Pharmacokinetic Analysis of Pharmacological Effects and Drug Disposition. II.[1] Effects of Salicylamide on Afebrile Rats[2]

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The purpose of this investigation was to represent quantitatively the relationship be-
tween the time course of pharmacological effects and drug disposition data after oral
administration of salicylamide, an antipyretic drug, in normal (afebrile) rats, using phar-
macokinetic method. After administration of salicylamide, rectal temperature and skin
temperature were measured continuously, and the changes in metabolic heat production
rate and in vaporization heat loss rate were also measured by indirect calorimetry. The
blood concentration of salicylamide *versus* time course was determined as the drug disposi-
tion data. From the observed data, an electrical analog was constructed to simulate the
effects of salicylamide including physiological thermoregulation in afebrile rats. The
results indicate that the time course of pharmacological effects of salicylamide are reason-
ably simulated by a mathematical model.

In the field of clinical pharmacokinetics, quantitative investigations for representing the
relationship between the pharmacological response intensity *versus* time course and plasma
or biophase concentrations after the administration of a drug becomes a matter of great concern
recently.[4] In the previous report,[1] studies on some antipyretics, such as acetaminophen and
as 4-aminoantipyrine in afebrile rats, revealed that the time course of pharmacological effects
i.e. hypothermic effect and effect for metabolic rate, were reasonably described with drug
disposition data, using simple pharmacokinetic models.

The purpose of present paper is to verify the applicability of the method to the other
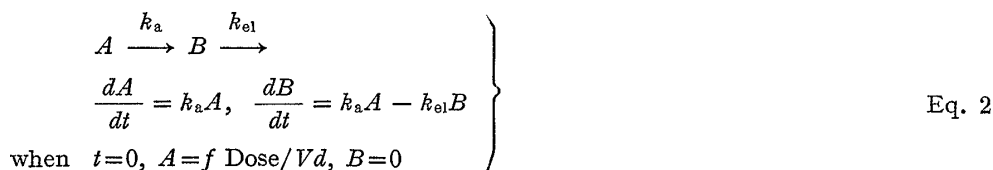kind of antipyretic drug, salicylamide.

Theoretical

A model for prediction of the time course of blood concentration and pharmacological
effects of salicylamide is as follows. A detailed description of the model has been published[1];
only a brief summary is repeated here.
Average body temperature (*set point*)

$$T_b = 0.6667T_c + 0.3333T_s$$
$$T_{b0} = 0.6667T_{c0} + 0.3333T_{s0}$$
$$\Delta T_b = T_b - T_{b0}$$

Eq. 1

Drug disposition (one compartment open model)

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

$$\frac{dA}{dt} = k_a A, \quad \frac{dB}{dt} = k_a A - k_{el}B$$

when $t=0$, $A=f$ Dose/Vd, $B=0$

Eq. 2

1) Part I: M. Kakemi, K. Masuda, M. Ueda, and T. Koizumi, *Chem. Pharm. Bull.* (Tokyo), 23, 736 (1975).
2) Presented in part at the 7th Simposium on Drug Metabolism and Action, Sapporo, October, 1975.
3) Location: *3190 Gofuku, Toyama, 930, Japan.*
4) G. Levy (ed.), "Clinical Pharmacokinetics," American Pharmaceutical Association, Washington, D.C.,
1974.

Drug effect term ($[D]$)

$$[D] = 0 \qquad (B < LL)$$
$$[D] = B - LL \quad (LL \leq B \leq HL) \qquad \qquad \text{Eq. 3}$$
$$[D] = HL - LL \quad (B > HL)$$

Metabolic heat production rate (M)

$$M = M_0(1 - \alpha_{md}[D]) - \alpha_m \varDelta T_b \qquad \qquad \text{Eq. 4}$$

Vaporization heat loss rate (V)

$$V = V_0 + \alpha_v \varDelta T_b \qquad \qquad \text{Eq. 5}$$

Thermal conductivity of wet tissue (K)

$$K = K_0 + \alpha_k \varDelta T_b + \gamma_k \frac{dT_b}{dt} + \alpha_{kd}[D] \qquad \qquad \text{Eq. 6}$$

Temperature change in core compartment

$$\frac{dT_c}{dt} = \frac{1}{cW_c}[\varDelta M - \varDelta V - K(\varDelta T_c - \varDelta T_s) - \varDelta K(T_{c0} - T_{s0})] \qquad \qquad \text{Eq. 7}$$

Temperature change in skin compartment

$$\frac{dT_s}{dt} = \frac{1}{cW_s}[K(\varDelta T_c - \varDelta T_s) + \varDelta K(T_{c0} - T_{s0}) - L\varDelta T_s] \qquad \qquad \text{Eq. 8}$$

where $\varDelta T_c = T_c - T_{c0}$, $\varDelta T_s = T_s - T_{s0}$, $\varDelta M = M - M_0$, $\varDelta V = V - V_0$ and $\varDelta K = K - K_0$, and each subscript 0 represents the steady state values of symbols.

Eq. 1 through Eq. 8 are solved simultaneously to derive the theoretical time course for drug disposition and for pharmacological drug effects, using an analog computer (Hitachi Ltd. Tokyo, type ALS 505E). The definition of all symbols presented here are same as previous paper.[1]

Experimental

Materials——Salicylamide (SAM) was J.P. grade, and was used without further purification. SAM was dissolved in purified water, and administered *per os*. Male albino rats (Wistar strain) weighing 200—250 g were used in all experiments.

Measurement of Body Temperatures——Rectal and skin temperatures were measured with thermister type self-resistering thermometer (Iio Denki Co. Ltd., Tokyo, type EP-670), by inserting the probe into rectum as far as 5 cm and by fastening the sensor on the skin of the tail with adhesive tape respectively. Measurements of the temperatures were continued for 10 hours after the drug administration.

Measurement of Heat Production Rate and Heat Loss Rate——The heat production rate and heat loss rate were determined by indirect calorimetry,[5] and these procedures and experimental conditions were detailed previously.[1]

Determination of SAM in Blood——The blood levels of unchanged SAM were determined by following procedures. After oral administration of SAM, blood samples of 1 ml each were obtained from juglar vein. These samples were hemolyzed and extracted into ethyl acetate. The ethyl acetate phases were evaporated to dryness, and the residues were dissolved into pyridine, and were submitted to analysis. Gas-liquid chromatographic analysis was carried out under following conditions.

Apparatus: Shimadzu model GC-4APF gas chromatograph with flame ionization detector.

Column: 80—100 mesh Gas-Chrom Q coated with 3% OV-17 packed into a 2 m, 4 mm i.d. glass tube and conditioned at 300° for 2 days before use. Operating Conditions: column temperature 170°, injection port temperature 200°, detector temperature 170°, flow rate of nitrogen 80 ml/min, hydrogen 0.6 kg/cm², air 0.9 kg/cm². Internal Standard: p-ethoxyacetanilide 10 μg/ml in ethyl acetate.

Results and Discussion

The circles shown in Fig. 1 are experimental data of blood concentrations, metabolic heat production rates and rectal temperatures after oral administration of SAM aqueous

5) J.R. Brobeck, "Medical Physiology and Biophysics," ed. by T.C. Ruth and J.F. Fulton, W.B. Saunders Co., London, 1960, p. 964.
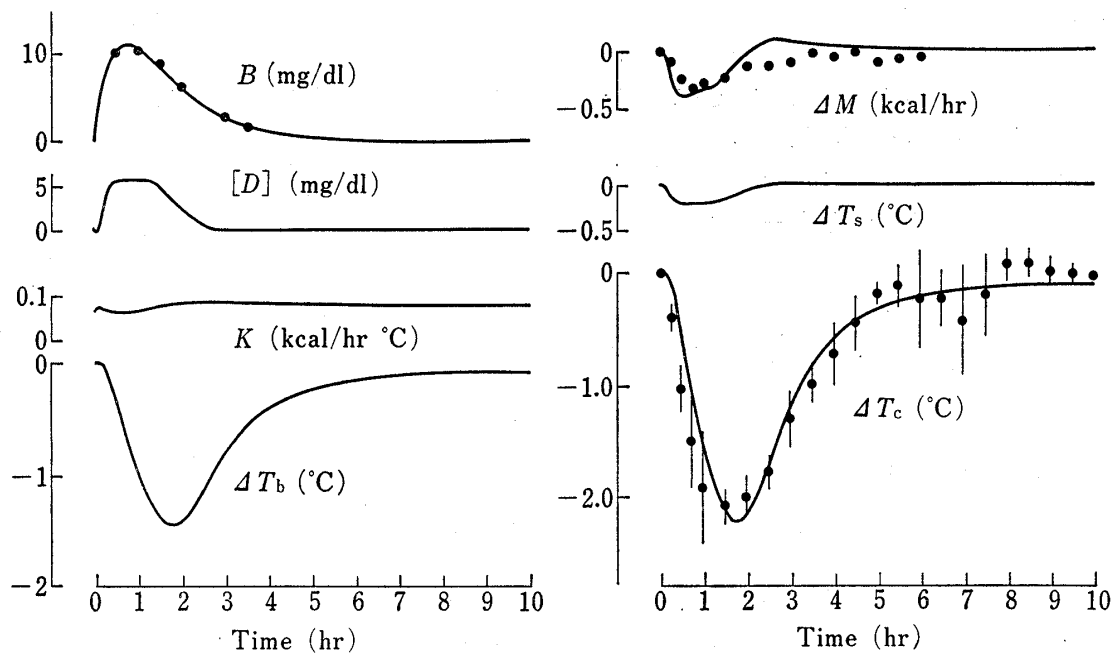
Fig. 1.   Comparison of Theoretical Values with Observed Data after Oral Administration of
Salicylamide 250 mg/kg in Afebrile Rats

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

solution in the dose level 250 mg/kg body weight, on normal rats.   Each plot represents the
average of 3 to 5 experiments, and vertical lines represent the standard errors.   The time
course of blood concentration increased rapidly just after the administration, and decreased
very quickly.   It is clear that the blood concentration of SAM follows two-step consecutive
first order kinetics, as presented in Eq. 2.   Administration of SAM produced a prompt fall
in rectal temperature and metabolic heat production rate.   The time for the maximum effect
were 1.5 hours in rectal temperature and 1 hour in metabolic heat production rate after the
drug administration.

The steady state values for rectal temperature, skin temperature, metabolic heat produc-
tion rate and vaporization heat loss rate were also measured, and listed in Table I.   The
steady state values for K, the specific thermal conductivity of wet tissue, and for L, the heat
transfer coefficient (skin to air) were calculated similarly as previous report.[1]

The solid lines shown in Fig. 1 are the computed solutions for Eq. 1 through Eq. 8.   The
computed curve B agrees with time course of SAM blood concentration.   The computed

TABLE I.   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[a]	0.133	kg
W_s[a]	0.067	kg

a)   The body weight of a rat was assumed to be 0.200 kg.

TABLE II. Rate Constants and Other Parameters Calculated from Pharmacological
Effects and Drug Disposition of Antipyretics in Afebrile Rats

Symbol	Salicylamide	Acetaminophen[a]	4-Aminoantipyrine[a]	Dimension
Dose	250	250	250	mg/kg b.w.
f Dose/Vd	22.40	20.77	33.92	mg/dl
k_a	1.790	4.280	2.490	hr^{-1}
k_{el}	0.908	0.591	0.131	hr^{-1}
α_m	0.233	0.232	0.232	kcal/hr °C
α_v	0.0	0.0	0.0	kcal/hr °C
α_k	0.028	0.028	0.028	kcal/hr (°C)^2
γ_k	0.051	0.078	0.051	kcal/(°C)^2
α_{md}	0.005	0.048	0.037	dl/mg
α_{kd}	0.012	0.005	0.003	(dl/mg) (kcal/hr °C)
HL[b]	9.575	11.38	22.47	mg/dl
LL[b]	3.605	1.625	14.21[c]	mg/dl

a) These data were from previous paper.[1]
b) These symbols, HL and LL, correspond to Hi-Lim and Lo-Lim respectively in the previous paper.[1]
c) Correction was made for the miscalculation in LL value (8.26 mg/dl) of the previous paper.[1]

value M, which is directly influenced by drug effect term [D], calculated by Eq. 3, also fit to the observed metabolic heat production rate obtained from indirect calorimetry. The computed solutions for T_c agree reasonably with observed rectal temperatures. All the parameters and other constants used are listed in Table II.

In Table II, the values of acetaminophen (NAPA) and 4-aminoantipyrine (4-AN) are from the previous paper.[1] The parameters α_m, α_v, α_k, and γ_k represent metabolic rate coefficient of proportional control, vaporization rate coefficient of proportional control, thermal conductivity coefficient of proportional control and thermal conductivity coefficient of rate control respectively, and these parameters have the physiological characteristics of a rat, and are considered independent of drugs. The values α_m, α_v, α_k and γ_k are identical for three types of antipyretics.

The terms LL and HL can be considered to be minimum effective blood concentration and minimum blood concentration that indicates the maximum drug effect, respectively. Comparison of the values of LL indicates that NAPA is the most potent drug among three types of antipyretics in afebrile rats. Comparison of the values, k_a and k_{el}, the rate constants for drug absorption and for drug disposition respectively, indicate that SAM, NAPA and 4-AN have quite different pharmaceutical characteristics each other. SAM is disposed and eliminated from blood two fold faster than NAPA and 7-fold faster than 4-AN. In spite of the differences in pharmaceutical and pharmacological properties, the time course of hypothermic effect of SAM could be simulated reasonably using a single mathematical model. These facts prove that the model used in the series of investigations is appropriate to simulate the pharmacological response of antipyretics in afebrile rats, as well as the physiological thermoregulation.

The studies on pharmacological effects of these three antipyretics in febrile rats have been reported in the 7th Symposium on Drug Metabolism and Action (Sapporo, October, 1975).[6]

6) M. Kakemi, T. Kobayashi, C. Mamuro, M. Ueda, and T. Koizumi, Abstracts of Papers, 7th Symposium on Drug Metabolism and Action, Sapporo, Oct., 1975, pp. 19—22.