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Effect of Simultaneous Administration of Drugs on Absorption and Excretion. XVIII.[1] Differential Effects of Oral and Rectal Administration of Chloral Hydrate on the Gastrointestinal Absorption of Sulfisoxazole in Rabbits

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The effects of oral and rectal administration of chloral hydrate (CH) on the gastrointestinal absorption of sulfisoxazole (SIX) were investigated in rabbits. The blood concentration data for SIX led us to conclude that the oral administration of CH causes an enhancement in SIX absorption, whereas the rectal administration of CH causes a reduction in SIX absorption. It is noteworthy that the route of administration plays an important role in the SIX–CH interaction involved in the gastrointestinal absorption. In addition, the factors determining the differential effects of oral and rectal administration of CH on the gastrointestinal absorption of SIX are discussed.

Keywords——sulfisoxazole; chloral hydrate; blood concentration; gastrointestinal absorption; oral administration; rectal administration; dissolution rate; gastric emptying time

There are many mechanisms of drug interaction involved in gastrointestinal absorption. Some mechanisms are physicochemical and some are physiological. In general, when two drugs are co-administered orally, the gastrointestinal absorption of one drug is affected by the changes in physicochemical and physiological properties induced by the other. However, when one drug is administered orally and the other is administered by a different route, since one drug cannot interact with the other in the gastrointestinal tract, the gastrointestinal absorption of the orally administered drug is affected mainly by the change in physiological properties induced by the other. Thus, the route of administration may play an important role in the drug interaction involved in the gastrointestinal absorption.

In this paper, we describe the differential effects of oral and rectal administration of chloral hydrate (CH) on the gastrointestinal absorption of sulfisoxazole (SIX) in rabbits.

Experimental

Materials——SIX of JP grade was kindly supplied by Yamanouchi Pharmaceutical Co., Ltd. CH was purchased from Wako Pure Chemical Industries, Ltd., and recrystallized from benzene. All other chemicals were of reagent grade. Distilled water was used throughout this study.

***In Vivo* Experiments**——Male albino rabbits weighing 2.0—3.5 kg were fasted for 38—42 h prior to all experiments, but drinking water was allowed *ad libitum*.

a) Oral Administration of CH: CH was dissolved in about 80 ml of water, and administered by the oral route. The dose of CH was 300 mg/kg.

b) Rectal Administration of CH: CH was dissolved in about 30 ml of water, and administered by the rectal route. The dose of CH was 300 mg/kg. A clip was used to prevent the leakage of CH solution.

c) Oral Administration of SIX: SIX (100 mesh powder) was suspended in about 80 ml of water, and administered by the oral route. The dose of SIX was 100 mg/kg.

d) Oral Administration of SIX with CH: SIX (100 mesh powder) was suspended in about 80 ml of CH solution,

and administered by the oral route. The doses of SIX and CH were 100 and 300 mg/kg, respectively.

e) Intravenous Bolus Injection of SIX: SIX was dissolved in 1—3 ml of saline solution containing the same molar amount of NaOH, and injected into the ear vein. The dose of SIX was 50 mg/kg.

f) Blood Sampling: Blood samples (0.5 ml) were collected periodically from the ear vein.

g) Measurement of the Blood Concentration of SIX: The blood concentration of SIX was measured by the Bratton–Marshall method.[2] Blood samples were deproteinized with 10% trichloroacetic acid. After centrifugation, the supernatants were used for the measurement of the blood concentration of SIX.

Pharmacokinetic Analysis——The blood concentration data of SIX after intravenous bolus injection were fitted to the following equation by nonlinear least-squares regression,[3]

$$C = Ae^{-\alpha t} + Be^{-\beta t} \tag{1}$$

where C is the blood concentration of SIX at time t after intravenous bolus injection. The total body clearance (Cl_{tot}), apparent volume of distribution ($V_{d\beta}$) and elimination half-life ($t_{1/2(\beta)}$) were calculated by means of the following equation using biexponential constants (A, α, B and β),[4]

$$Cl_{tot} = \frac{D}{A/\alpha + B/\beta} \tag{2}$$

$$V_{d\beta} = Cl_{tot}/\beta \tag{3}$$

$$t_{1/2(\beta)} = 0.693/\beta \tag{4}$$

where D is the dose of SIX.

Dissolution Rate Experiments——The dissolution rate experiments were carried out by means of the dispersed amount method of Nogami *et al.*[5] The dissolution medium was maintained at 25 °C and stirred at 150 rpm. At appropriate intervals, 0.1 ml aliquots were taken with a pipette through a cotton filter. The sample solution was diluted with 0.1 M phosphate buffer (pH 7.0) and the SIX concentration was measured by the Bratton–Marshall method.[2]

Solubility Experiments——SIX (100 mesh powder) was added to water or CH solution in a glass-stoppered tube and shaken for 48 h at 25 °C. After equilibration, a 0.1 ml aliquot was taken with a pipette through a cotton filter. The sample solution was diluted with 0.1 M phosphate buffer (pH 7.0) and the SIX concentration was measured by the Bratton–Marshall method.[2] The stability constant was calculated from the solubility diagram according to the method of Higuchi *et al.*[6]

Gastric Emptying Experiments——The gastric emptying experiments were carried out by means of a slight modification of the method of Goto *et al.*,[7] as described previously.[8] Eighty ml of phenol-red solution (10 μg/ml) was injected into the rabbit stomach through a vinyl tube. Phenol-red was used as a nonabsorbable marker. At 0.5 h after injection, the percentage of phenol-red remaining in the rabbit stomach was determined. Assays of phenol-red were performed spectrophotometrically after alkalization of samples by adding 1 N NaOH.

***In Vitro* Intestinal Absorption Experiments**——The *in vitro* intestinal absorption experiments were carried out as described previously.[9] The chamber was filled with 70 ml of drug solution, which was prepared by dissolving SIX (500 μg/ml) with or without CH (3000 μg/ml) in Krebs–Ringer phosphate buffer solution (pH 7.4), and the everted rabbit small intestine was filled with 7 ml of Krebs–Ringer phosphate buffer solution (pH 7.4). The apparatus was then kept for 1 h at 37 °C. Aliquots of 0.1 ml were sampled from the serosal solution and the SIX concentration was measured by the Bratton–Marshall method.[2]

Statistical Analysis——Statistical analysis was performed by means of the paired Student t-test. The differences between means were considered to be significant when $p < 0.05$.

Results and Discussion

Effect of Oral Administration of CH on the Blood Concentration of SIX

The effects of oral administration of CH on the blood concentration of SIX after oral administration and after intravenous bolus injection to rabbits are shown in Figs. 1 and 2, respectively. The oral administration of CH significantly increased the blood concentration of SIX at 2, 3, 4, 5, 6 and 8 h after oral administration. However, the oral administration of CH had no significant effect on the blood concentration of SIX after intravenous bolus injection. In addition, as shown in Table I, the oral administration of CH had no significant effect on the pharmacokinetic parameters of SIX related to elimination and distribution such as Cl_{tot}, $V_{d\beta}$ and $t_{1/2(\beta)}$. These findings indicate that the oral administration of CH causes an enhancement in the gastrointestinal absorption of SIX.

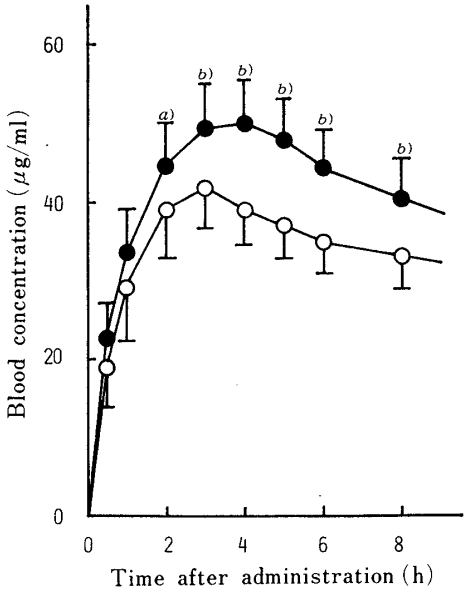

Fig. 1. Effect of Oral Administration of CH on the Blood Concentration of SIX after Oral Administration to Rabbits

Each point represents the mean ± S.E. of 5 rabbits. SIX was suspended in water or CH solution, and administered by the oral route. ○, SIX alone; ●, with CH (oral).
a) Significantly different from SIX alone, $p<0.05$.
b) Significantly different from SIX alone, $p<0.01$.

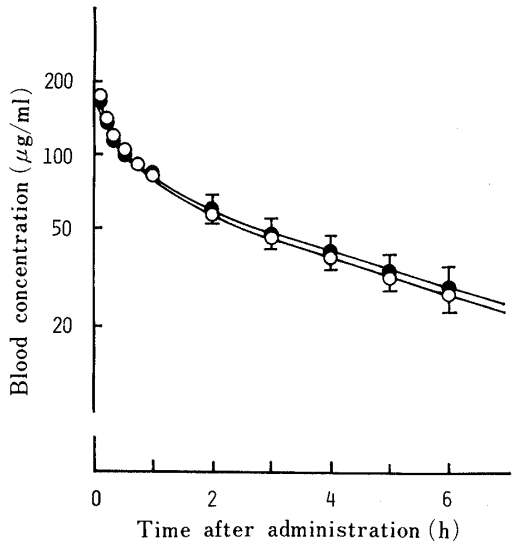

Fig. 2. Effect of Oral Administration of CH on the Blood Concentration of SIX after Intravenous Bolus Injection to Rabbits

Each point represents the mean ± S.E. of 4 rabbits. SIX was injected into the ear vein immediately after oral administration of CH. ○, SIX alone; ●, with CH (oral).

TABLE I. Effect of Oral Administration of CH on Pharmacokinetic Parameters of SIX in Rabbits

Parameter		SIX alone	With CH (oral)
Cl_{tot}	(ml/h/kg)	109 ± 14	112 ± 24
$V_{d\beta}$	(ml/kg)	530 ± 30	537 ± 51
$t_{1/2(\beta)}$	(h)	3.52 ± 0.40	3.56 ± 0.49

Values represent the means ± S.E. of 4 rabbits.

Effect of Rectal Administration of CH on the Blood Concentration of SIX

CH is often administered by the rectal route to avoid the problems of its metallic taste and gastric irritation. Thus, the effects of rectal administration of CH on the blood concentration of SIX after oral administration and after intravenous bolus injection were investigated in rabbits. The results are shown in Figs. 3 and 4. The rectal administration of CH significantly decreased the blood concentration of SIX at 0.5, 1 and 2 h after oral administration. However, the rectal administration of CH had no significant effect on the blood concentration of SIX after intravenous bolus injection. In addition, as shown in Table II, the rectal administration of CH had no significant effect on the pharmacokinetic parameters related to elimination and distribution such as Cl_{tot}, $V_{d\beta}$ and $t_{1/2(\beta)}$. These findings indicate that the rectal administration of CH causes a reduction in the gastrointestinal absorption of SIX.

Factors Determining the Differential Effects of Oral and Rectal Administration of CH on the Gastrointestinal Absorption of SIX

1) Dissolution Rate——The dissolution behavior of SIX powder in water and CH

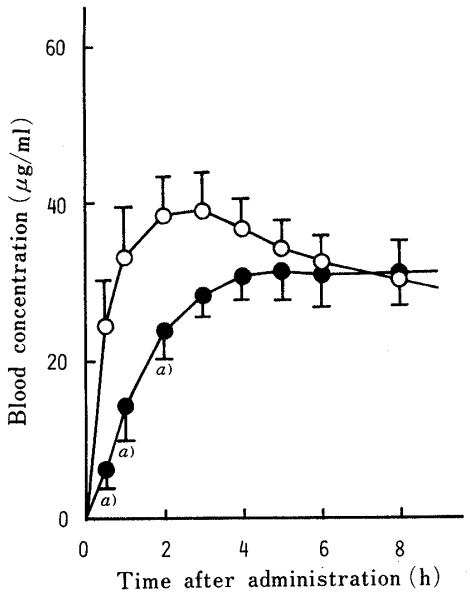

Fig. 3. Effect of Rectal Administration of CH on the Blood Concentration of SIX after Oral Administration to Rabbits

Each point represents the mean ± S.E. of 5 rabbits. SIX was administered by the oral route immediately after rectal administration of CH. ○, SIX alone; ●, with CH (rectal).
a) Significantly different from SIX alone, $p<0.05$.

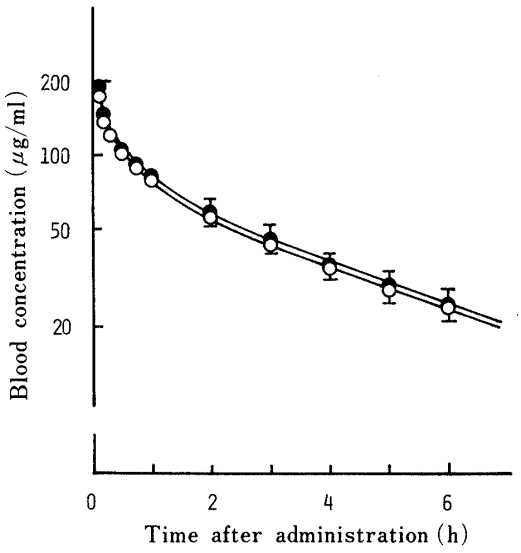

Fig. 4. Effect of Rectal Administration of CH on the Blood Concentration of CH after Intravenous Bolus Injection to Rabbits

Each point represents the mean ± S.E. of 4 rabbits. SIX was injected into the ear vein immediately after rectal administration of CH. ○, SIX alone; ●, with CH (rectal).

TABLE II. Effect of Rectal Administration of CH on Pharmacokinetic Parameters of SIX in Rabbits

Parameter		SIX alone	With CH (rectal)
Cl_{tot}	(ml/h/kg)	115 ± 9	111 ± 9
$V_{d\beta}$	(ml/kg)	545 ± 56	484 ± 47
$t_{1/2(\beta)}$	(h)	3.41 ± 0.57	3.10 ± 0.43

Values represent the means ± S.E. of 4 rabbits.

solution is shown in Fig. 5. As expected, SIX dissolved much more rapidly in CH solution than in water. Therefore, it is concluded that the oral administration of CH causes the enhancement in SIX absorption by increasing the dissolution rate of SIX in the gastrointestinal tract. The increased dissolution rate of SIX may be due to soluble complex formation. In fact, as shown in Fig. 6, the solubility of SIX was increased by the addition of CH, showing the features of an A_p type solubility diagram.[6] In addition, from the solubility diagram (assuming the formation of 1 : 1 and 1 : 2 complexes), the stability constants, $K_{1:1}$ and $K_{1:2}$, were estimated as 1.04 and 2.16 M^{-1}, respectively. Recently, Otagiri *et al.*[10] presented evidence that barbituric acid derivatives form 1 : 1 and 1 : 2 complexes with CH.

2) Gastric Emptying Time——The effects of oral and rectal administration of CH on the percentage of phenol-red remaining in the rabbit stomach at 0.5 h after injection are summarized in Table III. The rectal administration of CH significantly increased the percentage of phenol-red remaining in the rabbit stomach. This implies that the rectal administration of CH delays the gastric emptying time. Recently, many drugs which delay gastric emptying time have been reported to reduce the rate of drug absorption. For example, propantheline delays gastric emptying time and markedly reduces the rate of acetaminophen

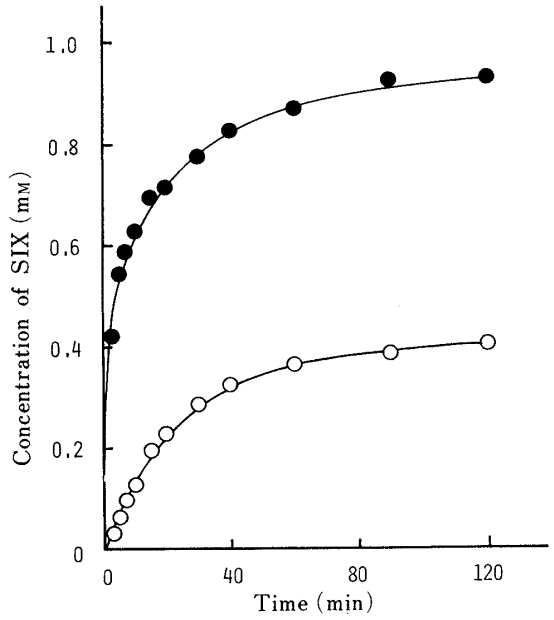

Fig. 5. Effect of CH on the Dissolution Behavior of SIX in Water at 25 °C as Determined by the Dispersed Amount Method

One mM of SIX is equivalent to 21.4 mg/80 ml. ○, water; ●, CH solution (0.5 M).

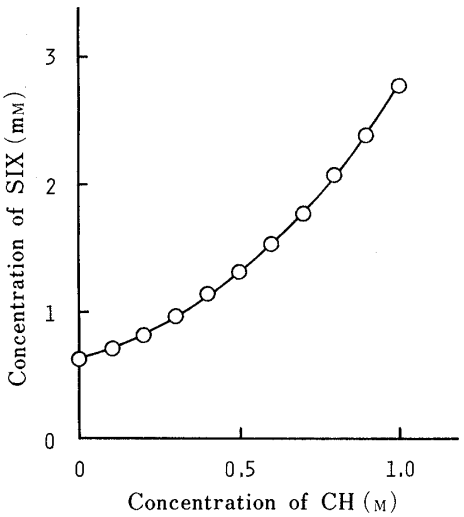

Fig. 6. Solubility Diagram of SIX–CH System in Water at 25 °C

One mM of SIX is equivalent to 21.4 mg/80 ml.

TABLE III. Effects of Oral and Rectal Administration of CH on the Percentage of Phenol-Red Remaining in the Rabbit Stomach at 0.5 h after Injection

Rabbit	% remaining			
	Oral		Rectal	
	Control	CH[a)]	Control	CH[b)]
A	25.1	36.4	34.2	34.7
B	17.8	21.3	21.0	52.1
C	20.3	27.2	18.2	24.5
D	24.4	38.7	19.4	49.1
E	25.5	32.3	23.6	42.7
Mean	22.6	31.2[c)]	23.3	40.6[d)]
S.E.	1.5	3.2	2.9	5.0

a) CH (300 mg/kg) was dissolved in 80 ml of phenol-red solution, and injected into the rabbit stomach through a vinyl tube.
b) CH (300 mg/kg) was dissolved in 30 ml of water, and administered by the rectal route.
c) Significantly different from the control in oral, $p<0.05$.
d) Significantly different from the control in rectal, $p<0.05$.

absorption.[11] Therefore, it may be concluded that the rectal administration of CH reduces the rate but not the extent of SIX absorption by delaying the gastric emptying time. However, further studies are necessary to demonstrate this conclusively.

The oral administration of CH also significantly increased the percentage of phenol-red remaining in the rabbit stomach. This implies that the oral administration of CH delays the gastric emptying time. In the case of the oral administration of CH, however, the enhancing effect on SIX absorption due to the increased dissolution rate more than counterbalances the

TABLE IV. Effect of CH on the *in Vitro* Intestinal Absorption of SIX in Rabbits

Rabbit	SIX transferred (mg)	
	Control	CH
F	0.27	0.32
G	0.33	0.43
H	0.32	0.35
I	0.20	0.29
J	0.25	0.28
Mean	0.27	0.33[a]
S.E.	0.02	0.03

a) Significantly different from the control, $p<0.05$.

decreasing effect on SIX absorption due to the delayed gastric emptying time.

3) Other Factors——The effect of CH on the *in vitro* intestinal absorption of SIX was investigated by the modified method of McElnay *et al.*[9,12] As shown in Table IV, CH caused a small but significant increase in the transfer of SIX from mucosal to serosal solution through the intestinal membrane. Consequently, increased intestinal membrane permeability may partly contribute to the enhancement in SIX absorption induced by the oral administration of CH.

CH is well known to possess anesthetic action.[13] Recently, Kojima *et al.*[14] demonstrated that an anesthetic drug, urethan, reduces the gastrointestinal absorption of certain drugs by decreasing the intestinal blood flow. We have also obtained evidence that some anesthetic drugs reduce the gastrointestinal absorption of sulfonamides by decreasing the intestinal blood flow,[15] although further studies are still necessary. Consequently, a decrease in the intestinal blood flow may contribute in part to the changes in SIX absorption induced by the oral and rectal administration of CH.

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References and Notes

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