Pharmacokinetic Analysis of Pharmacological Effects and Drug Disposition. II. Effects of Salicylamide on Afebrile Rats

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The purpose of this investigation was to represent quantitatively the relationship between the time course of pharmacological effects and drug disposition data after oral administration of salicylamide, an antipyretic drug, in normal (afebrile) rats, using pharmacokinetic 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 disposition 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 reasonably 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. In the previous report, 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; only a brief summary is repeated here.

Average body temperature (set point)

\[
\begin{align*}
T_b &= 0.6667T_s + 0.3333T_s \\
T_{b0} &= 0.6667T_{s0} + 0.3333T_{s0} \\
\Delta T_b &= T_b - T_{b0}
\end{align*}
\]

Eq. 1

Drug disposition (one compartment open model)

\[
\begin{align*}
A \xrightarrow{k_A} B \\
&\frac{dA}{dt} = k_A A, \quad dB \frac{dt} = k_B A - k_B B
\end{align*}
\]

when \(t=0, A=\text{Dose/Vd}, B=0\)

2) Presented in part at the 7th Symposium on Drug Metabolism and Action, Sapporo, October, 1975.
3) Location: 3190 Gofuku, Toyama, 930, Japan.
Drug effect term ([D])

\[
[D] = \begin{cases} 
0 & (B<LL) \\
B-LL & (LL \leq B \leq HL) \\
HL-LL & (B>HL)
\end{cases}
\]

Eq. 3

Metabolic heat production rate (M)

\[ M = M_0(1-a_m[D]) - a_m\Delta T_b \]

Eq. 4

Vaporization heat loss rate (V)

\[ V = V_v + a_v \Delta T_b \]

Eq. 5

Thermal conductivity of wet tissue (K)

\[ K = K_0 + a_v \Delta T_b + \gamma_k \frac{dT_v}{dt} + a_v[D] \]

Eq. 6

Temperature change in core compartment

\[ \frac{dT_c}{dt} = \frac{1}{cw_e} [\Delta M - \Delta V - K(\Delta T_v - \Delta T_c) - \Delta K(T_{ve} - T_{vo})] \]

Eq. 7

Temperature change in skin compartment

\[ \frac{dT_s}{dt} = \frac{1}{cw_s} [K(\Delta T_s - \Delta T_c) + \Delta K(T_{vo} - T_{vo}) - L\Delta T_s] \]

Eq. 8

where \( \Delta T_c = T_c - T_{vo} \), \( \Delta T_s = T_s - T_{vo} \), \( \Delta M = M - M_0 \), \( \Delta V = V - V_v \) and \( \Delta K = K - K_0 \), 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 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.\(^5\)

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 thermistor type self-resistenciering 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,\(^9\) and these procedures and experimental conditions were detailed previously.\(^4\)

**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 jugular 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: \( \beta \)-ethoxyacetylilde 10 \( \mu \)g/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

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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 production 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>
<thead>
<tr>
<th>Table I. List of Steady State Values of Symbols</th>
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<tbody>
<tr>
<td>Symbol</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>$T_{00}$</td>
</tr>
<tr>
<td>$T_{30}$</td>
</tr>
<tr>
<td>$T_{38}$</td>
</tr>
<tr>
<td>$T_{48}$</td>
</tr>
<tr>
<td>$M_0$</td>
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<tr>
<td>$V_0$</td>
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<tr>
<td>$L_0$</td>
</tr>
<tr>
<td>$K_0$</td>
</tr>
<tr>
<td>$c$</td>
</tr>
<tr>
<td>$W_{(a)}$</td>
</tr>
<tr>
<td>$W_{(b)}$</td>
</tr>
</tbody>
</table>

\(^{a)}\) The body weight of a rat was assumed to be 0.500 kg.
TABLE II. Rate Constants and Other Parameters Calculated from Pharmacological Effects and Drug Disposition of Antipyretics in Afebrile Rats

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Salicylamide Acetaminophen&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4-Aminoantipyrine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>f Dose/(V_d)</td>
<td>22.40</td>
<td>20.77</td>
<td>33.92</td>
</tr>
<tr>
<td>(k_k)</td>
<td>1,790</td>
<td>4,280</td>
<td>2,490</td>
</tr>
<tr>
<td>(k_{ei})</td>
<td>0.906</td>
<td>0.591</td>
<td>0.131</td>
</tr>
<tr>
<td>(x_m)</td>
<td>0.233</td>
<td>0.232</td>
<td>0.232</td>
</tr>
<tr>
<td>(x_v)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(x_k)</td>
<td>0.028</td>
<td>0.028</td>
<td>0.028</td>
</tr>
<tr>
<td>(\gamma_k)</td>
<td>0.051</td>
<td>0.078</td>
<td>0.051</td>
</tr>
<tr>
<td>(\alpha_m)</td>
<td>0.005</td>
<td>0.048</td>
<td>0.037</td>
</tr>
<tr>
<td>(\alpha_v)</td>
<td>0.012</td>
<td>0.005</td>
<td>0.003</td>
</tr>
<tr>
<td>(HL&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>9.575</td>
<td>11.38</td>
<td>22.47</td>
</tr>
<tr>
<td>(LL&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>3.605</td>
<td>1.625</td>
<td>14.21&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>) These data were from the previous paper.\textsuperscript{3}

<sup>b</sup>) These symbols, \(HL\) and \(LL\), correspond to Hi-Lim and Lo-Lim respectively in the previous paper.\textsuperscript{1}

<sup>c</sup>) Correction was made for the miscalculation in \(LL\) value (9.26 mg/dl) of the previous paper.\textsuperscript{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 \(T_\alpha\) 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.\textsuperscript{1} The parameters \(x_m\), \(x_v\), \(x_k\), and \(\gamma_k\) 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 \(x_m\), \(x_v\), \(x_k\) and \(\gamma_k\) 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, \(k_k\) and \(k_{ei}\), 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 pharmaceutical 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).\textsuperscript{6}

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