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Influence of Osmotic Pressure and Viscosity on Intestinal Drug Absorption. II.[1] Quinine Concentration Profile in Plasma after Oral Administration of Various Quinine Solutions to Rats

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The effects of osmotic pressure and viscosity have been examined on the intestinal absorption of quinine from solutions containing various amounts of sucrose or sodium carboxymethyl cellulose in the rat. The amount of quinine absorbed from 0 to 240 minutes was highest from the hypotonic and isotonic solutions and decreased with increasing osmotic pressure or viscosity. However, the effect was more marked with osmotic pressure than viscosity. Similar results were obtained on bioavailability. These results were consistent with the observations reported previously[1] that gastric emptying rate and quinine concentration of the gastric effluent were more markedly reduced by increasing osmotic pressure than by increasing viscosity.

Keywords——oral administration; intestinal absorption; quinine; osmotic pressure; viscosity; rate of bioavailability; rat

The previous report[1] descrived the variations in osmotic pressure, viscosity and quinine concentration of gastric effluent and gastric emptying rate following oral administration of quinine solutions with varying osmotic pressure and viscosity. The purpose of this study was to examine the effects of osmotic pressure and viscosity on the intestinal absorption of quinine, and to compare the results of this study with previous observations.

Experimental

Materials——Quinine sulfate (Q. sulf), sodium carboxymethyl cellulose (CMC-Na) and sucrose 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 at 1 mg/ml (purified water) were prepared with various values of osmotic pressure and viscosity (adjusted with sucrose and CMC-Na, respectively).

Table I. Compositions, Relative Osmotic Pressures and Viscosities of the Test Solutions

Test soln		Relative osmotic pressure	Relative viscosity
Drug	Additive(% w/v)		
Q. sulf +	0 (simple soln)	1.0	1.0
	9.5 (s), isotonic soln	9.7	1.0
	20.0 (s)	20.4	1.4
	50.0 (s)	50.9	4.5
	64.6 (s)	65.8	10.7
	81.6 (s)	83.3	31.0
Q. sulf +	0.5 (CMC–Na)	1.0	10.1
	0.8 (CMC–Na)	1.1	20.0
	1.0 (CMC–Na)	1.1	28.4

The test solutions were adjusted to pH 6.7 with a small amount of dilute HCl or NaOH solution. Relative osmotic pressure and viscosity values are based on the data from the previous report.[1]
Q. sulf: Quinine sulfate.
S: Sucrose.
CMC-Na: Sodium carboxymethyl cellulose.

All 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, relative osmotic pressures and viscosities of the test solutions are given in Table I. The test solutions include 81.6% sucrose and 0.8% CMC-Na solutions in addition to the solutions used in the previous study.[1] The osmotic pressure and viscosity of the test solutions were measured with the same equipment as used in the previous experiments.[1]

Drug Administration and Sampling——Male Wistar rats weighing 250±5 g were fasted for 20 hr prior to the experiments with free access to water. The femoral artery was cannulated with polyethylene tubing under ether anesthesia. A stomach catheter was introduced through the mouth 1 hr after the rats awakened from the anesthesia and 20 ml/kg of the test solution was given through the catheter. In addition, after the femoral artery had been cannulated, a bolus injection of Q. sulf (20 ml/kg) was given into the other femoral or portal vein. Blood samples were drawn through the cannula at appropriate intervals and then were centrifuged at 3000 rpm for 15 min.

Determination of Quinine in Plasma——The determination of quinine in plasma (100 μl) was carried out by the same procedure as described previously.[1]

Calculation of Area under the Quinine Plasma Concentration *versus* Time Curve (AUC)——The AUC from 0 to 240 min (AUC_0^{240}) was calculated by the trapezoidal method from the quinine concentrations in plasma.

Results and Discussion

The time courses of quinine concentration in plasma after oral administration of the test solutions are given in Figs. 1 and 2. Table II contains the maximum quinine concentration in plasma(C_{max}), the time to C_{max}(t_{max}) and the AUC_0^{240} values after oral administration of the test solutions. The AUC_0^{240} or C_{max} values of the test solutions were compared by a matched t test. No significant differences in rate of bioavailability were found between the simple, isotonic and 0.5% CMC-Na solutions. Significant differences were found between these solutions and 1.0% CMC-Na and 20.0% sucrose solutions. The C_{max} and t_{max} were not clear in the hypertonic solutions, 50.0, 64.6 and 81.6% sucrose solutions, as shown in Fig. 2. Significant differences were found between these hypertonic solutions and other test solutions in terms of the rate of bioavailability. The 0.5% CMC-Na and 64.6% sucrose solutions have

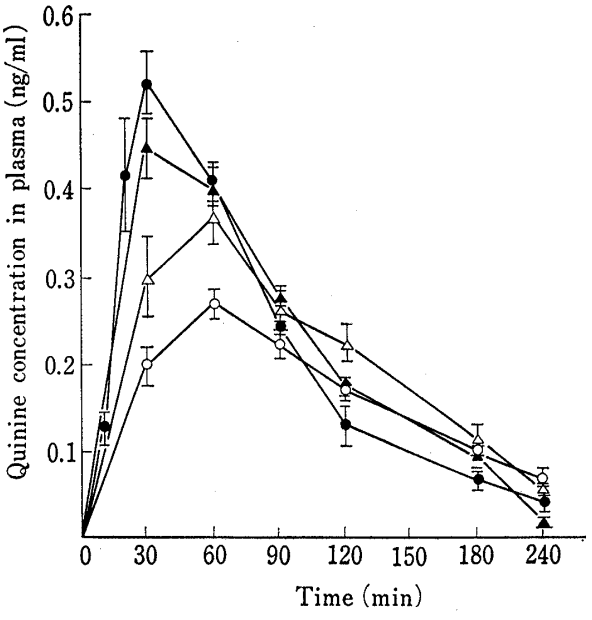

Fig. 1. Time Courses of Quinine Concentration in Plasma after Oral Administration of Simple and CMC–Na-containing Solutions

—●—, simple soln; —▲—, 0.5% CMC–Na soln; —△—, 0.8% CMC–Na soln; —○—, 1.0% CMC–Na soln. Each symbol is the mean for at least 8 animals and vertical bar is S.E. For details, see Table I.

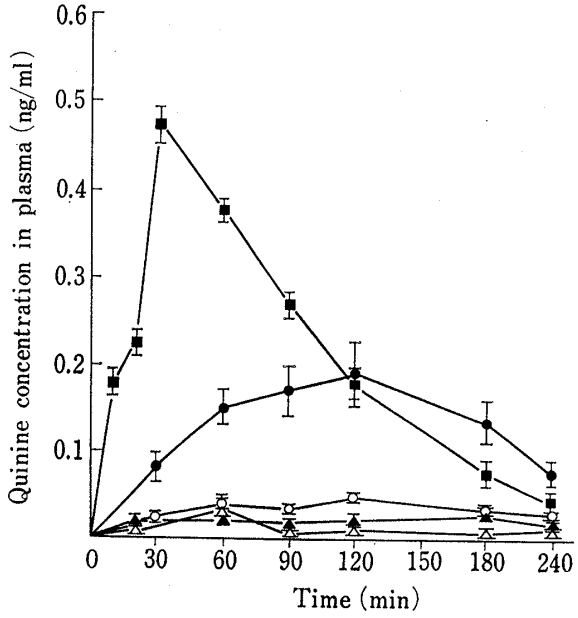

Fig. 2. Time Courses of Quinine Concentration in Plasma after Oral Administration of Sucrose-containing Solutions

—■—, 9.5% S soln; —●—, 20.0% S soln; —○—, 50.0% S soln; —△—, 64.6% S soln; —▲—, 81.6% S soln. Each symbol is the mean for at least 8 animals and the vertical bar is S.E. For details, see Table I.

TABLE II. The Bioavailability and Absorbability of Quinine in the Test Solutions

Test soln: Drug	Test soln: Additive (% w/v)	Soln no.	Maximum concentration (C_{max}) ng/ml	Time of C_{max} (t_{max}) min	AUC_0^{240} (±S.E.) ng·min/ml	AUC_0^{240}(oral) / AUC_0^{240}(*i.v.*)	AUC_0^{240}(oral) / AUC_0^{240}(portal)
0,	(simple soln)	1	0.52	30	47.50(2.92)	29.37	35.78
0.5	(CMC–Na)	2	0.45	30	46.38(4.54)	28.68	34.94
0.8	(CMC–Na)	3	0.34	60	46.26(4.88)	28.60	34.87
1.0	(CMC–Na)	4	0.27	60	33.83(4.08)	20.92	25.48
Q. sulf + 9.5	S	5	0.47	30	46.78(4.11)	28.92	35.24
20.0	S	6	0.19	120	30.77(7.56)	19.03	23.18
50.0	S	7	n.c.	n.c.	7.75(0.87)	4.79	5.84
64.6	S	8	n.c.	n.c.	5.21(0.39)	3.22	3.92
81.6	S	9	n.c.	n.c.	2.68(0.33)	1.66	2.02

AUC_0^{240}: Area under the plasma quinine concentration *versus* time curve from 0 to 240 min.
Each AUC_0^{240} value is the mean for at least 8 animals. Matched t test ($p<0.01$); AUC_0^{240}: 1—6>7, 8, 9. 7, 8>9. C_{max}: 1, 5>3, 4, 6. 2, 3>4, 6. 4>6.
n.c.: Not clear. For other details, see in Figs. 1 and 2 and Table I.

similar viscosity but differ markedly in osmotic pressure. There was a significant difference between these solutions in terms of the rate of bioavailability, as there was between 1.0% CMC-Na and 81.6% sucrose solutions. Between the 0.8% CMC-Na and 20.0% sucrose solutions, significant differences were found in C_{max} and t_{max} but not in AUC_0^{240} values. These results suggest that C_{max} and t_{max} were influenced more by the osmotic pressure than the viscosity. The observations described above are consistent with the previous results[1] on the gastric emptying rate and the quinine concentration of gastric effluent, which were influenced more by the osmotic pressure than the viscosity. As shown by AUC values for oral and intravenous administrations, the bioavailability up to 240 minutes was about 30% in the simple solution, which showed the highest AUC_0^{240} value. As estimated from the AUC_0^{240} values for oral and portal administrations, the absorbability of quinine from the small intestine was more markedly reduced by increasing the osmotic pressure than the viscosity.

Marvola *et al.*[2] reported that the bioavailability of sulfafurasol (AUC_0^{∞}) was highest from water and very clearly lowest from 1.8% NaCl solution. In addition, the bioavailability of the drug (AUC_0^{∞} and C_{max}) decreased with increasing osmotic pressure. The report also suggested that the rate of intestinal absorption of a drug would be highest from an isotonic solution and that the amount of a drug absorbed would be lower from hypertonic solution than from hypotonic or isotonic solutions. These observations are in accord with the results in this study.

References

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