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Effect of Fluid Volume on the Gastric Emptying and Absorption of Quinine in Mice, Rabbits and Humans^{1,2)}

OSAMI TSUZUKI,* JUNKO KOTSUBO (née SUMI), YASUHIRO TANAKA,
YASUHIRO MATSUMOTO, and KIMIHIKO KOUNO

*Daiichi College of Pharmacy, 22-1 Tamagawa-cho Minami-ku,
Fukuoka 815, Japan*

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The effect of coadministered fluid volume on the gastrointestinal absorption of quinine was investigated in mice, rabbits and humans. In mice, an increase in fluid volume from 5 to 40 ml/kg resulted in a significant increase in the maximum plasma quinine concentration (C_{\max}); the time required to reach C_{\max} (T_{\max}) was reduced. However, fluid volume had little effect on the area under the plasma concentration-curve (AUC_{0-180}). The gastric emptying of quinine in the initial stage after administration increased in proportion to the fluid volume. These results indicate that in mice, an increase in fluid volume enhances the rate of gastrointestinal absorption of quinine by producing an early increase of the gastric emptying. In rabbits, quinine was introduced *via* a tube into the washed and emptied stomach; an increase in fluid volume had little effect on C_{\max} , T_{\max} and AUC of quinine. Furthermore, the fluid volume did not affect the gastric emptying rate. In humans, C_{\max} , T_{\max} and AUC of quinine after oral administration were not affected even when the fluid volume was increased from 20 to 500 ml. These results show that in mice, the effect of fluid intake on gastric emptying is different from that in rabbits and humans.

Keywords—fluid volume; gastric emptying; oral administration; absorption; plasma concentration; quinine; mouse; rabbit; human

We previously reported^{1,2)} that in mice, the absorption rates of orally administered aminopyrine, dihydrocodeine and thiopental in the small intestine, and the plasma concentrations of these drugs in the initial stage after administration, were enhanced as a result of an increase of the gastric emptying rate brought about by an increase in the coadministered fluid volume. In addition, an increase in the fluid volume increased the pharmacological effects and toxicity of these drugs. In the present study, we compared the effect of fluid volume on the plasma quinine concentration in mice, rabbits and humans in order to elucidate the relationship between coadministered fluid volume and drug absorption in different species.

Experimental

Materials—Quinine hydrochloride was purchased from Houei Pharmaceutical Co., Inc., Osaka. Other reagents were of analytical reagent grade.

Drug Administration and Sampling—a) Mice: Male ddN mice, weighing 24 ± 1 g, were fasted for 16–20 h; water was available *ad libitum* up to 2 h before the experiments. A water solution (5 or 40 ml/kg) containing quinine (10 mg/kg) was infused through a stomach catheter. Blood samples (0.3 ml) were collected by heart puncture at various times after dosing and were centrifuged at 3000 rpm for 15 min.

b) Rabbits: Male rabbits, weighing 3.0–3.5 kg, received a commercial solid diet, but were fasted for 16–20 h before the experiments; water was available *ad libitum*. A vinyl tube (0.5 × 30.0 cm) was inserted into the stomach and 50–70 ml of warm isotonic solution (pH 1.2, 37°C) was injected. The fluid in the stomach was then rapidly withdrawn with a syringe. This procedure (gastric washout) was repeated until the withdrawn fluid contained almost no solid material. After washing and emptying of the stomach, a known volume of water solution (37°C) containing quinine (50 mg/kg) was instilled into the stomach through the vinyl tube, which was then removed. Blood samples (1.0 ml) were collected periodically from the ear vein.

c) Humans: Six healthy male volunteers, 23–52 years old (mean 31) and weighing 57–78 kg (mean 66), participated in the study after giving their informed consent. None of the subjects had taken any drugs for the 2 weeks preceding the study. Subjects were fasted overnight before each dose of quinine; water was available *ad libitum* up to 9 h before the experiments. Quinine (50 mg), dissolved in 20 or 500 ml of warm tap water (37°C) was administered orally at 9:00 a.m.; water and food were withheld for 4 h after dosing. The subjects were seated upright for 4 h after dosing; blood samples (5 ml) were collected from a forearm vein.

Gastric Emptying Experiment—a) Mice: Gastric emptying experiments were performed by a slight modification of the method of Watanabe *et al.*³⁾ The details were described previously.¹⁾

b) Rabbits: The gastric emptying rate was estimated by the same method as described previously.⁴⁾

Date and Statistical Analysis—The apparent absorption rate constants in rabbits and humans were calculated according to the Wagner–Nelson method⁵⁾ which can be regarded as corresponding to a one-compartment open model. Statistical analyses were performed by the paired Student *t*-test. A *p*-value of 0.05 was considered significant.

Analytical Methods—a) Quinine: The method of determination was according to Watanabe *et al.*³⁾ with some modifications. Two ml of 2.5 N NaOH and 15 ml of CHCl₃ were added to the sample, and the mixture was shaken for 10 min then centrifuged at 2500 rpm for 5 min. The water layer was removed and 10 ml of 0.1 N KOH was added to the CHCl₃ layer. This mixture was shaken for 5 min, and centrifuged at 2500 rpm for 5 min, then the upper layer was aspirated off. The lower layer (10 ml) was placed in another vessel and 5 ml of 0.1 N H₂SO₄ was added. This mixture was shaken for 10 min and centrifuged at 2500 rpm for 10 min. The fluorescence of the water layer was measured at excitation and emission wavelengths of 365 and 445 nm, respectively.

b) Phenol Red: To 0.5 ml of the sample, 5 ml of 0.1 N NaOH was added. The developed color was determined at 550 nm using a spectrophotometer.

Results and Discussion

Relationship between Fluid Volume and Quinine Absorption

a) Mice—Figure 1 shows the time course of plasma quinine concentration after oral administration at coadministered fluid volumes of 5 and 40 ml/kg. At the higher fluid volume, the plasma concentration was significantly higher until 15 min after oral administration. Further, at the higher fluid volume, the maximum plasma concentration (C_{\max}) was significantly elevated from 32.5 ± 2.7 to 41.7 ± 2.5 $\mu\text{g}/\text{ml}$ and the time to C_{\max} (T_{\max}) was reduced from 30 to 10 min. However, the area under the plasma concentration–time curve ($AUC_{0 \rightarrow 180}$) was not greatly affected by the increase in fluid volume (291.8 $\mu\text{g} \cdot \text{min}/\text{ml}$ at 5 ml/

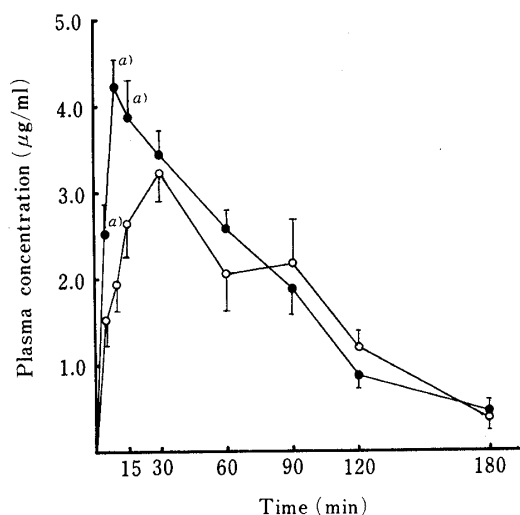


Fig. 1. Time Courses of Plasma Quinine Concentration in Mice after Oral Administration (10 mg/kg) at 5 (○) and 40 (●) ml/kg Fluid Volumes

Each point represents the mean \pm S.E. of 8 mice.

a) Significantly different from 5 ml/kg fluid volume, $p < 0.05$.

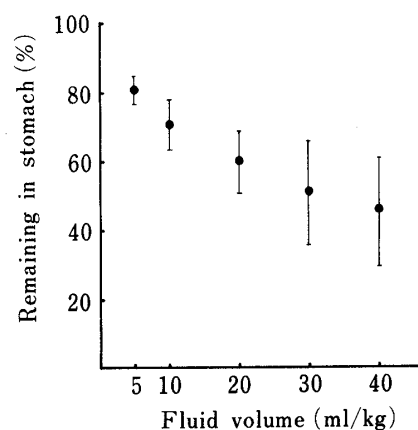


Fig. 2. Relationship in Mice between the Gastric Emptying of Quinine at Zero Time^{a)} and the Coadministered Fluid Volume

Each point represents the mean \pm S.E. of 8 mice.

a) The measurements were performed immediately after oral administration.

TABLE I. Remaining Amount (Percent) of Quinine in the Stomach and Intestine after Oral Administration (10 mg/kg) in Mice

Fluid volume (ml/kg)	Segment	Time (min)				
		0 ^{a)}	5	10	20	30
5	Stomach	80.6 ± 4.4	62.0 ± 6.2	44.4 ± 5.3	38.2 ± 3.9	20.9 ± 8.2
	Intestine ^{b)}					
	Proximal	18.1 ± 7.1	15.9 ± 4.7	13.6 ± 3.9	12.1 ± 3.0	4.7 ± 1.3
	Middle	0.0	0.0	2.9 ± 2.3	5.0 ± 1.8	5.5 ± 3.0
	Distal	0.0	0.0	0.0	2.5 ± 3.9	2.7 ± 1.6
40	Total	98.7 ± 6.1	77.9 ± 8.7	60.9 ± 2.9	57.8 ± 3.9	33.8 ± 8.5
	Stomach	46.2 ± 16.4 ^{c)}	32.3 ± 5.9 ^{c)}	30.6 ± 6.8 ^{c)}	8.1 ± 3.6 ^{c)}	7.5 ± 1.8 ^{c)}
	Intestine ^{b)}					
	Proximal	51.4 ± 14.2	18.1 ± 5.7	10.2 ± 4.5	12.3 ± 5.4	5.7 ± 2.3
	Middle	0.0	4.9 ± 1.8	7.2 ± 4.2	6.4 ± 2.2	5.1 ± 4.0
	Distal	0.0	0.0	1.6 ± 0.9	3.3 ± 1.8	2.3 ± 1.8
	Total	97.6 ± 11.4	55.3 ± 9.5 ^{c)}	49.6 ± 3.7 ^{c)}	30.1 ± 4.0 ^{c)}	25.2 ± 3.8 ^{c)}

Each value represents the mean ± S.E. of 8 mice.

a) The measurements were performed immediately after oral administration.

b) Trisection of the small intestine from the pylorus to the end of the ileum.

c) Significantly different from the value in mice given 5 ml/kg fluid ($p < 0.05$).

kg and $312.5 \mu\text{g} \cdot \text{min}/\text{ml}$ at 40 ml/kg). These results suggest that the increase in coadministered fluid volume increases the rate, but not the extent, of quinine absorption. Henderson *et al.*⁶⁾ reported that in rats, an increase in the fluid volume enhanced the plasma concentration of quinine or phenobarbital. Furthermore, Borowitz *et al.*⁷⁾ observed that the plasma levels of salicylic acid in rats were higher after the oral administration of drug in dilute, rather than concentrated solution. These observations are in accord with the results obtained in this study on mice.

At given times after oral administration of quinine at a fluid volumes of 5 or 40 ml/kg, the remaining amount (percent) of quinine in the stomach and small intestine was measured (Table I). At a coadministered fluid volume of 40 ml/kg, the percent of administered quinine remaining in the stomach was significantly lower than at 5 ml/kg. The same observation was made when the remaining amount (percent) of quinine in the total gastrointestinal tract was measured, except for the time point immediately after dosing ($t = 0$). These results support the view that in mice, an increase in fluid volume enhanced the plasma quinine concentration at the initial stage after dosing.

Generally, basic drugs such as quinine are absorbed rapidly from the small intestine, while there is little absorption from the stomach. Therefore, the gastric emptying rate after the oral administration of quinine solution affects the drug absorption rate. We previously reported¹⁾ that in mice orally given dihydrocodeine, this drug was transferred at a relatively fast rate at the initial stage after dosing from the stomach to the small intestine, and was then gradually evacuated according to first-order kinetics. In addition, the initial fast gastric emptying rate increased in proportion to the coadministered fluid volume. As shown in Fig. 2, there was clearly a negative correlation between the amount of quinine remaining in the stomach immediately after oral administration ($t = 0$) and the coadministered fluid volume. This finding supports our conclusion that in mice orally administered quinine at large fluid volumes, the increased gastric emptying rate in the initial post-administration stage leads to an increase in the drug absorption rate.

b) Rabbits—The mean plasma quinine concentration–time curves for five rabbits,

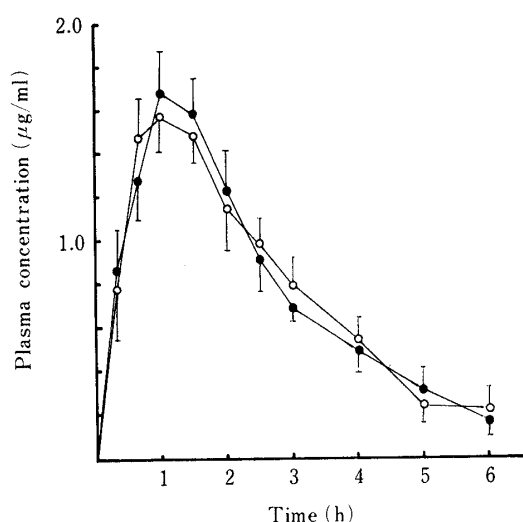


Fig. 3. Time Courses of Plasma Quinine Concentration in Rabbits after Oral Administration (50 mg/kg) at 5 (○) and 40 (●) ml/kg Fluid Volumes

Each point represents the mean \pm S.E. of 5 rabbits.

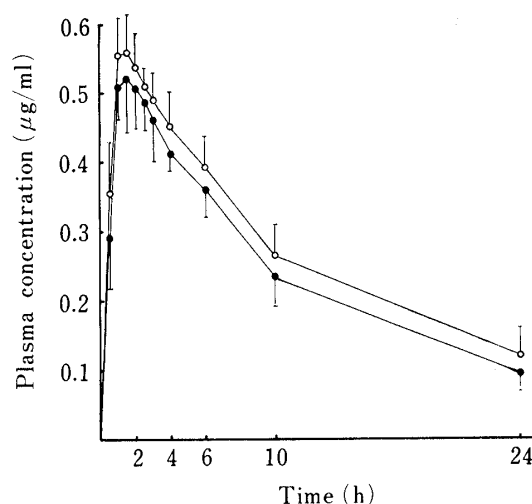


Fig. 4. Time Courses of Plasma Quinine Concentration in Humans after Oral Administration (50 mg) at 20 (○) and 500 (●) ml Fluid Volumes

Each point represents the mean \pm S.E. of 6 male volunteers.

TABLE II. Pharmacokinetic Parameters for Oral Administration of Quinine (50 mg/kg) in Rabbits with Various Fluid Volumes

Fluid volume (mg/kg)	K_a^a (h^{-1})	C_{max} ($\mu g/ml$)	T_{max} (h)	AUC_{0-6h} ($\mu g \cdot h/ml$)	K_e^b (h^{-1})
5	0.76 ± 0.1	1.6 ± 0.1	1.1 ± 0.2	5.0 ± 0.1	0.28 ± 0.2
20	0.89 ± 0.1	1.7 ± 0.1	1.3 ± 0.2	3.9 ± 0.1	0.39 ± 0.1
40	1.00 ± 0.2	1.7 ± 0.04	1.3 ± 0.1	5.6 ± 0.1	0.43 ± 0.1
55	0.83 ± 0.2	1.6 ± 0.1	1.3 ± 0.1	4.7 ± 0.1	0.33 ± 0.1

Each value represents the mean \pm S.E. of 5 rabbits.

a) Apparent absorption rate constant.

b) Elimination rate constant.

TABLE III. Pharmacokinetic Parameters for Oral Administration of Quinine (50 mg) to Humans with 20 and 500 ml Fluid Volumes

Fluid volume (ml)	K_a^a (h^{-1})	C_{max} ($\mu g/ml$)	T_{max} (h)	AUC_{0-24h} ($\mu g \cdot h/ml$)	K_e^b (h^{-1})
20	0.88 ± 0.3	0.56 ± 0.06	1.4 ± 0.1	7.9 ± 0.8	0.074 ± 0.01
500	0.83 ± 0.5	0.54 ± 0.08	1.3 ± 0.1	7.6 ± 0.7	0.066 ± 0.01

Each value represents the mean \pm S.E. of 6 humans.

a) Apparent absorption rate constant.

b) Elimination rate constant.

after oral administration of quinine at fluid volumes of 5 or 40 ml/kg, are shown in Fig. 3. The C_{max} of quinine at 5 ml/kg fluid volume occurred at 1.1 ± 0.2 h and the mean plasma drug concentration was 1.6 ± 0.1 $\mu g/ml$. Similar values were obtained at 40 ml/kg fluid volume. These findings are different from those in mice. Table II shows the pharmacokinetic parameters after the coadministration of 4 different fluid volumes.

To elucidate the relationship between drug absorption and coadministered fluid volume, the gastric emptying rate was measured using phenol red as the indicator. The gastric emptying of phenol red after intubation of 5, 20, 40 or 55 ml/kg fluid volume was exponential. Unlike mice, however, rabbits did not show fast gastric emptying at the initial stage after dosing and the rate constant of the gastric emptying was not affected by increases in the coadministered fluid volume.

c) **Humans**—Figure 4 shows the mean plasma quinine concentration–time curves in six males after oral drug administration at fluid volumes of 20 or 500 ml. At the lower fluid volume, the mean plasma concentration at each time point was slightly higher than at the greater fluid volume, but the difference was not statistically significant. As in the rabbits, there was no difference in C_{\max} and T_{\max} values at the lower and higher fluid volumes (Table III).

The presence of food and the variation in fluid volumes with which a drug is orally administered can markedly influence drug bioavailability.⁸⁾ Welling *et al.*^{9,10)} reported that in humans, the C_{\max} values of salicylic acid and amoxillin after the oral administration of aspirin tablets and amoxillin capsules are enhanced when the coadministered fluid volume is increased from 20 to 250 ml. However, this enhancement may reflect an increase in drug solubility. In our human study, we administered quinine in solutions of 20 or 500 ml in volume. If the gastric emptying rate were enhanced by an increase in the fluid volume, the absorption rate of quinine would be expected to be increased in the initial post-administration stage and C_{\max} of the drug would be expected to be increased. However, Hunt and MacDonald¹¹⁾ have shown that in man, the gastric emptying rate was delayed as the administered water volume was increased. Therefore, an increase in the water intake may result in a delayed transit of the drug to the optimal absorption sites in the small intestine and a decrease in the C_{\max} of the drug. In this study, the C_{\max} of quinine slightly decreased as the fluid volume increased from 20 to 500 ml, but there was no significant difference between the C_{\max} values at the lower and higher fluid volumes.

It was observed that in mice, an increase in the coadministered fluid volume resulted in a higher quinine absorption rate due to an early increase of gastric emptying at the initial stage and enhanced C_{\max} values for the drug. However, fluid volume had little effect on gastric emptying in rabbits or on the quinine plasma concentration–time curves of rabbits and humans. There was thus a marked species difference regarding the effect of coadministered fluid volume on the gastric emptying and bioavailability of quinine. Gastric emptying is affected by physiological conditions, *e.g.*, osmotic pressure and body position. Nimmo and Prescott¹²⁾ reported that the plasma paracetamol concentrations at the initial post-administration stage in ambulant subjects are increased as compared to those in supine subjects. In addition, Hunt *et al.*¹³⁾ reported that saline test solutions empty from the stomach more rapidly in subjects lying on the right side than in those lying on the left side or in a sitting position. Body position thus has an important effect on the rate of gastric emptying, and the relationship between body position and gastric emptying in various species will be discussed in the following paper.

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