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159. Teishiro Kushima[*1]: Studies on the Metabolism of Sulfadimethoxine. III.[*2] Kinetics of Sulfadimethoxine Metabolism.

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The kinetic constants defining the rate of sulfadimethoxine metabolism were calculated using analog computer. Observed values were in good agreement with theoretical values calculated by an equation developed to account for the various processes involved in the transformation and excretion of sulfadimethoxine.

The theoretical curve for the amount of unchanged sulfadimethoxine remained in the body was obtained. From this curve, the half life of unchanged sulfadimethoxine in the body was decided to be 25 hours.

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In the previous paper,[*2] we determined the amounts of sulfadimethoxine metabolites in human and in rabbit urine separately using paper chromatography.

Presented here is a kinetic study of the excretion of sulfadimethoxine, consulting the technique of E. Nelson, *et al.*[1] for the kinetics of acetylation of sulfisoxazole.

As sulfadimethoxine-N^1-glucuronide and N^4-glucuronide are very soluble in water, the rate constants for the excretion would be large enough to neglect. Consequently the model for sulfadimethoxine metabolism is assumed as follows:

S. D $\xrightarrow{k_1}$ N^4-acetyl S. D $\xrightarrow{k_2}$ excreted N^4-acetyl S. D

$\xrightarrow{k_3}$ excreted S. D-N^1-glucuronide

$\xrightarrow{k_4}$ excreted S. D-N^4-glucuronide

$\xrightarrow{k_5}$ excreted S. D

(S. D: sulfadimethoxine)

The differential equations describing the scheme are

$$\frac{dS}{dt} = -(k_1+k_3+k_4+k_5)S \quad (1)$$

$$\frac{dS_a}{dt} = k_1S - k_2S_a \quad (2)$$

$$\frac{dS_{ae}}{dt} = k_2S_a \quad (3)$$

$$\frac{dS_{1ge}}{dt} = k_3S \quad (4)$$

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*2 Part II. T. Uno, T. Kushima, T. Hiraoka: This Bulletin **15**, 1272 (1967).

*3 This work was reported at the 86th Annual Meeting of the Pharmaceutical Society of Japan, April 8, (1966).

1) E. Nelson, I. O'Reilly: J. Pharmacol. Exptl. Therap., **129**, 368 (1960).

$$\frac{dS_{4ge}}{dt}=k_4S \qquad (5)$$

$$\frac{dS_e}{dt}=k_5S \qquad (6)$$

It was assumed that a drug in blood was in equilibrium with the drug in other fluids of distribution 8 hours after drug administration.

In the above scheme, the k's with number subscripts are the first order rate constants in reciprocal hours for the respective process, S is the amount of sulfadimethoxine in the body in mg., S_a the amount of N^4-acetylsulfadimethoxine in the body, S_{ae} the amount of excreted N^4-acetylsulfadimethoxine, S_{1ge} the amount of excreted sulfadimethoxine-N^1-glucuronide, S_{4ge} the amount of excreted sulfadimethoxine-N^4-glucuronide, and S_e the amount of excreted sulfadimethoxine. All these amounts are represented in mg. sulfadimethoxine.

In equation (1), $k_1+k_3+k_4+k_5$ was set equal to K, and f, f' and f'' are the fractions of a dose of excreted sulfadimethoxine-N^1-glucuronide, excreted sulfadimethoxine-N^4-glucuronide, and excreted sulfadimethoxine respectively.

Then, the products Kf, Kf', and Kf'' are equal to k_3, k_4, and k_5

$$f=\frac{k_3}{k_1+k_3+k_4+k_5}=\frac{k_3}{K},\ f'=\frac{k_4}{K},\ f''=\frac{k_5}{K}$$

Excretion data were corrected by subtracting amounts of drug excreted in the first 8 hours following drug administration (mean values) from the cumulative amounts (mean values) shown in Table IV in the previous paper.*[1)] They were shown in Table I.

TABLE I. Corrected mean Values of the Amounts of Sulfadimethoxine Metabolites in Human Urine

Time	Unchanged Sulfadimethoxine	N^4-Acetyl-sulfadimethoxine	Sulfadimethoxine-N^1-glucuronide	Sulfadimethoxine-N^4-glucuronide
8	0	0	0	0
24	14.8	33.5	217.3	1.6
48	29.1	66.5	398.4	3.4
96	38.6	114.2	561.7	4.4
168	39.1	137.5	616.4	6.7

Equation (1) and (4) may be written respectively, as

$$\frac{dS}{dt}=-KS \qquad (7)$$

$$\frac{dS_{1ge}}{dt}=fKS \qquad (8)$$

Integration of equation (7) and evaluation of the constant of integration at 8 hours after drug administration yields,

$$S=S^8(\exp[-Kt]) \qquad (9)$$

where S^8 is the amount of unchanged sulfadimethoxine in the body at 8 hours after drug administration, and t is time in hours.

The expression describing excretion of sulfadimethoxine-N[1]-glucuronide is obtained by substituting equation (9) in equation (8).

$$\frac{dS_{1ge}}{dt}=fKS^8(\exp[-Kt]) \qquad (10)$$

Integration of equation (10) gave

$$S_{1ge}=-fS^8(\exp[-Kt])+C$$

where C is a constant.

Aa S_{1ge} excreted after equilibrium is 0 at 8 hours after drug administration,

$$C=fS^8$$

The resulting equation is

$$S_{1ge}=S^8f(1-\exp[-Kt])$$

Hence, $$-Kt=\ln\left(1-\frac{S_{1ge}}{S^8f}\right) \qquad (11)$$

The fractions f, $f,'$ and f'' were calculated from the Table Ⅳ in the previous paper.*[2] The product of S^8 and f equals to the total amount of sulfadimethoxine-N[1]-glucuronide excreted after equilibrium shown in Table I, from which S^8 was obtained.

Now, K was obtained by plotting $\ln(1-S_{1ge}/S^8f)$ *vs.* time since such a plot allows its determination from the slope as can be seen from equation (11). The constants k_1, k_3, k_4, and k_5 were calculated from K since

$$k_3=K\times f,\ k_4=K\times f',\ k_5=K\times f'',\ k_1=K-(k_3+k_4+k_5)$$

The value of $S_a{}^8$ which represents the amounts of N[4]-acetylsulfadimethoxine in the body at 8 hours after drug administration was found in the following manner :

If S_{ae}^{∞}, S_{1ge}^{∞}, S_{4ge}^{∞}, and S_e^{∞} are the total amounts of excreted N[4]-acetylsulfadimethoxine, excreted sulfadimethoxine-N[1]-glucuronide, excreted sulfadimethoxine-N[4]-glucuronide, and excreted unchanged sulfadimethoxine respectively, and if $S_{ae}{}^8$, $S_{1ge}{}^8$, $S_{4ge}{}^8$, and $S_e{}^8$ are the amounts of excreted N[4]-acetylsulfadimethoxine, excreted sulfadimethoxine-N[1]-glucuronide, excreted sulfadimethoxine-N[4]-glucuronide, and excreted unchanged sulfadimethoxine respectively in 8 hours after drug administration, also if $S_{1g}{}^8$ and $S_{4g}{}^8$ are the amounts of sulfadimethoxine-N[1]-glucuronide and N[4]-glucuronide in the body at 8 hours after drug administration (All these amounts are represented in mg. sulfadimethoxine.), total drug amount in the body 8 hours after drug administration=

$$S^8+S_a{}^8+S_{1g}{}^8+S_{4g}{}^8=(S_{ae}^{\infty}+S_{1ge}^{\infty}+S_{4ge}^{\infty}+S_e^{\infty})-(S_{ae}{}^8+S_{1ge}{}^8+S_{4ge}{}^8+S_e{}^8) \quad (12)$$

The amount of $S_a{}^8+S_{1g}{}^8+S_{4g}{}^8$ was calculated from the equation (12), which amount was very little compared with any other amounts in the practical calculation. The amounts of $S_{1g}{}^8$ and $S_{4g}{}^8$ was considered to be very small, since the produced N[1]-glucuronide and N[4]-glucuronide were rapidly excreted.

The amount obtained from the calculation of equation (12) was set to be equal to the amount of $S_a{}^8$.

An explicit solution for the constant k_2 is not easily determined, hence the value of this constant was obtained by a trial and error procedure using an analog computer.

Results and Discussion

The values of f, f', and f'' were 0.771, 0.009 and 0.049 respectively, which were directly found from the ratio of metabolite excreted in 168 hours *vs.* total amount of excretion (as mg. of unchanged sulfadimethoxine).

The total amount of sulfadimethoxine-N^1-glucuronide after equilibrium equals to 616.4 mg. from the data of Table I, and also is approximately equal to the product of S^8 and f.

Namely $616.4 = S^8 \times f$

Hence $S^8 = 616.4/f = 799.5$

The plot of $\ln(1 - S_{1ge}/S^8 f)$ *vs.* time was linear, and K was determined to be 0.0274 hour^{-1}. The product of f and K gave k_3 as 0.0211 hour^{-1}. Similarly, the values of k_4 and k_5 were 0.0003 hour^{-1} and 0.0013 hour^{-1}.

k_1 was $0.0274-(0.0211+0.0003+0.0013)$ or 0.0047 hour^{-1}.

From equation (12) and the data of Table I, $S_a{}^8 + S_{1g}{}^8 + S_{4g}{}^8$ was calculated to be 0.2 mg. which was very small compared with any other amounts appeared in this report, and perhaps $S_{1g}{}^8$ and $S_{4g}{}^8$ are less than $S_a{}^8$. Assigning $S_a{}^8$ was 0.2 mg., and both $S_{1g}{}^8$ and $S_{4g}{}^8$ were 0, then the constants are as following:

S^8	799.5 mg.	k_1	0.0047
$S_a{}^8$	0.2 mg.	k_2	?
$S_{1g}{}^8$	0	k_3	0.0211
$S_{4g}{}^8$	0	k_4	0.0003
		k_5	0.0013
		K	0.0274

These constants were treated with the analog computer (Hitachi ALM-502T), and the resulting computer diagram is given in Fig. 1.

The value of k_2 was determined to be 0.0950 by try and error.

Recently, G. Levy[2] studied metabolism of salicylic acid derivatives and reported that, on administration over a definite dosis, salicyluric acid resulted by conjugation of salicylate with glycine reached to a limiting amount, whose excretion was followed by zero order kinetics.

However, in the case of administration of ordinary dosis (1 g.) of sulfadimethoxine, the calculated elimination curves coincided very well with the observed values as shown in Fig. 2, which were followed by first order kinetics, and no zero order kinetics was observed.

2) G. Levy: J. Pharm. Sci. **54**, 959 (1965).

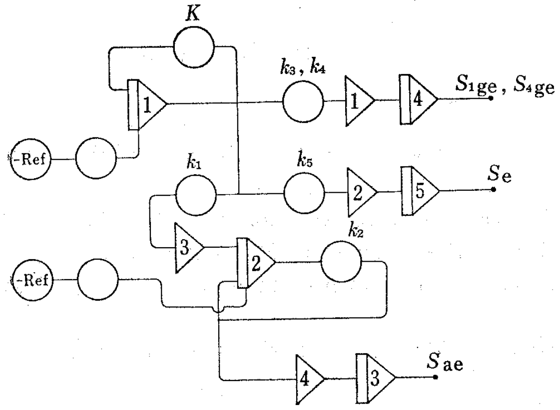

Fig. 1. Diagram for Analog Computer

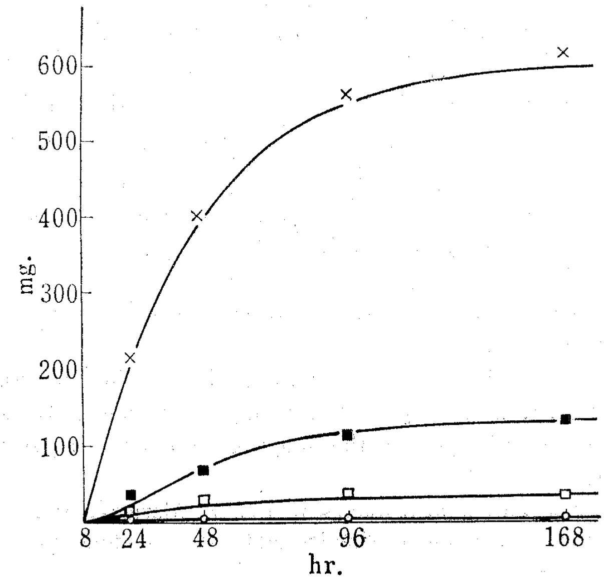

Fig. 2. Observed and Calculated Values of Sulfadimethoxine Metabolites in Human Urine

Observed Values

□ : Sulfadimethoxine
■ : N^4-Acetylsulfadimethoxine
× : Sulfadimethoxine-N^1-glucuronide
○ : Sulfadimethoxine-N^4-glucuronide
Calculated Values : ———

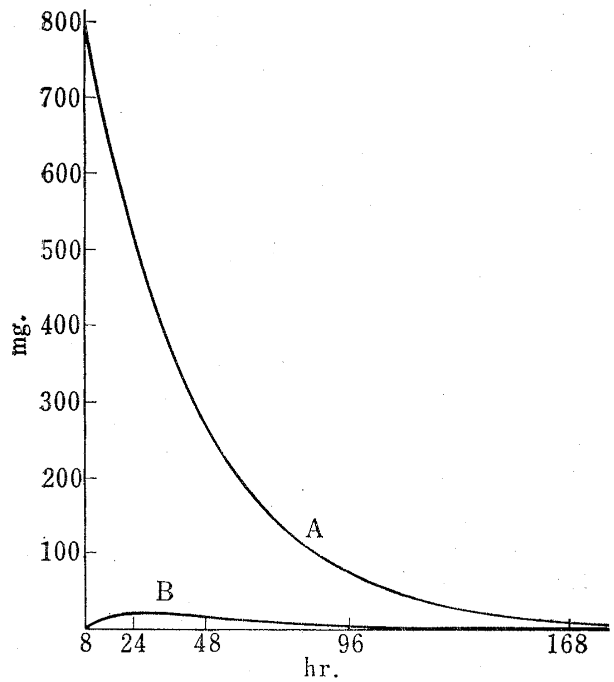

Fig. 3. Estimated Values of Sulfadimethoxine and N^4-Acetylsulfadimethoxine remained in the Human Body.

A : Sulfadimethoxine
B : N^4-Acetylsulfadimethoxine

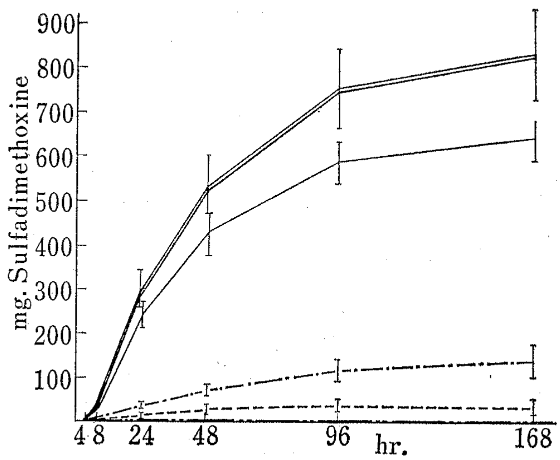

Fig. 4. Excretion Curves of Sulfadimethoxine Metabolites in Human Urine.
(Administered Dosage : 1.0 g.)

═══ Total Excretion
-------- Unchanged Sulfadimethoxine
— — — — N^4-Acetylsulfadimethoxine
——— Sulfadimethoxine-N^1-glucuronide
— — — — Sulfadimethoxine-N^4-glucuronide

Secondary, alteration of S was obtained from alteration of voltages of integrator 1, and also alteration of S_a is likely obtained from integrator 2. These results are shown in Fig. 3.

Half life of unchanged sulfadimethoxine in the body could be determined from either the curve A in Fig. 3 or equation (9), and was found to be about 25 hours after drug administration.

E. Krüger-Thiemer,[3] *et al.*[4] claimed that the half excretion time of sulfadimethoxine was 41 hours, which nearly coincided with our result, that is, half of administered dose was excreted in human urine during about 44 hours from Fig. 4.

However, it does not mean the amount of the effective sulfadimethoxine in the body reduced by half by 44 hours.

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3) E. Krüger-Thiemer: Klin. Wochschr., **40**, 153 (1962).
4) P. Bünger, W. Diller, J. Führ, E. Krüger-Thiemer: Arzneimittel Forsch., **11**, 247 (1961).