[Chem. Pharm. Bull. 29(2) 539—544 (1981)]

Influence of Osmotic Pressure and Viscosity on Intestinal Drug Absorption. I. Studies on the Gastric Effluent following Oral Administration of Various Quinine Solutions to Rats

Yoko Sakiya,* Yoshiko Miyauchi, and Yoshiji Tsuemura

Faculty of Pharmaceutical Science, Tokushima University of Arts and Science, Yamashiro-cho, Tokushima-shi, 770, Japan

(Received July 17, 1980)

Variations in osmotic pressure, viscosity, gastric emptying rate, and drug concentration in the gastric effluent following oral administration of quinine solutions prepared with various amounts of sucrose or sodium carboxymethyl cellulose (CMC–Na) were examined. The osmotic pressure of the gastric effluent after the administration of a hypertonic or hypotonic quinine solution tended to approach isotonicity with increase of the elapsed time after administration. In the case of a high viscosity solution, there was a gradual decrease in the viscosity of the effluent, while in the case of a low viscosity solution, little difference was seen between the original viscosity and that of the effluent during the overall time course. The solution administered was diluted in the stomach and thereafter flowed out at a definite quinine concentration. However, this concentration was varied by the effects of the added agents, sucrose and CMC-Na. In the absence of these agents, the quinine concentration of the effluent was the highest among the test solutions, and the concentration decreased markedly with increasing osmotic pressure. It was found that osmotic pressure had a greater influence on the quinine concentration of the effluent than did viscosity. The time course of the cumulative volume of effluent differed with each test solution. The ratio of quinine amount remaining in the stomach per dose versus time was expressed in terms of a biexponential expression for all the test solutions except for the most hypertonic solution. The gastric emptying rate estimated from the curves mentioned above was greatly influenced by osmotic pressure rather than viscosity, and decreased with increase in osmotic pressure.

Keywords——oral administration; gastric effluent; osmotic pressure; viscosity; quinine concentration of effluent; gastric emptying rate; rat

Considerable attention has been paid to certain factors which affect gastric emptying rate, drug absorption, and bioavailability. Reports have appeared on the influence of osmotic pressure,[1] volume of drug solution,[2] volume of water administered with the drug,[3] and the constituents of test meals.[4] However, little is known regarding the characteristics of the effluent flowing from the stomach to the small intestine following the oral administration of drug solutions of varying osmotic pressure and viscosity. This study was therefore aimed at examining the variation of osmotic pressure, viscosity, and volume of gastric effluent flowing from the stomach. The variation in the outflow rate of quinine, which is used as a model of a barely absorbable drug in the stomach,[2b] was also examined.

Experimental

Materials——Quinine sulfate (Q. sulf), sodium carboxymethyl cellulose (CMC-Na), and sucrose used were of J.P.IX grade. Ethylene dichloride (EDC) was distilled before use. All other reagents were commercial products of analytical grade. Test solutions containing Q. sulf amounting to 1 mg/ml (purified water) and of varying osmotic pressure and viscosity were prepared with sucrose and CMC-Na, respectively. The mean pH value of the test solutions prepared was 6.7 and all the test solutions were adjusted to pH 6.7 with a small amount of dilute HCl or NaOH solution in order to avoid any effect of pH on the experimental results. The compositions, the osmotic pressures, and the viscosity values of the test solutions are shown in Table I.

Drug Administration and Sampling——Male Wistar rats weighing 250±5 g were fasted for 20 hr prior to the experiments, but allowed free access to water. The body temperature of rats was determined rectally,

Table I. Composition, Osmotic Pressure and Viscosity of the Test Solutions

Drug	Test soln. (% w/v)	Osmotic pressure at room temperature (mOs)	Viscosity at 37° (cps)
Q. sulf.	+0% S (simple soln.)	30	1.0
Q. sulf.	+9.5% S (isotonic soln.)	290	1.0
Q. sulf.	+20.0% S	611	1.4
Q. sulf.	+50.0% S	1528	4.5
Q. sulf.	+64.6% S	1974	10.7
Q. sulf.	+0.5% CMC–Na	30	10.1
Q. sulf.	+1.0% CMC–Na	33	28.4

The pH values of the test solutions were adjusted to 6.7 with a small amount of dilute HCl or NaOH solution. Q. sulf amounting to 1.0 mg/ml was contained in all test solutions. Q. sulf: quinine sulfate. S: sucrose. CMC–Na: carboxymethyl cellulose.

and infrared lamps were used to maintain the temperature during the experiment. A polyethylene cannula was introduced into the bile duct under ether anesthesia to prevent the mixing of bile and effluent and another similar cannula was introduced into the upper portion of the duodenum in order to sample effluent flowing from the stomach. A stomach catheter was introduced through the mouth one hour after each rat awakened from the anesthesia and 20 ml/kg of a test solution was introduced through the catheter. Gastric effluent was collected at appropriate intervals. The volume and pH of the effluent at each collection were determined.

Determination of Quinine——The determination method for quinine was based on that of Watanabe *et al.*[7b] with some modification. Two ml of 2.5 N NaOH and 15 ml of EDC were added to 100 μl of sample solution and the mixture was shaken for 30 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 EDC layer. The mixture was shaken for 5 min and centrifuged at 2500 rpm for 5 min. The upper layer was removed by aspiration. Ten ml of the lower layer was placed in another vessel and 7 ml of 0.1 N H_2SO_4 was added. The mixture was shaken for 30 min and centrifuged at 3000 rpm for 10 min. The fluorescence of the water layer was measured at excitation and emission wavelengths of 365 and 445 nm, respectively. The reference solution was prepared by the same procedure using gastric effluent obtained after administration of water (20 ml/kg). The standard solution was prepared by the same procedure using a Q. sulf solution of known concentration.

Determination of Quinine in Plasma——The Q plasma level in cannulated rats given a simple solution was determined by the procedure described above. Blood samples were drawn through a cannula in the femoral artery at appropriate intervals and then were centrifuged at 3000 rpm for 15 min. Plasma samples of 100 μl were used, with plasma obtained before dosing of a simple solution as the blank.

Measurement of Osmotic Pressure and Viscosity——Five μl and 1.1 ml solution samples were used to measure the osmotic pressure and viscosity, respectively. The equipment used was a 5100A vapor pressure osmometer (Wescor, Inc.,; sensitivity, less than ±3 mOs) and a Visconic ELD-form viscometer (Tokyo Keiki, Co., Ltd.; sensitivity, less than ±2%, cp).

Results and Discussion

Osmotic Pressure and Viscosity Variations in the Effluent

The time courses of the osmotic pressure and the viscosity varistions in the effluent following oral administration of the test solutions are shown in Fig. 1. Individual standrd errors were less than 15.2% in all cases. The mean osmotic pressure of the effluent after administration of the hypertonic solutions decreased sharply in the early stage in comparison with the original osmotic pressure. Thereafter, the rate of decrease gradually slowed down. A similar decrease was seen in the viscosity following the administration of CMC-Na solutions. The osmotic pressure and viscosity of the effluent by 4 hours after the administration of the simple solution approached approximately isotonicity without large variation of viscosity during the experiments. Although the data are not shown in Fig. 1, less variation in the osmotic pressure of the effluent was observed after the administration of isotonic solution.

Cumulative Amount of Quinine versus Cumulative Volume of Effluent

The correlations between the cumulative quinine percentage per dose and the cumulative volume of effluent after the administration of the test solutions are shown in Figs. 2 and 3.

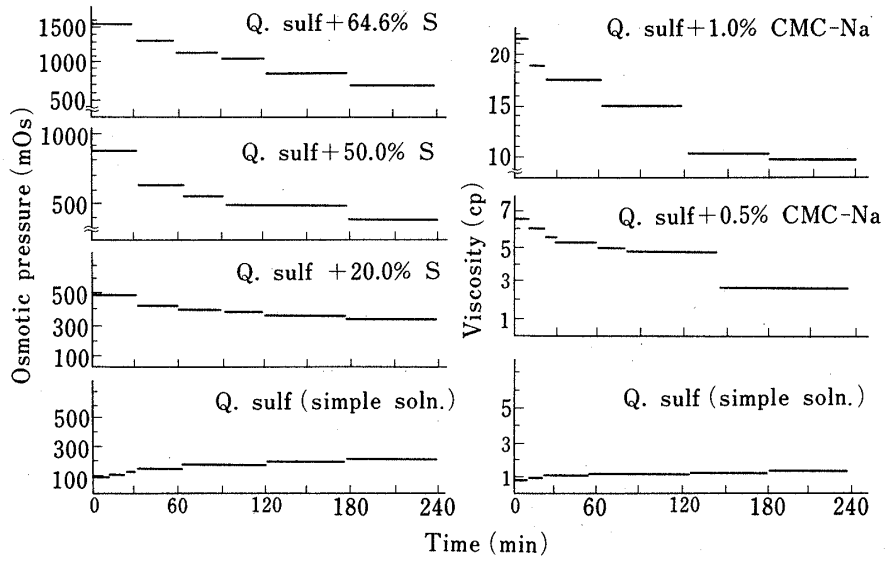

Fig. 1. Time Courses of Osmotic Pressure and Viscosity in the Gastric Effluent following Oral Administration of Various Quinine Solutions

Individual data represent the mean at least 7 animals. For details of test solutions, see Table I.

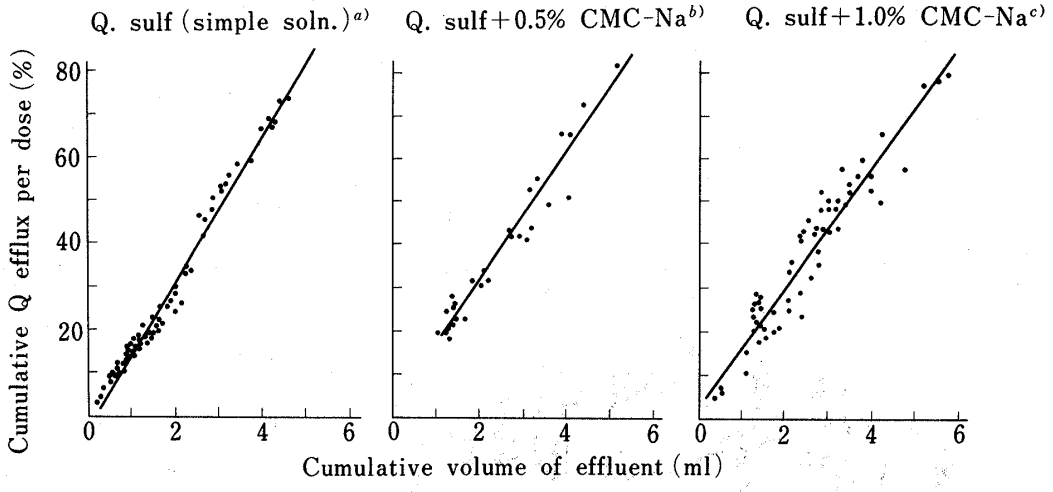

Fig. 2. Cumulative Efflux of Quinine versus Cumulative Volume of the Effluent following Oral Administration of Various Quinine Solutions

Regression coefficients (reg. Coeffi) were calculated from the regression lines by the least-squares method. *a*): Reg. Coeffi=17.3 (r=0.989, n=65). *b*): Reg. Coeffi=15.4 (r=0.957, n=28). *c*): Reg. Coeffi=14.4 (r=0.965, n=59). Q; Quinine. For details, see Table I.

The relationship was linear for the individual test solutions except 64.6% sucrose solution. Thus, the quinine solution diluted in the stomach flowed out with time-independent concentration. However, the concentrations varied among the solutions administered. The differences of regression coefficients among the individual test solutions were statistically tested, but no significant differences were found among the simple, isotonic, and CMC-Na solutions. However, significant differences were found between the solutions described above and the 20.0 and 50.0% sucrose solutions. Thus, it was concluded that the osmotic pressure had a greater influence on the quinine concentration in the effluent from the stomach than did the viscosity.

Cumulative Volume of Effluent *versus* Time

Three examples of the time course of the cumulative effluent volume are shown in Fig. 4. As can be seen, the courses varied with the solutions administered. The largest cumulative

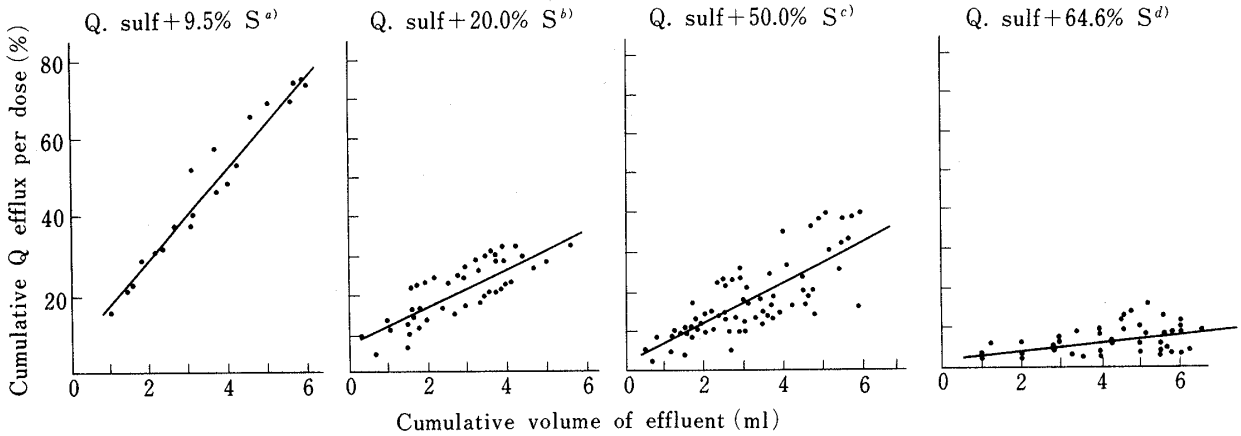

Fig. 3. Cumulative Efflux of Quinine versus Cumulative Volume of the Effluent following Oral Administration of Various Quinine Solutions

Regression coefficients (reg. Coeffi) were calculated from the regression lines by the least-squares method. *a*): Reg. Coeffi=11.9 (r=0.984, n=20). *b*): Reg. Coeffi=5.1 (r=0.813, n=43). *c*): Reg. Coeffi=4.9 (r=0.756, n=68). *d*): Reg. Coeffi=1.2 (r=0.278, n=42). For details, see Table I and Fig. 1.

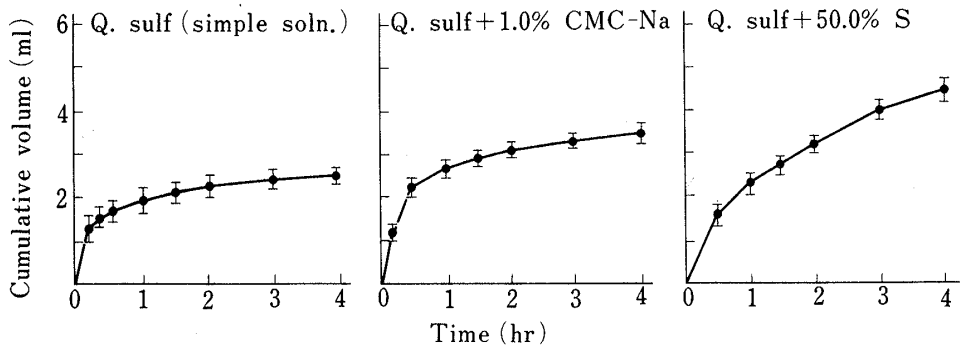

Fig. 4. Time Courses of Cumulative Volume of Gastric Effluent following Oral Administration of Various Test Solutions

Points are the means for at least 10 animals and the vertical bars indicate S.E. In other test solutions, the mean cumulative volume (ml±S.E.) for at least 10 animals in 4 hours following the administration were 5.20±0.56 (9.5% S soln), 4.54±0.43 (20.0% S soln), 4.05±0.54 (64.6% S soln), and 3.01±0.29 (0.5% CMC-Na soln). For details, see Table I.

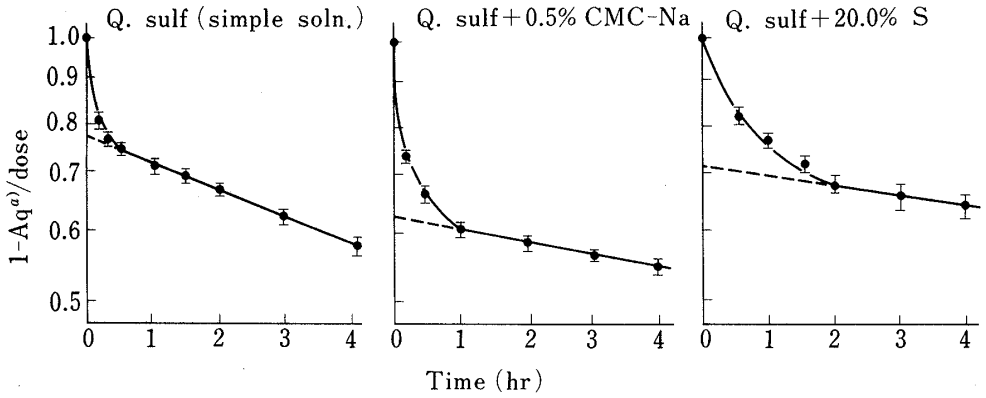

Fig. 5. Sigma-minus Plots for Quinine Outflow from the Stomach

a): Cumulative amount of quinine flowing from the stomach after oral administration. Points are the means for at least 8 animals and the vertical bars indicate S.E. Lines are regression lines calculated by the least-squares method. For other details, see Table I.

volume was found with the isotonic solution, and the least volume was found with the simple solution.

Rate of Quinine Outflow from the Stomach

The plasma levels of quinine during the experiment were measured in order to determine the absorption of quinine from the small portion between the pylorus and the cannulated upper duodenum. The quinine plasma levels were negligible. Therefore, on the assumption that the total amount of quinine administered had flowed out from the stomach, signma-mius values calculated from the quinine outflow were plotted. Three examples are shown in Fig. 5. Sigma-minus values fitted graphically to equation 1 in all cases except that of 64.6% sucrose.

$$Q_e = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where Q_e and t are the sigma-minus value and time, respectively. Data for the 64.6% sucrose solution could not be analyzed by equation 1 because of the small amount of quinine that flowed out during the experiment. The parameters of the available data were calculated by means of the SALS computer program.[5] The results are shown in Table II. The largest rate constants, α and β, were obtained from the data for the simple and isotonic solutions. These rate constants decreased with increasing amount of sucrose or CMC-Na added. However, the rate constant values of the hypertonic solutions were less than those of the high viscosity solutions.

Table II. The Parameters for Outflow Rate of Quinine from the Stomach after Oral Administration of Various Test Solutions

Test soln.	A	B	α, $min^{-1} \times 100$	β $min^{-1} \times 100$
Q. sulf (simple soln)	0.235	0.765	15.9	0.111
Q. sulf+9.5% S	0.331	0.659	12.3	0.311
Q. sulf+20.0% S	0.276	0.722	2.63	0.0502
Q. sulf+50.0% S	0.098	0.779	0.294	0.0131
Q. sulf+0.5% CMC–Na	0.363	0.636	11.9	0.0590
Q. sulf+1.0% CMC–Na	0.584	0.419	1.63	0.0754

The parameters were calculated by means of the SALS[5] computer program based on a biexponential equation ($Q_e = Ae^{-\alpha t} + Be^{-\beta t}$) for sigma-minus values (Q_e) of quinine amount per dose. t: time. For details, see Table I and Fig. 5.

Table III. Variation in CMC–Na Solution Viscosity at Different pH Values[a]

CMC–Na % w/v	Viscosity (cp) at 37°				
	pH				
	5.0	4.0	3.0	2.0	1.0
0.5	9.0	6.8	4.7	4.1	3.6
1.0	28.0	20.5	18.3	15.2	13.7

a) The solutions were adjusted to each pH with dilute HCl solution. For details, see Table I.

The viscosity of the CMC-Na solutions varied with the pH as shown in Table III, decreasing with decrease in pH. The viscosity of the administered CMC-Na solution might be influenced by the acidic gastric juice. As the pH values of initially collected effluent after the administration were lower than that of the administered solution, the viscosity might be decreased by the influence of the gastric juice (Fig. 6). As shown in Fig. 6, the pH values of the effluent showed major individual differences and also varied with the sampling times. However, the effluent viscosity decreased with time after administration, as shown in Fig. 1.

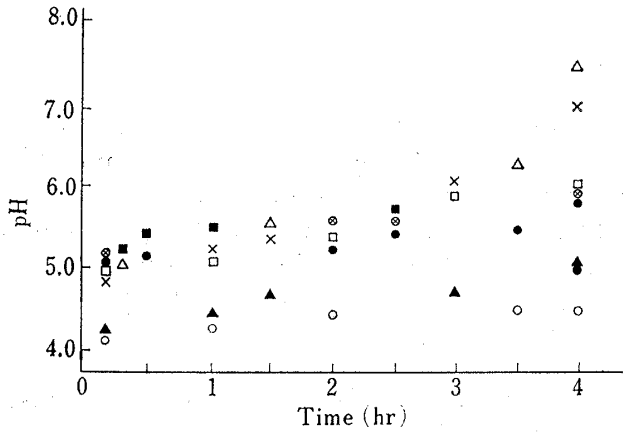

Fig. 6. The Time Course of pH of the Effluent Flowing from the Stomac after Oral Administration of Quinine Solution Containing 1.0 Per Cent CMC–Na

Each symbol represents 8 independent experiments. The pH data are positioned at the final times of the appropriate sampling time intervals.

It was concluded that the osmotic pressure had a greater influence on the outflow rate of quinine than did the viscosity.

A report on the gastric emptying rate of quinine has been published.[2] It was reported that quinine in the stomach was transfered to the small intestine at a relatively fast rate during the early stage, and then gradually evacuated in accordance with first-order kinetics. Quinine given orally as a simple solution showed faster gastric emptying rates of *SL*-512(1-cyclopropyl-4-phenyl-6-chlor-2-[1H]-quinazoline) solutions of varying viscosity have also been reported.[6] Although the viscosities of these solutions were higher (28—270 cp) than those of the solutions used in this study, the gastric emptying rate decreased with increase of the viscosity. These two experiments were carried out in inatct animals. Although our experiment used operated rats, the effects of the osmotic pressure and viscosity on the gastric emptying time were similar to the reported results. However, further work is necessary on the influences of osmotic pressure and viscosity of orally administered drug solutions on the blood drug levels in intact animals.

References and Notes

1) R. Kato, A. Tanaka, K. Onoda, and Y. Omori, *Jap. J. Pharmacol.*, **19**, 331 (1969); M. Marovola, A. Reinikainen, M.L. Heliovaara, and A. Huikari, *J. Pharm. Pharmacol.*, **31**, 615 (1979).
2) *a*) M.L. Henderson, A.L. Pichioni, and L. Chin, *J. Pharm. Sci.*, **55**, 1311 (1966); *b*) J. Watanabe, H. Okabe, T. Ichihashi, K. Mizojiri, H. Yamada, and R. Yamamoto, *Chem. Pharm. Bull.*, **25**, 2147 (1977).
3) P.A. Koch, C.A. Schultz, R.J. Wills, S.L. Hallquist, and P.G. Welling, *J. Pharm. Sci.*, **67**, 1533 (1978).
4) S. Rosenthal and E.S. Nasset, *J. Nutrition*, **66**, 91 (1958); S.L. Malhotra, *Am. J. Physiol.*, **213**, 169 (1967); P.G. Welling, *J. Pharmaco. Biopharm.*, **5**, 291 (1977).
5) T. Nakagawa, Y. Koyanagi, and H. Togawa, Computer Center of University of Tokyo, *Center News*, **11**, (4), 70 (1979).
6) Y. Yamahira, T. Noguchi, H. Takenaka, and T. Maeda, *J. Pharm. Dyn.*, **1**, 160 (1978).