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Pharmacokinetic Analysis of Pharmacological Effects and Drug Disposition Acetaminophen and 4-Aminoantipyrine[1]

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After the administration of antipyretics, the pharmacological response intensity versus time course was expressed quantitatively using a pharmacokinetic method.

Acetaminophen and 4-aminoantipyrine were used as the antipyretics. After the administration of these drugs, plasma level, brain level and urinary excretion of the drug were determined as the drug disposition data. Metabolic rate, vaporization rate, rectal temperature and skin temperature were also determined as the pharmacological effects.

From the observed data, an electrical analog was constructed to simulate the effects of antipyretics including physiological thermoregulation.

The results indicate that the time course of pharmacological effects are reasonably simulated by a single mathematical model.

Pharmacokinetics have been functioning successfully to represent the time course of drug concentrations and amounts in various tissues and in excreta. It is self-evident that the quantitative representation of pharmacological response intensity versus time course is essential for such a variety of problems as control of drug action, prevention of adverse reactions, drug dosage regimen, development of drug formulation and so on.

Reports on the application of pharmacokinetics to pharmacological response, however, are quite few,[3] due to an ambiguous relationship between drug disposition and pharmacological response intensity in intact animals including man.

Recently, in the field of biomedical engineering, attempts have been made to simulate physiological temperature regulation in man to various environmental conditions using an analog or a digital computer to solve the basic equations for heat balance. Crosbie and his co-workers[4] have constructed an electrical analog to simulate the physiological response of man to heat and cold, assuming a one-dimensional physical model. Similar attempts have been made by Stolwijk and his co-workers[5] assuming a cylindrical physical model.

Studies on antipyretics revealed that the disposition of these drugs are beautifully described with simple kinetic models. Thereupon, phemacokinetic interpretation of the hypothermic effect of antipyretics was designed by constructing a mathematical model that represents the pharmacological response of antipyretics as well as the physiological response of thermoregulation.[6]

In the study of this report, the analog of Crosbie, *et al.*,[4] was modified in order that the system was able to respond quantitatively to the introduction of antipyretics. The purpose

1) Presented at the Fifth Symposium on Drug Metabolism and Action, Shizuoka, November, 1973.
2) Location: *3190 Gofuku, Toyama, 930, Japan.*
3) G. Levy, *Clin. Pharmacol. Therap.*, **7**, 362 (1966); G. Levy and M. Gibaldi, *Ann. Rev. Pharmacol.*, **12**, 85 (1972); V.F. Smolen, *J. Pharm. Sci.*, **60**, 878 (1971); V.F. Smolen and W.A. Weigand, *J. Pharmacok. Biopharm.*, **1**, 329 (1973).
4) R.J. Crosbie, J.D. Hardy, and E. Fessenden, *IRE Trans. Bio-Med. Electron.*, **8**, 245 (1961).
5) J.A.J. Stolwijk and J.D. Hardy, *Pflügers Arch. ges. Physiol.*, **291**, 129 (1966).
6) J.D. Hardy, A.P. Gagge, and J.A.J. Stolwijk, "Physiological and Behavioral Temperature Regulation," C.C. Thomas Publisher, Springfield, III., 1970.

of this paper is to describe the mathematical model, the results of simulation and to verify its applicability.

Theoretical

General Description of the Model

Diagram of the model is shown in Fig. 1. The rat body is divided into two compartments, core and skin. Each compartment is considered to have uniform thermal properties and a single value of temperature. Each compartment loses or gains heat from adjacent compartment in proportion to the temperature difference between them. In Fig. 1, thick and thin solid lines represent heat flows and controlling pathways, respectively. Metabolic heat (M) is generated in the core compartment. Heat loss by vaporization (V) is mainly respiratory effect and, therefore, occurrs in the core compartment.

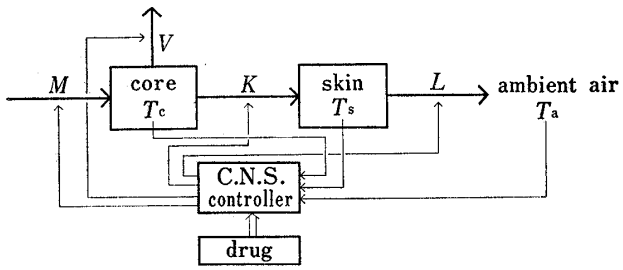

Fig. 1. Diagrammatic Representation of Heat Flow, Thermoregulating System and Drug Action

heavy arrows heat flow
thin arrows controlling pathway

At the skin compartment, heat is gained from the core compartment by conduction, and is transferred to the ambient air by radiation and convection.

As the controller, central nervous system (C.N.S.) comands the efferent signals for M, K and V to change their values according to the changes in afferent signals from core temperature (T_c) and skin temperature (T_s). The effects of antipyretics are assumed to act as afferent signals to the controller.

Mathematical interpretation of the model shown in Fig. 1 is as follows. Eq. 1 and Eq. 2 give the amount of heat stored per unit time in the core and skin compartment respectively.

$$W_c c\frac{dT_c}{dt} = M - V - K(T_c - T_s) \qquad \text{Eq. 1}$$

$$W_s c\frac{dT_s}{dt} = K(T_c - T_s) - L(T_s - T_a) \qquad \text{Eq. 2}$$

The symbols used in all the equations are defined in Table I.

At steady state, Eq. 1 and Eq. 2 are reduced to Eq. 3 and Eq. 4.

$$0 = M_0 - V_0 - K_0(T_{c0} - T_{s0}) \qquad \text{Eq. 3}$$

$$0 = K_0(T_{c0} - T_{s0}) - L_0(T_{s0} - T_{a0}) \qquad \text{Eq. 4}$$

Expressing temperatures and coefficients as variations from the steady state values, Eq. 5 and Eq. 6 are obtained.

$$W_c c\frac{dT_c}{dt} = \Delta M - \Delta V - K(\Delta T_c - \Delta T_s) - \Delta K(T_{c0} - T_{s0}) \qquad \text{Eq. 5}$$

$$W_s c\frac{dT_s}{dt} = K(\Delta T_c - \Delta T_s) + \Delta K(T_{c0} - T_{s0}) - L(\Delta T_s - \Delta T_a) - \Delta L(T_{s0} - T_{a0}) \qquad \text{Eq. 6}$$

where $\Delta T_c = T_c - T_{c0}$, $\Delta T_s = T_s - T_{s0}$, $\Delta M = M - M_0$, $\Delta K = K - K_0$ and $\Delta L = L - L_0$.

Assumptions on Physiological Response

The average body temperature is defined as Eq. 7.

$$T_b = \frac{W_c T_c + W_s T_s}{W_c + W_s} \qquad \text{Eq. 7}$$

TABLE I. List of Symbols and Definitions

Symbol	Definition	Dimension
W_c	mass weight of core compartment	kg
W_s	mass weight of skin compartment	kg
ρ	density of the tissue	g/cm^3
c	specific heat of the tissue	kcal/kg °C
T	temperature in degrees centigrade	°C
T_c	temperature of core compartment	°C
T_s	temperature of skin compartment	°C
T_b	average body temperature	°C
T_a	ambient temperature	°C
t	time in hours	hr
K	specific thermal conductivity of wet tissue	kcal/hr °C
α_k	thermal conductivity coefficient of proportional control	kcal/hr (°C)^2
γ_k	thermal conductivity coefficient of rate control	kcal/ (°C)^2
α_{kd}	thermal conductivity coefficient due to medication	(dl/mg) (kcal/hr °C)
M	metabolic rate	kcal/hr
α_m	metabolic rate coefficient of proportional control	kcal/hr °C
α_d	metabolic rate coefficient due to medication	dl/mg
V	vaporization rate	kcal/hr
α_v	vaporization rate coefficient of proportional control	kcal/hr °C
L	heat transfer coefficient (skin to air)	kcal/hr °C
V_d	apparent idstribution volume of a drug	dl
k_a	rate constant for drug absorption	/hr
k_{el}	rate constant for drug disposition and elimination	/hr
Hi-Lim	(see text)	mg/dl
Lo-Lim	(see text)	mg/dl

When W_c/W_s is assumed to be 2/1, Eq. 7 reduces to Eq. 8.

$$T_b = 0.67T_c + 0.33T_s \qquad \text{Eq. 8}$$

At steady state, Eq. 9 is obtained.

$$T_{b0} = 0.67T_{c0} + 0.33T_{s0} \qquad \text{Eq. 9}$$

This steady-state average body temperature, T_{b0}, is considered as the *set point* in the present model. According to the change in T_b, values of M, V and K are modified by means of proportional control ($\alpha \Delta T_b$) and/or rate control ($\gamma dT_b/dt$). These conceptions about the proportional control and rate control have been reviewed by Hardy[7] in detail.

Assumptions on Pharmacological Response

After oral administration of antipyretics, it is assumed that the drug is absorbed and disposed by first order rate steps. This is expressed as Eq. 10.

$$\mathrm{A} \xrightarrow{k_a} \mathrm{B} \xrightarrow{k_{el}}$$

$$\left.\begin{aligned} &\frac{dA}{dt} = -k_a A, \quad \frac{dB}{dt} = k_a A - k_{el} B \\ &\text{when } t=0,\ A = \mathrm{Dose}/V_d \text{ and } B=0. \end{aligned}\right\} \qquad \text{Eq. 10}$$

Where B is blood concentration of the drug, k_a and k_{el} are rate constants for absorption and disposition, respectively.

Because of its simplicity, the authors of this report adopted linear dose-response relationship instead of conventional log-dose correlation. The drug effect is assumed proportional to the drug blood level when blood concentration is between "Lo-Lim" and "Hi-Lim." When blood level is below "Lo-Lim," drug effect is set to zero, and when blood level is above "Hi-Lim," drug effect is fixed to the maximum value. These relationship is shown in Fig. 2.

7) J.D. Hardy, *Physiol. Rev.*, **41**, 521 (1961).

Mathematical Expression of the Whole Model

Using the assumptions mentioned above, Eq. 11 through Eq. 16 are obtained.

$$M = M_0(1-\alpha_d[D]) - \alpha_m \Delta T_b \quad \text{Eq. 11}$$

$$V = V_0 + \alpha_v \Delta T_b \quad \text{Eq. 12}$$

$$K = K_0 + \alpha_k \Delta T_b + \gamma_k \frac{dT_b}{dt} + \alpha_{kd}[D] \quad \text{Eq. 13}$$

$$\frac{dT_c}{dt} = \frac{1}{cW_c}[\Delta M - K(\Delta T_c - \Delta T_s) - \Delta K(T_{c0} - T_{s0})] \quad \text{Eq. 14}$$

$$\frac{dT_s}{dt} = \frac{1}{cW_s}[K(\Delta T_c - \Delta T_s) + \Delta K(T_{c0} - T_{s0}) - L\Delta T_s] \quad \text{Eq. 15}$$

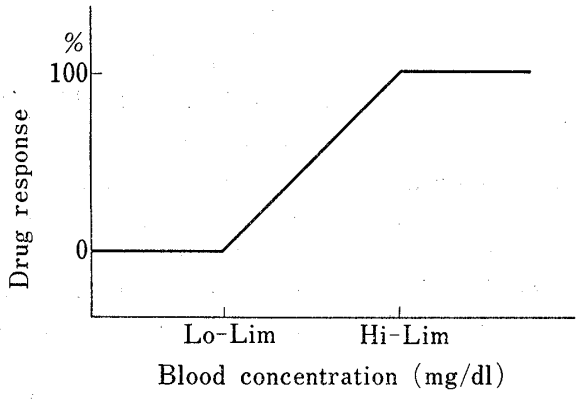

Fig. 2. Schematic Representation of the Relationship between Blood Concentration and Drug Response

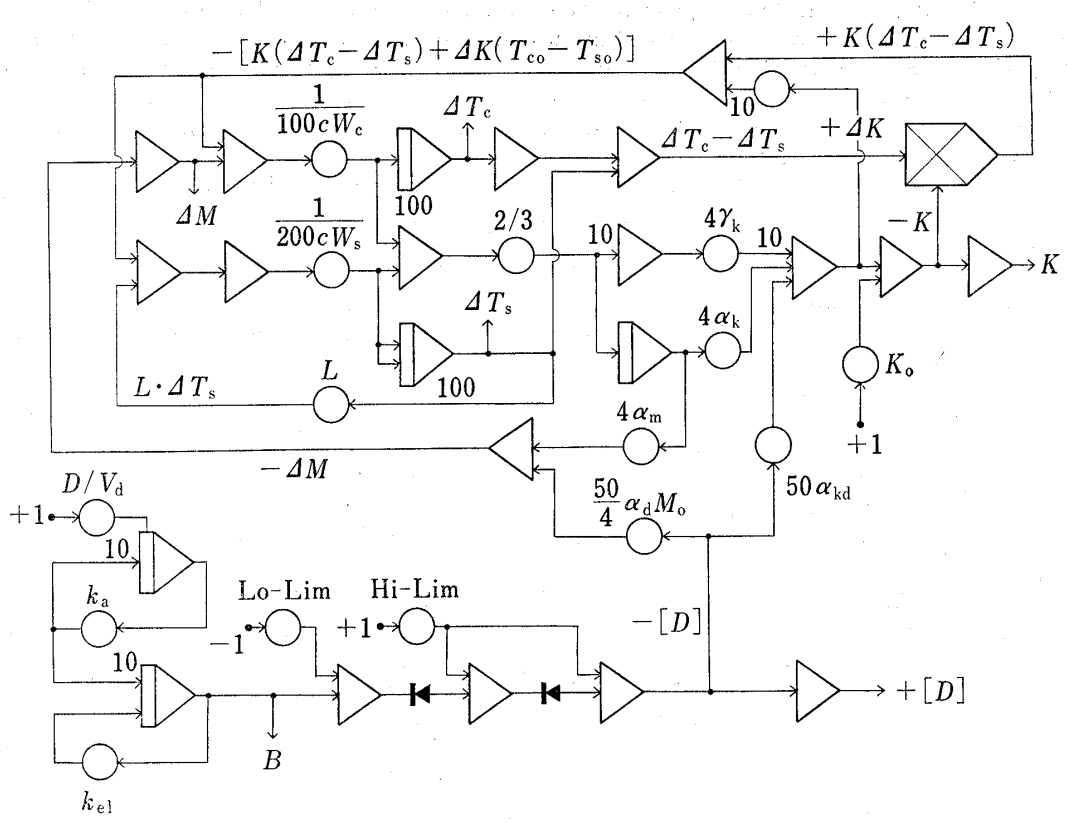

Fig. 3. Analog Computer Program for the Simulation

TABLE II. Scaling of the Variables in Eq. 7 through Eq. 16

Variable	Maximum	100 Volt/Magnitude	Scaled quantity
ΔT_c	4 °C	25 volt/°C	$[\Delta T_c/4]$
ΔT_s	4 °C	25 volt/°C	$[\Delta T_s/4]$
ΔT_b	4 °C	25 volt/°C	$[\Delta T_b/4]$
ΔM	4 kcal/hr	25 volt/ kcal/hr	$[\Delta M/4]$
K	1 kcal/hr °C	100 volt/ kcal/hr °C	$[K]$
ΔK	1 kcal/hr °C	100 volt/ kcal/hr °C	$[\Delta K]$
B	50 mg/dl	2volt/ mg/dl	$[B/50]$
$[D]$	50 mg/dl	2 volt/mg/dl	$[[D]/50]$
t	10 hr	10 volt/hr	

where $L=L_0$ and $T_a=T_{a0}$.

$$\left.\begin{aligned} [D] &= 0 \quad (B<\text{Lo–Lim}) \\ [D] &= \text{B} - \text{Lo–Lim} \quad (\text{Lo–Lim}\leq B\leq\text{Hi–Lim}) \\ [D] &= \text{Hi–Lim} - \text{Lo–Lim} \quad (B>\text{Hi–Lim}) \end{aligned}\right\} \qquad \text{Eq. 16}$$

Experimental results, which will be shown below, indicated that the antipyretics exhibit no appreciable effects on V and L. This is the reason for Eq. 12 to lack $[D]$ term.

Eq. 7 through Eq. 16 are programmed on an analog computer (Hitachi Ltd., Tokyo, Type ALS 505E) as presented in Fig. 3. Scaling factors which make the equations suitable for programming on an analog computer are shown in Table II.

Experimental

Materials——Acetaminophen (NAPA) was J.P. grade. 4-Aminoantipyrine (4-An) was reagent grade and obtained from Nakarai Chemical Co. Ltd. Both drugs were used without further purification.

Measurement of Body Temperature——Male albino rats (Wistar strain) weighing 200 to 250 g were used in all the experiments. About 6 hours prior to the experiment, rats were fasted in the breeding cage. Two hours before the experiment, rats were placed in individual cages at environmental temperature of $21\pm1°$. Rectal temperature was measured with a thermister type self-resistering thermometer (Iio Electric Co. Ltd., Tokyo, Type EP-670), by inserting the probe into rectum of the rat as far as 5 cm. Skin temperature was measured with a thermister type thermometer (Showa Rikagaku Co. Ltd., Tokyo), by fastening its sensor on the skin of the tail with thread.

NAPA and 4-An were dissolved in purified water and were administered *per os*. Measurement of rectal and skin temperatures were continued for 8 hours after drug administration.

Measurement of Heat Production and Heat Loss——The heat production rate was determined by indirect calorimetry.[8] The energy released with in the body can be calculated from the elimination rate of the oxidative end-product, carbon dioxide. Carbon dioxide in expired air was absorbed by an absorbent, sodium hydroxide. The amount of carbon dioxide taken up was determined from the gain in weight of the absorbent. It was assumed in calculation that one liter of carbon dioxide expired is equivalent to 5.0 kcal of heat production.

The rate of heat loss due to vaporization was also determined by indirect calorimetry. Water in the expired air was absorbed on calcium chloride. The amount of water was determined from the gain in weight of the absorbent. Since the latent heat of water vaporization is 0.6 kcal per gram of water, the rate of heat loss can be calculated. In all the experiments, the ambient temperature was maintained at $21\pm1°$.

Determination of Drug Disposition——Plasma level and urinary excretion of unchanged NAPA were determined by G.L.C.[9] and of conjugated NAPA were determined spectrophotometrically by the method of Brodie, *et al.*[10] Plasma level and urinary excretion of conjugated and unchanged 4-An were measured by spectrophotometric method after diazotization.[11] After oral administration of antipyretics, blood samples were taken by cardiac puncture.

The amount of drugs distributed in the brain tissue was determined as follows. After the drug administration, brains were taken out and homogenized. Drugs were isolated from the homogenate by extraction into ethyl acetate. The ethyl acetate phase was evaporated to dryness and the residue was submitted to analysis. Correction was made after Beach, *et al.*[12] for the amount of drugs distributed in the plasma space of the brain.

Results and Discussion

Disposition of NAPA

Fig. 4 presents urinary excretion rate, brain disposition and plasma concentration of unchanged NAPA after oral administration (100 mg/200 g rat body weight). The time course of plasma concentration increased rapidly just after the administration and decreased quickly.

8) J.R. Brobeck, "Medical Physiology and Biophysics," ed. by T.C. Ruth and J.F. Fulton, W.B. Saunders Co., London, 1960, p. 964.
9) L.F. Prescott, *J. Pharm. Pharmacol.*, **23**, 807 (1971).
10) B.B. Brodie and J. Axelrod, *J. Pharmacol. Exptl. Therap.*, **94**, 22 (1948).
11) B.B. Brodie and J. Axelrod, *J. Pharmacol. Exptl. Therap.*, **99**, 171 (1950).
12) V.L. Beach and B.G. Steinetz, *J. Pharmacol. Exptl. Therap.*, **131**, 400 (1961).

It is clear that the plasma concentration of NAPA follows two-step consecutive first order kinetics. The time of peak concentration was identical with that in brain, and the elimination of the drug from the brain was parallel with that from plasma. These results indicate that, as far as NAPA is concerned, brain in which thermoregulatory system exists is included in the same compartment as plasma.

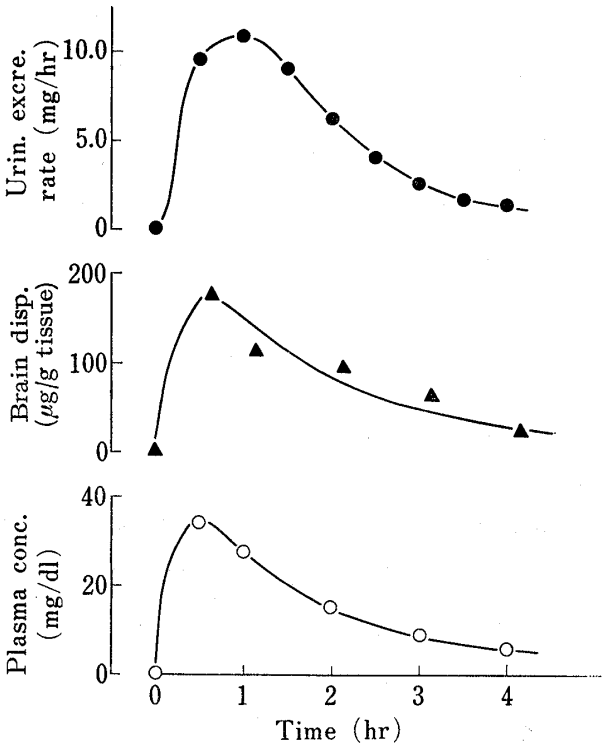

Fig. 4. Urinary Excretion Rate, Brain Disposition and Plasma Concentration of Unchanged NAPA after Oral Administration of NAPA 100 mg/200 g Body Weight in the Rat

● : urinary excretion rate, ▲ : brain disposition
○ : plasma concentration

Effects of NAPA

Fig. 5 presents the effects of NAPA on rectal and skin temperatures after oral administration. Each plot represents the average of 5 to 6 experiments. Administration of NAPA (50 mg or 100 mg/200 g rat body weight) produced a prompt dose dependent fall in rectal temperature. The time for the maximum hypothermic effect was about 2 to 3 hours after the administration. The effect of NAPA on skin temperature was scarcely observed.

Fig. 6 presents the effects of NAPA on the metabolic heat production rate and vaporization heat loss rate. The metabolic heat production rate was remarkably reduced just after the administration of the drug, but the change on vaporization rate was hardly observed.

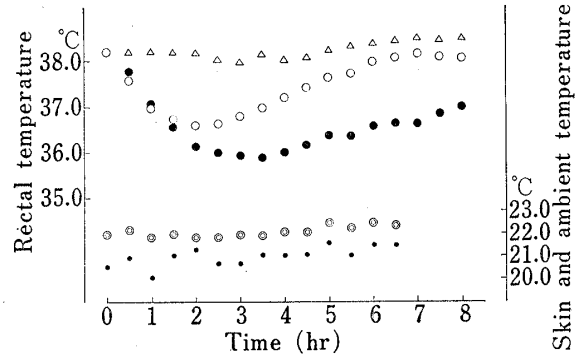

Fig. 5. Rectal and Skin Temperature after Oral Administration of NAPA in the Rat

△ : rectal temp. control
○ : rectal temp. NAPA 50 mg/200 g body weight *p.o.*
● : rectal temp. NAPA 100 mg/200 g body weight *p.o.*
◎ : skin temp. NAPA 100 mg/200 g body weight *p.o.*
· : ambient temp.

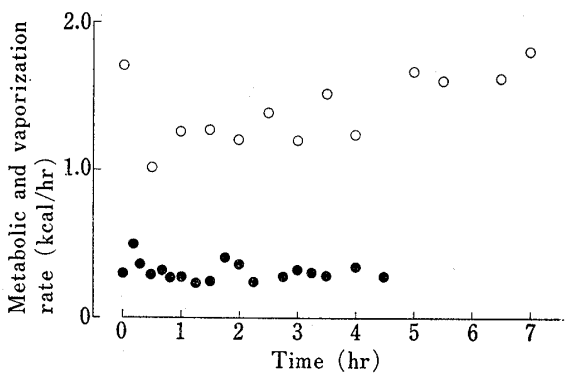

Fig. 6. Effects of NAPA on Metabolic Rate and Vaporization Rate after Oral Administration in the Rat

NAPA : 100 mg/200 g body weight
○ : metabolic rate
● : vaporization rate

Disposition of 4-An

Fig. 7 presents urinary excretion rate, brain distribution and plasma level of unchanged 4-An after oral administration (50 mg/200 g rat body weight). Maximum plasma and brain concentrations were reached around 1.5 hours after the administration of the drug, and both concentration patterns resemble each other. The elimination of the drug from plasma,

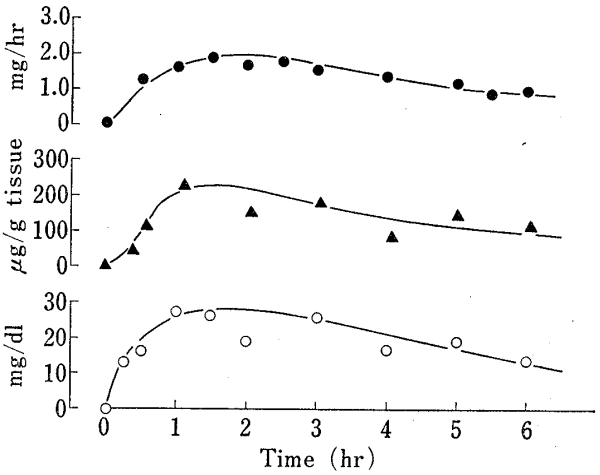

Fig. 7. Urinary Excretion Rate, Brain Disposition and Plasma Concentration of Unchanged 4-An after Oral Administration of 4-An 50 mg/200 g Body Weight in the Rat

● : urinary excretion rate ▲ : brain disposition
○ : plasma concentration

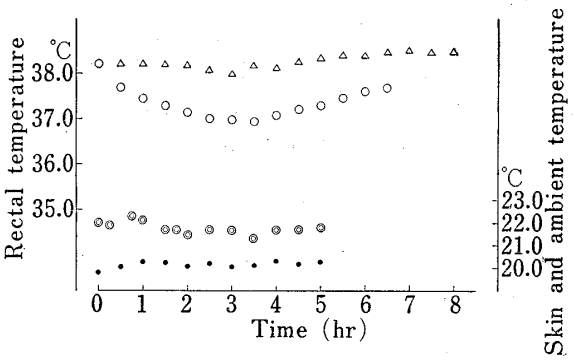

Fig. 8. Rectal and Skin Temperature after Oral Administration of 4-An in the Rat

△ : rectal temp. control
○ : rectal temp. 4-An 50 mg/200 g body weight *p.o.*
◎ : skin temp. 4-An 50 mg/200 g body weight *p.o.*
• : ambient temp.

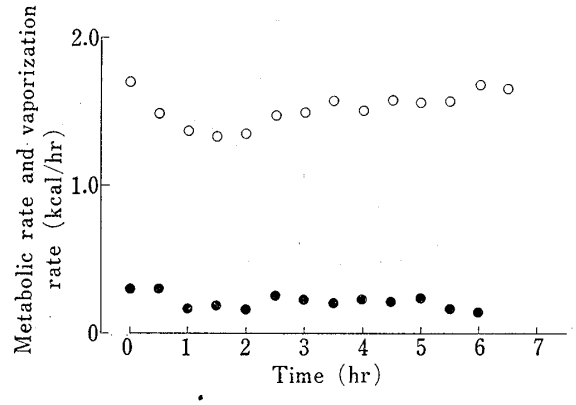

Fig. 9. Metabolic Rate and Vaporization Rate after Oral Administration of 4-An 50 mg/200 g Body Weight in the Rat

○ : metabolic rate ● : vaporization rate

TABLE III. List of Steady-state Values of Symbols

Symbol	Value	Dimension
T_{c0}	38.2	°C
T_{s0}	22.0	°C
T_{b0}	32.8	°C
T_{a0}	21.0	°C
M_0	1.70	kcal/hr
V_0	0.20	kcal/hr
L_0	1.50	kcal/hr °C
K_0	0.092	kcal/hr °C
c	0.5	kcal/kg °C
W_c	0.133	kg
W_s	0.067	kg

along with the elimination from brain, was slower than the case in NAPA. These results indicate that the brain is includes in the plasma compartment with respect to 4-An as well as NAPA.

Effects of 4-An

Fig. 8 shows the effects of 4-An on rectal and skin temperatures. Each plot represents the average of 5 to 6 experiments. Administration of 4-An (50 mg/200 g rat body weight) produced gradual fall in rectal temperature. Maximum hypothermic effect was reached in 3.5 hours after the administration of the drug.

Fig. 9 shows the effects of 4-An on metabolic rate and vaporization rate. Metabolic rate was reduced gradually and the minimum level was reached 1.5 hours after drug administration. Recovery of the metabolic rate was attained in 6 hours. The change in value of vaporization rate due to 4-An administration, however, was not observed.

Physiological Parameters observed at Steady State

At environmental temperature of T_{a0}, without administration of antipyretics, core temperature T_{c0}, skin temperature T_{s0}, metabolic rate M_0, and vaporization rate V_0 were determined. With these values, steady state values of K_0, L_0 and T_{b0} were calculated by Eq. 3, Eq. 4 and Eq. 9, respectively. Values obtained are shown in Table III.

Analog Computer Simulation

On performing analog computer simulation, physiological parameters α_m, α_k, γ_k *etc.* for man[4] were re-evaluated for rats, on the body surface area basis, and set the values on potentiometers. Pharmacokinetic parameters k_a, k_{el} and v_d were calculated by conventional way from plasma level data and also set on potentiometers.

For the rest of parameters α_{kd}, α_d, Hi-Lim and Lo-Lim, the procedure looking for the values was as follows. At first arbitrary values were set on potentiometers and tried to bring the simulated curves close to the observed data, correcting the setting on each of potentiometers.

Since the procedure of obtaining the best fit parameters is as described above, the authors do not intend to claim that the combination of values for parameters shown below is unique, but that a combination of values does exist with which the mathematical model proposed is able to simulate the time course of the antipyretic effect as well as the drug disposition.

Fig. 10 shows the comparison of simulated curves with observed data after oral administration of NAPA 100 mg per 200 g body weight in rats. The computed solutions for Eq. 7 through Eq. 16 are shown in solid lines and experimental results in open circles. The computed curve B agrees with time course of blood concentration. The computed value M, which is directly influenced by curve B, also fits to the observed metabolic rate obtained by indirect calorimetry.

The computed solution for T_c seems to agree fairly well with the observed hypothermic effect as far as 3 hours after drug administration, the recovery of rectal temperature, however, is slower than the theoretical prediction shown by dotted line in Fig. 10. Assuming that the *set point* shifts by some secondary physiological effect, this gap can be explained. Reducing the value of T_b by 0.9° at 3.25 hours after drug administration, computed value of T_c fits beautifully to observed data (solid line).

Fig. 11 shows similar comparisons of computation with observation on NAPA in the dose level of 50 mg per 200 g rat body weight. The hypothermic effect on rectal temperature is beautifully traced by the theory without the correction of *set point* in this case. In computation, all the parameters but D were same as used in 100 mg dose experiments.

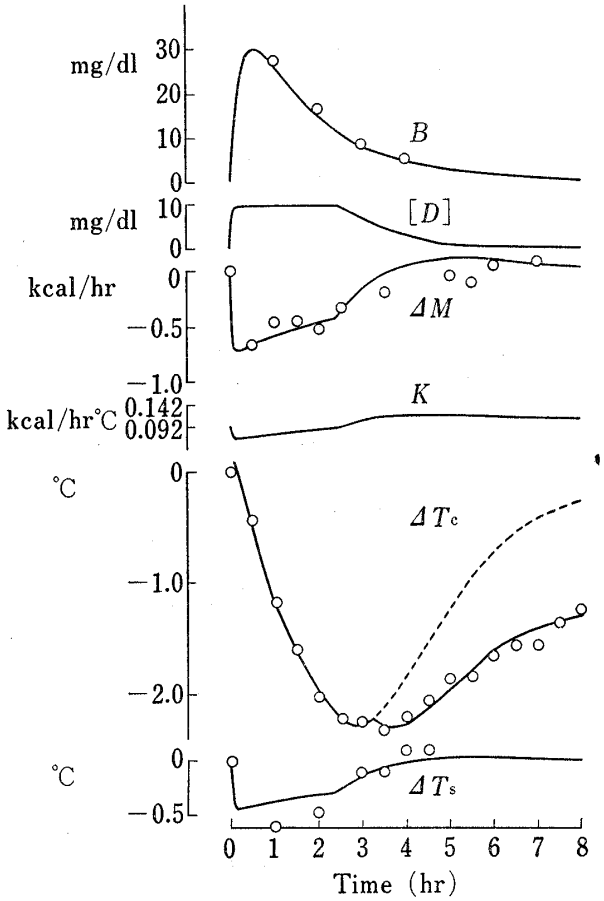

Fig. 10. Comparison of Theoretical Values with Observed Data after Oral Administration of NAPA 100 mg/200 g Body Weight in the Rats

Plotted points are observed values and solid lines are theoretical curves drawn by an analog computer.

Fig. 12 represents the comparisons of theoretical values with observed data on 4-An in the dose level of 50 mg per 200 g rat body weight. The values of physiological parameters, except γ_k, were same as were used on NAPA. Simulated curves agree reasonably with observed data.

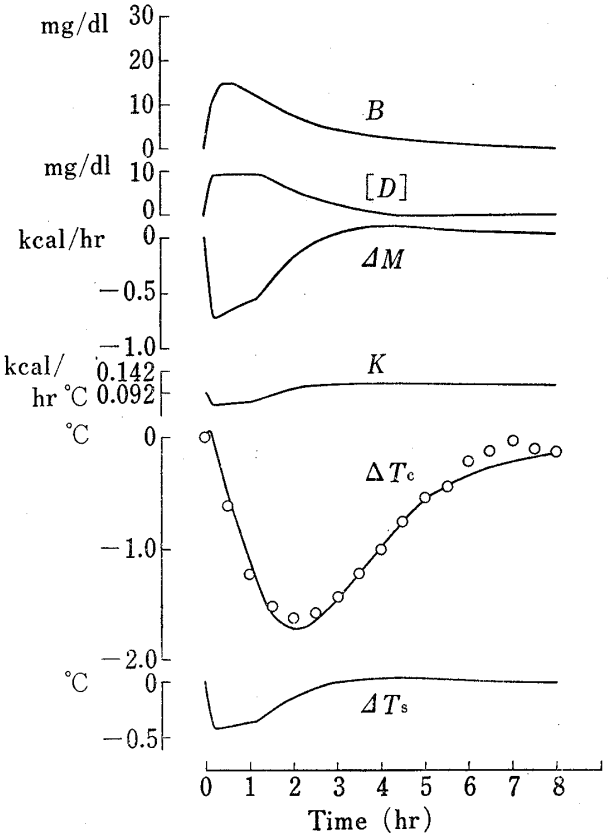

Fig. 11. Comparison of Theoretical Values with Observed Data after Oral Administration of NAPA 50 mg/200 g Body Weight in the Rats

Plotted points are observed values and solid lines are theoretical cuvres drawn by an analog computer.

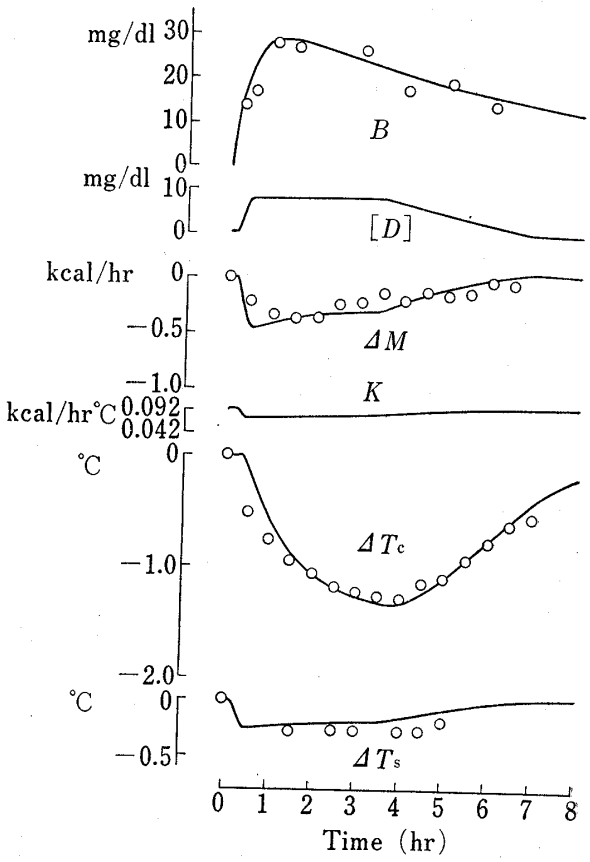

Fig. 12. Comparison of Theoretical Values with Observed Data after Oral Administration of 4-An 50 mg/200 g Body Weight in the Rats

Plotted points are observed values and solidlines are theoretical curves drawn by an analog computer.

TABLE IV. Rate Constants and Other Parameters calculated from Hypothermic Effect and Disposition of Acetaminophen and 4-Aminoantipyrine

Symbol	Dimension	NAPA	4-An
V_d	dl	2.41	1.47
k_a	hr^{-1}	4.28	2.49
k_{el}	hr^{-1}	0.591	0.131
α_m	kcal/hr °C	0.232	0.232
α_k	kcal/hr$(°C)^2$	0.028	0.028
γ_k	kcal/$(°C)^2$	0.078	0.051
α_{kd}	(dl/mg) (kcal/hr °C)	0.005	0.003
α_d	dl/mg	0.048	0.037
Hi-Lim	mg/dl	11.38	22.47
Lo-Lim	mg/dl	1.63	8.26

All the parameters and other constants used are listed in Table IV. The parameters α_m, α_k and γ_k represent the physiological characteristics of rats, and are considered independent of drugs. Although the values of α_k and α_m are identical for the both antipyretics, γ_k is slightly different among the drugs. The reason for this is unknown and a further investigation is required for the elucidation.

In the present model, the regulating temperature was defined as Eq. 8. As the regulating temperature, the sum of various percentage of the skin and rectal temperatures were used

by the previous investigators.[13] Götte[14] expressed the controlling temperature as $0.65T_{rectal}+0.35T_{skin}$ in the experiments on dogs. Therefore, the definition of Eq. 8 is appropriate.

Comparison of the values of k_a and k_{el} indicates that NAPA and 4-An have quite different pharmaceutical properties each other. NAPA is absorbed two-fold faster and excreted four-fold faster than 4-An in rats. Similarly, the values of parameters, α_{kd}, α_d, Hi-Lim and Lo-Lim indicate that these two antipyretics have quite different pharmacological characteristics each other. In spite of the differences in pharmaceutical and pharmacological properties, the hypothermic effect of these drugs could be simulated reasonably using a single mathematical model. This fact indicates that the model used in this paper is appropriate to simulate the pharmacological response of antipyretics as well as the physiological thermoregulation.

On the basis of body surface area, all the parameters and other constants, except γ_k, α_v and L_0, are identical with those of literature reported by Crosbie, *et al.*,[4] regardless of species. These are shown in Table V. In calculation, the surface area of a rat was assumed to be 0.03 m^2.

TABLE V. Comparison of Parameters on Physiological Thermoregulation in Man and in Rat

Symbol	Dimension	Man[a]	Rat[b]
c	cal/cm^3	1.0	1.0
T_{c0}	°C	36.6	38.2
T_{s0}	°C	29.9	22.0
T_{b0}	°C	34.3	32.8
T_{a0}	°C	21.0	21.0
M_0	kcal/m^2 hr	55.0	56.7
α_m	kcal/m^2 hr °C	11.1	7.7
V_0	kcal/m^2 hr	7.0	6.7
α_v	kcal/m^2 hr °C	11.0	0.0
K_0	kcal/m hr °C	0.21	
	kcal/hr °C		0.09
α'_k	(°C)$^{-1}$	0.147 (α_{k+})	
		0.066 (α_{k-})	0.307[c]
γ'_k	sec/°C	3.5	
	hr/°C		0.845 (NAPA)[c]
			0.522 (4-An)[c]
L_0	kcal/m^2 hr °C	5.3	50.5

a) These data were from the literature reported by Crosbie and his co-workers.[4]
b) The surface area of a rat was assumed to be 0.03 m^2.
c) Since Crosbie's definition of K is slightly different from the present paper, α'_k corresponds to α_k/K_0, and γ'_k corresponds to γ_k/K_0.

In the pharmacological research, quantitative and analytical approaches will become more and more necessary. Such quantitative studies are destined, however, to the complete intact system with all the control loops. Treatment of such a system is quite complex and difficult. An analog model as described in the present study can assist the interpretation of such pharmacological data. Even though the model is a simplification of actual system, it is able to describe with good accuracy the data on pharmacological effects of antipyretics.

The applicability of this model to the other kind of antipyretics will be revealed on the further examination.

13) T. Nakayama, "Taion to Sono Chosetsu," Chugai Igaku-Sha, Tokyo, 1970, p. 18.
14) D. Götte, *Pflügers Arch. ges. Physiol.*, **274**, 192 (1961).