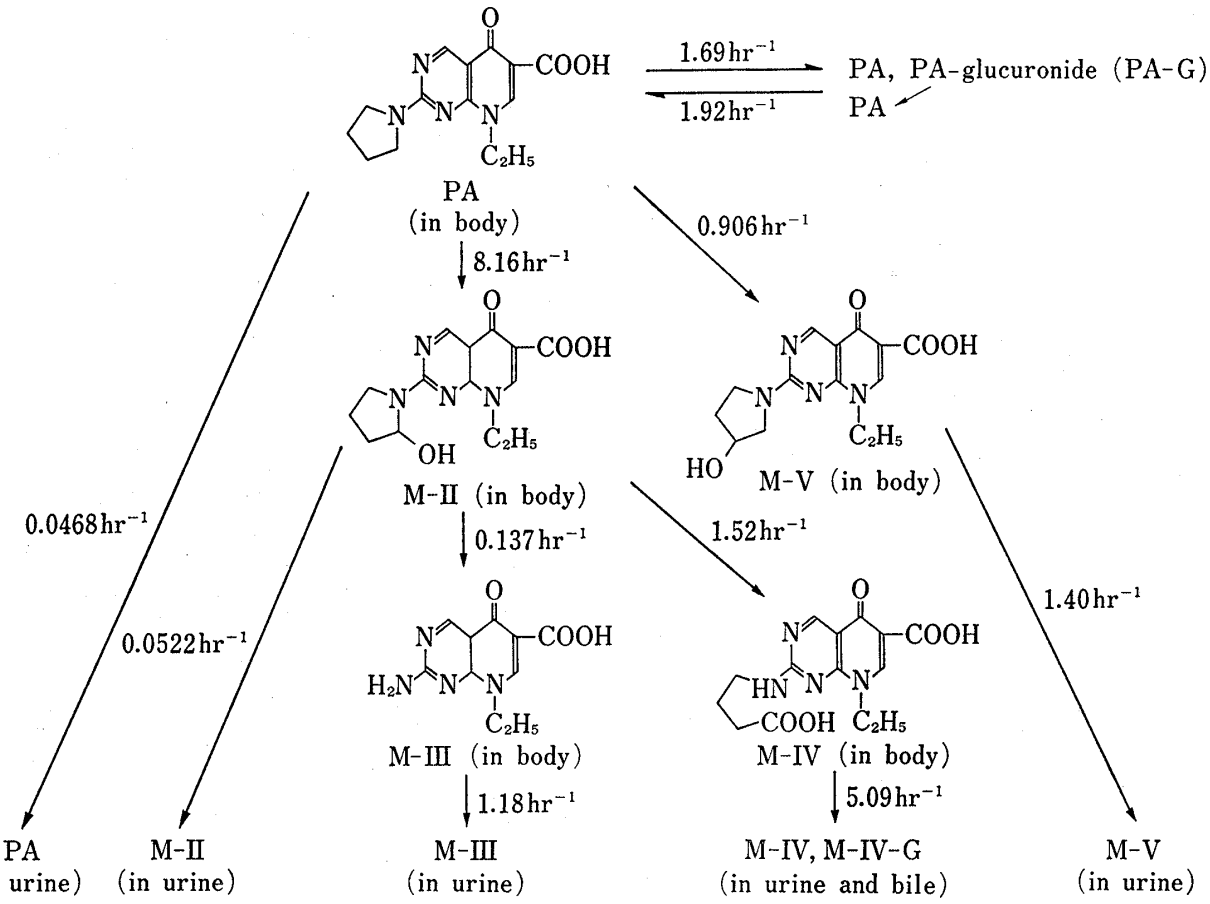

Chart 3. Kinetic Pathway of PA in Rats after Intravenous Administration

its glucuronide, exerting the major antibacterial activity in the urinary tract. On the contrary, the latter M-II was converted to M-IV and M-III, both with markedly decreased antibacterial activity.[3a] M-IV was rapidly excreted into urine and feces (*via* bile) with a rate of 5.09 hr^{-1}, exceeding its metabolic formation rate of 1.52 hr^{-1}. A eight-fold exceeding elimination rate as compared with the formation rate was found for M-III leading to its markedly low blood levels.

The peripheral compartment was attributed to enterohepatic circulation of PA which may to some extents contribute to elongate the antibacterial activity in rats.

This pharmacokinetic model may possibly applied on human subjects, since urinary metabolic patterns were similar in rats and human subjects receiving PA.

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