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## Gastric Emptying Rate Constants after Oral Administration of Drug Solution to Mice, Rats, and Rabbits[1)]


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Gastric emptying rates of quinine and phenol red were investigated after oral administration of the syrup or the simple solution to mice, rats, and rabbits. These drugs in the stomach were transferred to the small intestine at a relatively fast rate in the early stage and then gradually evacuated according to first-order kinetics. In mice and rats, 24-hr fasting increased the gastric emptying rate for the simple solution of quinine. In rats, an increased volume of the simple solution gave a larger gastric emptying rate constant. Generally, smaller animals in this work had larger gastric emptying rate constants. Drugs given orally as the syrup showed slower gastric emptying rates than those given as the simple solution in almost all animals examined. The gastric emptying rate of quinine was faster than that of phenol red in 24-hr fasting rabbits. The simulated calculation for slow gastric emptying indicated that the drug level in the body is mainly controlled by the gastric emptying rate and scarcely affected by intestinal absorption rate constant, $k_2$, in the region where $k_2$ is more than 2 ($hr^{-1}$).



**Keywords**——gastric emptying rate constants; first-order kinetics; mouse; rat; rabbit; quinine; phenol red; syrup solution


Many drugs or new drug candidates are administered orally to experimental animals such as mice, rats, and rabbits in preclinical tests. However, not much attention has been paid to gastric emptying, which is one of the rate processes in overall absorption from the intestine and may be sometimes a predominant factor controlling blood levels of drugs in the body.

The gastric emptying rate or time has been studied mainly in the field of physiology, and some factors which affected gastric emptying of test meals or drugs were: osmotic pressure,[3)] volume,[4)] temperature,[5)] constituents of test meals,[6)] simultaneously adminis-

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3) J.N. Hunt, I. MacDonald, and W.R. Spurrel, *J. Physiol.*, **115**, 185 (1951); R. Kato, A. Takanaka, K. Onoda, and Y. Omori, *Jap. J. Pharmacol.*, **19**, 331 (1969).

4) J.N. Hunt, *Physiol. Rev.*, **39**, 491 (1959); M.L. Henderson, A.L. Picchioni, and L. Chin, *J. Pharm. Sci.*, **55**, 1311 (1966).

5) C.W. Wirts, M.E. Rehfuss, and W.J. Snape, *J. Am. Med. Assoc.*, **155**, 725 (1954).

6) S. Rosenthal and E.S. Nasset, *J. Nutrition*, **66**, 91 (1958); S.L. Malhotra, *Am. J. Physiol.*, **213**, 169 (1967).

tered drugs,[7] body position,[8] gastrointestinal diseases,[9] and microorganisms in the intestine.[10]

However, little is known about the kinetic features of gastric emptying rates of drugs in experimental animals. In this paper, the gastric emptying rates of quinine and phenol red in mice, rats, and rabbits are expressed by kinetic constants after oral administration of the syrup or the simple solution. The constants were compared to characterize the syrup solution and the experimental animals with regard to the gastric emptying rate. Furthermore, we discuss the area of constants for intestinal absorption, where alimentary absorption was mainly controlled by the gastric emptying rate and the intestinal absorption itself had little influence on the drug level in the body.

## Experimental

**Materials**——Quinine hydrochloride was purchased from Ishizu Seiyaku, Ltd. and phenol red from Kanto Chemical Co., Inc. They were used without further purification. All other reagents were commercially available and of analytical grade.

A quinine hydrochloride solution of 0.5 mg free quinine in one ml of distilled water was used. Quinine hydrochloride syrup contained 0.5 mg/ml free quinine and 50% (w/v) sucrose. The quinine simple solution and syrup, which were administered to mice or rats, were of pH 7.00 and 6.70, respectively. In the experiments with rabbits, the solutions given in Table I were used.

Table I. Compositions of the Test Solutions

| Test soln.[a] | | Quinine (mg/ml) | Phenol red (mM) | Sucrose (% w/v) |
|---|---|---|---|---|
| Simple soln. | (a) | 2.5 | 0.25 | 0 |
| | (b1) | 5.0 | 0 | 0 |
| | (b2) | 0 | 0.50 | 0 |
| Syrup | (a) | 2.5 | 0.25 | 50 |
| | (b1) | 5.0 | 0 | 50 |
| | (b2) | 0 | 0.50 | 50 |

*a*) The pH of these solutions was adjusted to 7.0 with a small amount of NaOH.

**Experimental Procedure**——(1) Gastric Emptying Rate of Quinine in Mice: Male DS mice weighing 20±2 g were used. Ten or 20 ml/kg of test solution was administered to normally feeding or 24-hr fasting mice with a stomach catheter. The animal was sacrificed by decapitation at 0, 10, 20, or 30 min after the administration and the quick abdominal incision and ligation at the esophagus and pylorus were carried out. The isolated stomach was homogenized with 10 ml water. Enough water and a few drops of 1 N HCl were added to the homogenate to make 25 ml of homogenate of pH 1. After centrifugation of the homogenate for 3 min at 2500 rpm, 0.5 ml of the supernatant was analyzed for its quinine concentration.

(2) Gastric Emptying Rate of Quinine in Rats: Male Wistar rats weighing 240±30 g were used after normal feeding or 24-hr fasting. Five or ten ml/kg of test solution was given with a stomach catheter. The rats were sacrificed by decapitation at 0, 20, 40, or 60 min after the administration. Then the stomach with its content was removed and homogenized with 10 ml water. Ten drops of 1 N HCl, one drop of *n*-octyl alcohol and enough water were added to make 100 ml of homogenate. After centrifugation of the homogenate for 3 min at 3000 rpm, 0.5 ml of the supernatant was analyzed for its quinine concentration.

(3) Gastric Emptying Rate of Quinine or Phenol Red in Rabbits: Commercially available male albino rabbits were used. The rabbits, weighing 2.0—3.9 kg, were deprived of food but not water for 24 hr

7) E. Sögnen, *Acta Pharmacol. et Toxicol.*, **22**, 31 (1965); D.W. Northup and E.J. Van Liere, *J. Pharmacol. Exptl. Therap.*, **109**, 358 (1953); S. Consolo and S. Garattini, *Eur. J. Pharmacol.*, **6**, 322 (1969).

8) J.N. Hunt, M.T. Knox, and A. Oginski, *J. Physiol.*, **178**, 92 (1965); C.A. Chang, R.D. McKenna, and I.T. Beck, *Gut*, **9**, 420 (1968).

9) J.D. George, *Am. J. Digestive Diseases*, **13**, 376 (1968); G.H. Griffith, G.M. Owen, S. Kirkman, and R. Shields, *Lancet*, **I**, 1244 (1966); W.R.J. Middleton, and G.R. Thompson, *J. Lab. Clin. Med.*, **74**, 19 (1969).

10) B. Tennant, M. Reina-Guerra, D. Harrold, and M. Goldman, *J. Nutrition*, **97**, 65 (1969).

prior to dosing. Ten ml/kg of test solution was administered through a stomach catheter. The rabbits were anesthetized by bolus *i.v.* injection of 67 mg/kg Nembutal (pentobarbital sodium) at 0, 0.25, 0.5, 1.0, or 2.0 hr after oral administration of the test solution. (a) The stomach including its content was removed and homogenized with 200 ml water. Enough water was added to make 500 ml of homogenate, and 50 ml of this was again diluted with 150 ml of water. One or 20 ml of the diluted homogenate was analyzed for quinine or phenol red, respectively. (b) To determine the amount of quinine and phenol red in the fluid portion of the stomach, the contents were separated from the stomach tissue then centrifuged for 15 min at 3000 rpm. After its volume had been measured, this fluid portion was analyzed for quinine or phenol red. The solid portion of the stomach content was homogenized with the stomach tissue and the procedure described in (a) was carried out.

**Determination of Quinine and Phenol Red**——(1) Determination of Quinine: In the experiment on mice and rats, 2 ml of 2.5 N NaOH and 15 ml of water-saturated ether were added to 0.5 ml of sample solution, and the mixture was shaken for 10 min. After removal of the water layer, 10 ml of 0.1 N KOH was added to the ether layer. The mixture was shaken for 5 min and centrifuged for 5 min at 2500 rpm. Ten ml of the ether layer was taken into another vessel, and 7 ml of 0.1 N $H_2SO_4$ was added. The mixture was shaken for 10 min and centrifuged for 5 min at 2500 rpm before the ether layer was eliminated and the fluorescence intensity of the water layer was measured. The excitation and analysis wavelengths were 365 and 445 nm, respectively. The reference solution was prepared by the same procedure using quinine-free stomach with its content. The standard solution was a quinine solution of known concentration in 0.1 N $H_2SO_4$. In the experiment on rabbits, the same procedure was used but the amounts of all reagents were doubled since 1 ml of the sample solution was used instead of 0.5 ml.

(2) Determination of Phenol Red: Five ml of 10% $ZnSO_4 \cdot 7H_2O$ and 5 ml of 0.5 N NaOH were added to 20 ml of sample solution. After shaking and filtration, 5 ml of 1 N NaOH was added to 15 ml of the filtrate. The optical density of the solution was measured at 560 nm. The reference solution was made by adding 5 ml of 1 N HCl instead of 1 N NaOH to 15 ml of the filtrate.

Before the determination of quinine and phenol red, calibration curves were made by adding known amounts of the respective drugs to the excised stomachs of animals, and using the curves corrections were made for data obtained by the procedures (1) and (2).

## Results and Discussion

### Gastric Emptying in Mice, Rats, and Rabbits

**Gastric Emptying of Quinine in 24-hr Fasting and Control Mice**——Mean values of residual percentage of quinine in mouse stomach are shown in Table II. Under various conditions, the mean residual percentage decreased exponentially with time. Two sets of data are graphically shown in Fig. 1.

Table II. Remaining Percentage of Quinine in Stomach of Mice after Oral Administration

| Test soln. | Time in min | Control (normal feeding) mice Volume administered | | 24-hr fasting mice Volume administered | |
|---|---|---|---|---|---|
| | | 10 ml/kg | 20 ml/kg | 10 ml/kg | 20 ml/kg |
| Syrup | 0 | 93.1± 7.9(7)[a] | 90.5± 6.7(4) | 78.5± 9.9(7) | 81.5± 9.7(6) |
| | 10 | 82.7± 7.3(7) | 81.9± 6.9(4) | 68.0± 3.9(7) | 82.0±10.4(6) |
| | 20 | 63.8± 9.0(7) | 69.2±13.4(4) | 56.4±11.8(8) | 70.7± 5.4(6) |
| | 30 | 54.3± 8.4(7) | 65.7±18.3(4) | 48.8±10.6(7) | 64.7± 8.0(6) |
| Simple soln. | 0 | 89.0± 5.5(7) | 81.2± 8.6(4) | 69.9± 9.6(9) | 75.9± 8.0(6) |
| | 10 | 60.9±14.3(8) | 42.8±11.7(4) | 30.5±14.2(8) | 34.8±17.8(6) |
| | 20 | 53.7±15.4(7) | 46.0±13.1(4) | 13.3±10.7(6) | 24.0± 9.0(6) |
| | 30 | 40.7±12.0(7) | 28.9± 6.2(5) | 10.7± 5.9(6) | 12.5± 8.2(6) |

a) Mean ± S.D. (standard deviation). The figure in parentheses is the number of experiments.

**Gastric Emptying of Quinine in 24-hr Fasting and Control Rats**——Mean values of the residual percentage of quinine in rat stomach are shown in Table III. The mean residual amount of quinine decreased exponentially. Two sets of data are graphically shown in

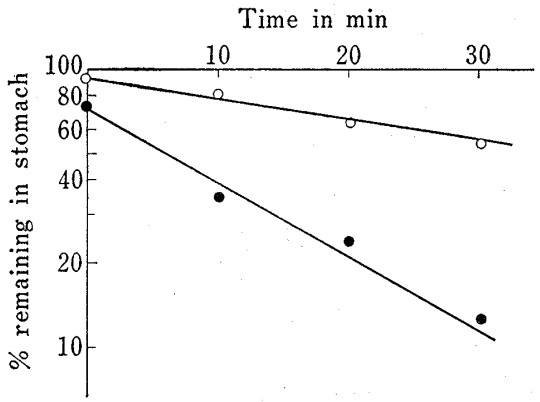



Fig. 1. Gastric Emptying of Quinine in Mice

—○—: Syrup, 10 ml/kg, control mice.
—●—: Simple soln., 20 ml/kg, 24-hr fasting mice.

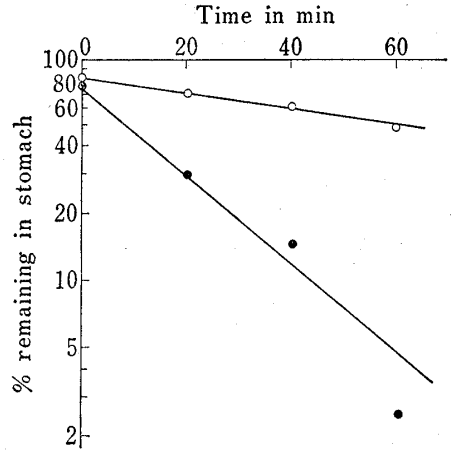



Fig. 2. Gastric Emptying of Quinine in Rats

—○—: Syrup, 5 ml/kg, control rats.
—●—: Simple soln., 10 ml/kg, 24-hr fasting rats.

TABLE III. Remaining Percentage of Quinine in Stomach of Rats after Oral Administration

| Test soln. | Time in min | Control (normal feeding) rats Volume administered | | 24-hr fasting rats Volume administered |
|---|---|---|---|---|
| | | 5 ml/kg | 10 ml/kg | 10 ml/kg |
| Syrup | 0 | 82.9±12.3(4) a) | 87.1± 7.2(6) | 84.2±12.0(6) |
| | 20 | 70.7± 6.1(4) | 79.0± 9.9(6) | 72.0±12.4(6) |
| | 40 | 60.9± 8.4(4) | 70.4± 8.6(6) | 61.0± 7.2(5) |
| | 60 | 49.2±11.9(4) | 66.5± 4.5(6) | 54.0± 3.7(7) |
| Simple soln. | 0 | 73.8±12.2(4) | 75.3±10.4(4) | 75.6± 9.4(6) |
| | 20 | 68.1± 5.3(4) | 46.3± 5.1(4) | 29.8± 8.5(3) |
| | 40 | 47.7± 5.1(4) | 36.4± 5.6(4) | 14.5± 4.9(6) |
| | 60 | 43.0±14.8(4) | 22.0± 6.8(4) | 2.5± 1.5(6) |

a) Mean ± S.D. (standard deviation). The figure in parentheses is the number of experiments.

Fig. 2. When the residual percentage took a very small value like 2.5% at the end of sampling time, the value did not fall on the regression line in semi-logarithmic plots.

**Gastric Emptying of Quinine and Phenol Red in 24-hr Fasting Rabbits**——Mean values of residual percentage of quinine and phenol red in rabbits stomach are shown in Tables IV and V. The significant differences between the estimated variances for most classes in Column (a) and those in column (b) were not observed by F-test ($p>0.10$). Furthermore, no significant differences between means in column (a) and those in column (b) were found by t-test ($p>0.10$). Therefore data in column (a) and (b) were summed up to give column (c). The drugs decreased exponentially with time as in the case of mice and rats. The gastric emptying of quinine and phenol red is graphically shown in Fig. 3 and Fig. 4, respectively.

Since the semi-logarithmic plots of the residual amounts of quinine and phenol red in the stomach gave straight lines as shown in Fig. 1—4, these drugs were assumed to be transferred into the small intestine approximately according to first-order kinetics. The mean residual percentage of the drugs at $t=0$ should be 100% theoretically, but the observed values were less than 100%. This was probably because that it took 30—60 seconds to ligate the esophagus and pylorus after the sacrifice of the animals. The intercepts of the straight lines shown in Fig. 1—4 seemed to depend upon the gastric emptying rate of the drugs in the early

TABLE IV. Remaining Percentage of Quinine in Stomach of 24-hr Fasting Rabbits after Oral Administration (10 ml/kg)

| Test soln. | Time in hr | (a) Quinine with phenol red | (b) Quinine without phenol red | (c) (a)+(b) |
|---|---|---|---|---|
| Syrup | 0 | — | 86.9±10.6(4) | 86.9±10.6(4) |
| | 0.25 | 71.9± 1.6(2)[a] | 62.8±10.6(4) | 65.9± 8.9(6) |
| | 0.50 | 79.0±21.1(6) | 55.4± 7.3(3) | 71.1±20.9(9) |
| | 1.00 | 60.7±17.9(6) | 59.7± 3.2(3) | 60.3±10.6(9) |
| | 2.00 | 38.7±12.9(6) | 28.9± 6.3(3) | 35.4±11.9(9) |
| Simple soln. | 0 | — | 82.7± 6.9(4) | 82.7± 6.9(4) |
| | 0.25 | 66.0± 1.1(2) | 63.7±20.8(4) | 64.5±15.9(6) |
| | 0.50 | 49.3± 7.7(6) | 46.6± 5.5(3) | 48.4± 6.8(9) |
| | 1.00 | 27.8± 9.6(6) | 34.4± 5.6(3) | 30.0± 8.7(9) |
| | 2.00 | 12.9± 8.0(6) | 21.3±15.3(3) | 15.7±11.3(9) |

a) Mean ± S.D. (standard deviation). The figure in parentheses is the number of experiments.

TABLE V. Remaining Percentage of Phenol Red in Stomach of 24-hr Fasting Rabbits after Oral Administration (10 ml/kg)

| Test soln. | Time in hr | (a) Phenol red with quinine | (b) Phenol red without quinine | (c) (a)+(b) |
|---|---|---|---|---|
| Syrup | 0 | 94.8± 3.9 (4)[a] | 100.2± 3.1(2) | 96.6± 4.4 (6) |
| | 0.25 | 80.0± 7.8 (6) | 84.7± 9.7(5) | 82.2± 8.2(11) |
| | 0.50 | 78.5±12.7(10) | 84.0± 7.8(5) | 80.3±11.6(15) |
| | 1.00 | 68.1±12.8(10) | 73.5± 8.0(5) | 69.9±11.3(15) |
| | 2.00 | 56.8±13.0(10) | 57.4±20.9(5) | 57.0±15.3(15) |
| Simple soln. | 0 | 97.9± 5.3 (4) | 92.3± 9.3(2) | 96.0± 6.8 (6) |
| | 0.25 | 73.9± 7.9 (5) | 76.0± 7.1(5) | 74.9± 7.7(10) |
| | 0.50 | 63.3±14.3(10) | 73.6± 5.4(5) | 66.7±13.0(15) |
| | 1.00 | 51.5±17.4(10) | 57.5±18.5(5) | 53.5±17.6(15) |
| | 2.00 | 43.5±17.2(10) | 41.7±10.1(5) | 42.9±14.9(15) |

a) Mean ± S.D. (standard deviation). The figure in parentheses is the number of experiments.

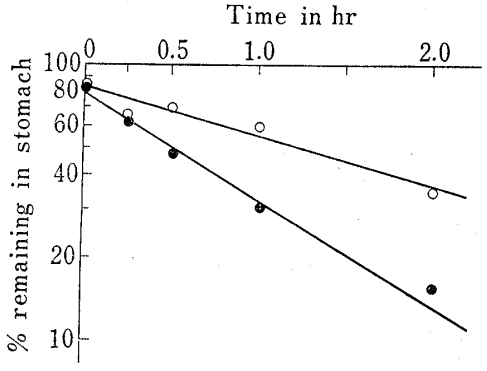



Fig. 3. Gastric Emptying of Quinine in Rabbits

—○—: Syrup, 10 ml/kg, 24-hr fasting rabbits.
—●—: Simple soln., 10 ml/kg, 24-hr fasting rabbits.

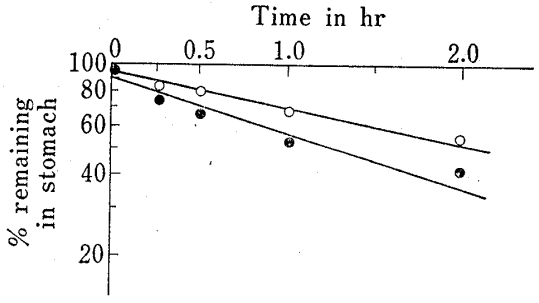



Fig. 4. Gastric Emptying of Phenol Red in Rabbits

—○—: Syrup, 10 ml/kg, 24-hr fasting rabbits.
—●—: Simple soln., 10 ml/kg, 24-hr fasting rabbits.

stage after dosing. Since the gastric absorption of quinine and phenol red was assumed to be negligibly small by the experimental data of Schanker, *et al.*,[11] a drug administered orally as solution seemed to be transferred to the small intestine at a relatively fast rate in the early stage and then gradually evacuated according to the first-order kinetics, though these rates were affected by other experimental conditions.

Therefore the residual percentage ($S_1$) of a drug in the stomach may be expressed by the following equation:

$$S_1 = \alpha \exp(-k_g t) \quad (1)$$

where $\alpha$ is the intercept of the regression line in semi-logarithmic plots, $k_g$ the first-order rate constant for the gastric emptying and t the time in hours after dosing. To find the best estimates of the parameters $\alpha$ and $k_g$, Equation 1 was fitted to the original data, which had given the mean values in Tables II—V, by least squares method[12] using a digital computer. The best estimates of the parameters with the standard errors are shown in Table VI. They were used to express the gastric emptying rates of drugs under various conditions and comparisons were made as follows.

Table VI. Parameters for Gastric Emptying in Mice, Rats, and Rabbits

| Species | Condition | Drug | (a) Syrup | | (b) Simple soln. | | (c) Ratio |
|---|---|---|---|---|---|---|---|
| | | | $k_{gI}$[a] ± S.E.[b] | $\alpha_I$[c] ± S.E. | $k_{gII}$ ± S.E. | $\alpha_{II}$ ± S.E. | $k_{gI}/k_{gII}$ |
| Mice | Non-fasting | Quinine 10 ml/kg | 1.10 ±0.12 (28)[d] | 94.8±2.7 | 1.57 ±0.22 (29) | 86.3±4.3 | 0.700 |
| | | Quinine 20 ml/kg | 0.690±0.208 (16) | 90.5±5.1 | 2.03 ±0.35 (16) | 76.7±5.6 | 0.340 |
| | 24-hr Fasting | Quinine 10 ml/kg | 0.968±0.164 (29) | 78.8±3.3 | 4.72 ±0.53 (29) | 69.6±3.3 | 0.205 |
| | | Quinine 20 ml/kg | 0.487±0.122 (24) | 84.1±3.0 | 3.83 ±0.48 (24) | 74.6±4.5 | 0.127 |
| Rats | Non-fasting | Quinine 5 ml/kg | 0.503±0.100 (16) | 83.3±4.2 | 0.579±0.124 (16) | 75.9±4.6 | 0.869 |
| | | Quinine 10 ml/kg | 0.283±0.056 (24) | 86.7±2.7 | 1.20 ±0.13 (16) | 74.2±3.4 | 0.236 |
| | 24-hr Fasting | Quinine 10 ml/kg | 0.454±0.073 (24) | 83.9±3.2 | 5.18 ±0.44 (21) | 75.4±2.5 | 0.088 |
| Rabbits | 24-hr Fasting | Quinine 10 ml/kg | 0.388±0.071 (37) | 82.9±4.7 | 0.945±0.095 (37) | 80.8±3.9 | 0.411 |
| | 24-hr Fasting | Phenol red 10 ml/kg | 0.243±0.032 (62) | 90.6±2.7 | 0.399±0.052 (61) | 85.2±3.6 | 0.609 |

*a*) $k_g$ (hr$^{-1}$): First order rate constant for gastric emptying.
*b*) S.E.: Standard error.
*c*) $\alpha$ (%): Calculated amount of drug in stomach at $t=0$.
*d*) The figure in parentheses is the number of experiments.

## Influence of Fasting

In mice and rats, 24-hr fasting increased the gastric emptying rate constant ($k_{gII}$) for the simple solution of quinine as shown in Column (b) of Table VI. The value for $k_{gII}$ in mice became 4.72 (hr$^{-1}$) from 1.57 (hr$^{-1}$) after the administration of 10 ml/kg of simple quinine solution, and 3.83 from 2.03 after 20 ml/kg. Similarly, 24-hr fasting in rats increased the rate constant and the value became 5.18 from 1.20 after 10 ml/kg dosing.

However, after administration of quinine syrup the effect of 24-hr fasting was scarcely observed in mice as shown in Column (a) of Table VI, where no significant differences were

11) L.S. Schanker, P.A. Shore, B.B. Brodie, and C.D.M. Hogben, *J. Pharmacol. Exptl. Therap.*, **120**, 528 (1957).
12) W.E. Deming, "Statistical Adjustment of Data," John Wiley and Sons, Inc., New York, 1946.

found both between 1.10 and 0.968 ($p>0.50$), and between 0.690 and 0.487 ($p>0.50$). Only a little difference was observed in rats between the constant for non-fasting and that for 24-hr fasting after 10 ml/kg dosing of the syrup ($p<0.20$). Ten or 20 ml/kg of 50% sucrose syrup seemed enough to cancel almost all the effect of 24-hr fasting in mice and rats.

**Influence of Volume**

In rats, an increased volume of the simple solution administered gave a larger gastric emptying rate constant, $k_{gII}$. The value of $k_{gII}$ increased from 0.579 ($hr^{-1}$) for 5 ml/kg to 1.20 ($hr^{-1}$) for 10 ml/kg. Such a distinct effect was not observed in mice, though in non-fasting mice, $k_{gII}$ for 20 ml/kg was slightly larger than that for 10 ml/kg as shown in Table VI. Therefore the decreasing effect of the larger volume of the syrup administered, shown in column I of Table VI for non-fasting or 24-hr fasting mice and rats, was not due to the volume administered itself, but due to the increased amount of sucrose which caused a high osmotic pressure in the stomach.

**Species Difference**

After dosing with the simple quinine solution, no significant difference was found between mice and rats. The values of $k_{gII}$ after 10 ml/kg dosing in non-fasting mice and rats were 1.57 and 1.20, and in 24-hr fasting ones 4.72 and 5.18 ($hr^{-1}$), respectively. In 24-hr fasting rabbits the value was 0.945, which was considerably lower.

After administration of quinine syrup, the gastric emptying rate constant, $k_{gI}$, was 0.968, 0.454, and 0.388 ($hr^{-1}$) for 24- hr fasting mice, rats, and rabbits, respectively; and the value for mice was approximately twice that for rats and rabbits. In non-fasting mice, the value of $K_{gI}$ was also larger than that for rats after 10 ml/kg dosing as shown in Table VI.

**Gastric Emptying Rate Constant after Administration of Syrup**

In all the experimental animals examined, oral administration of syrup caused a delayed gastric emptying rate, except in the case of 5 ml/kg syrup administration to rats. All the values for the ratio of $k_{gI}$ to $k_{gII}$ are shown in column III of Table VI. When 10 ml/kg of the syrup was administered to 24-hr fasting animals the ratio, $k_{gI}/k_{gII}$, was 0.411 in rabbits, 0.205 in mice, and 0.088 in rats, *i. e.*, the most profound effect was in rats. This effect decreased as the administered volume decreased, and 5 ml/kg of quinine syrup in non-fasting rats had no significant decreasing effect on the gastric emptying rate. This suggests that the effect of syrup in other species would also be hardly detectable after administration of a volume (ml/kg) less than that used in these experiments especially under a non-fasting condition.

The delayed gastric emptying rate with syrup solution which has a high osmotic pressure, is assumed to subsequently retard the overall gastrointestinal absorption of a drug which is mainly absorbed from the intestine. On the other hand, the fluid content in the upper part of the small intestine of 24-hr fasting mice, rats, and rabbits showed about twofold isotonicity 5 min after administration of 10 ml/kg of quinine syrup, though the isotonicity of the fluid content after simple quinine solution dosing was almost equal to or slightly less than unity. Accordingly, the delayed absorption of drugs from the gastrointestinal tract by syrup dosing seems to be caused by the decreased gastric emptying rate, and partially by the decreased intestinal absorption rate from a hypertonic solution of a drug.

**Difference of Gastric Emptying Rate between Quinine and Phenol Red**

As shown in Table VI, the gastric emptying rate of phenol red in simple solution or syrup was slower than that of quinine in rabbits. After phenol red and quinine had been simultaneously administered orally to rabbits, the gastric content of the sacrificed animal was centrifuged and drugs in the liquid and the solid portions were determined. The results are shown in Table VII.

Table VII. Difference of Distribution in Gastric Contents between Quinine and Phenol Red

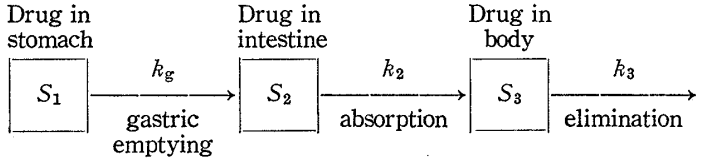
| Test soln. | Gastric contents | Drug | Remaining percentage 0.5 (hr) | 1.0 (hr) | 2.0 (hr) |
|---|---|---|---|---|---|
| Simple soln. | Liquid portion | Quinine | 29.2±4.7[a)] | 12.0±4.8 | 3.1± 1.2 |
| | | Phenol red | 15.4±3.1 | 7.7±4.5 | 4.5± 1.7 |
| | Solid portion | Quinine | 17.9±5.0 | 15.4±6.3 | 7.2± 5.2 |
| | | Phenol red | 30.9±1.7 | 29.5±1.9 | 24.9±10.1 |
| Syrup | Liquid portion | Quinine | 36.6±6.6 | 34.8±9.4 | 17.4± 5.9 |
| | | Phenol red | 12.9±2.9 | 12.3±5.0 | 8.6± 2.1 |
| | Solid portion | Quinine | 27.7±4.8 | 16.8±4.0 | 17.8± 3.8 |
| | | Phenol red | 53.7±6.2 | 41.5±2.6 | 41.9± 7.9 |

a) Mean ± S.E. (standard error), $n=3$.

Table VII indicates that the distribution of quinine in the gastric content was different from that of phenol red, *i.e.*, the residual percentage of quinine in the liquid portion was larger than that of phenol red, while in the solid portion, it was smaller. These tendencies were observed both with the simple solution and syrup administration experiments. The results in Tables VII and VI suggest that drugs co-administered are not always distributed homogeneously in the stomach, and that the drug in the liquid portion is more readily transferred to the small intestine than that in the solid portion. Therefore the gastric emptying rates of drugs should sometimes be distinguished from the emptying of the gastric content itself.

## Influence of Gastric Emptying Rate on Drug Level in the Body

In order to evaluate the influence of the gastric emptying rate on intestinal absorption of drugs, the time course of the drug level in the body was calculated according to Chart 1 and the following equation:




$$t=0:\ S_1=\frac{\alpha}{100}D^0,\ S_2=\frac{(100-\alpha)}{100}D^0$$

Chart 1. Model for Gastrointestinal Absorption

$k_g$, $k_2$, $k_3$: First-order rate constants for the respective rate processes.
$S_1$, $S_2$, $S_3$: Amount of the drug in the respective compartments.
$D^0$: Drug dose.

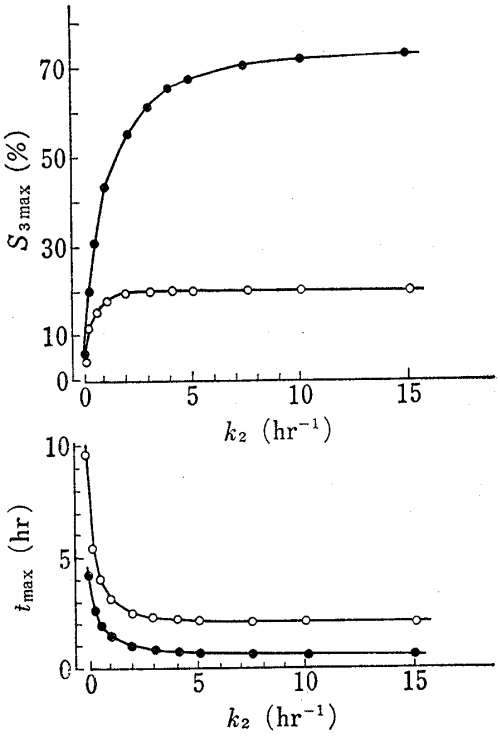



Fig. 5. Maximum Levels of Drugs in the Body and $t_{max}$ after Oral Administration

—●—: Simple soln., $k_g=5.2$ ($hr^{-1}$), $\alpha=75$ (%), $k_3=0.693$ ($hr^{-1}$).
—○—: Syrup, $k_g=0.240$ ($hr^{-1}$), $\alpha=91$ (%)., $k_3=0.693$ ($hr^{-1}$).
For further details, see text.

$$S_3=D^0k_gk_2\left\{\frac{1}{(k_g-k_2)(k_g-k_3)}\exp(-k_gt)+\frac{1}{(k_2-k_g)(k_2-k_3)}\exp(-k_2t)\right.$$
$$\left.+\frac{1}{(k_3-k_g)(k_3-k_2)}\exp(-k_3t)\right\}-\frac{(100-\alpha)D^0}{100}\left\{\frac{k_gk_2}{(k_g-k_2)(k_g-k_3)}\exp(-k_gt)\right.$$
$$\left.+\frac{k_2k_2}{(k_2-k_g)(k_2-k_3)}\exp(-k_2t)+\frac{k_2k_3}{(k_3-k_g)(k_3-k_2)}\exp(-k_3t)\right\} \quad (2)$$

where $D^0$ is the dose, and $k_g$, $k_2$, and $k_3$ are the first-order rate constants defined in Chart 1. The constants $k_g$ and $\alpha$ have the same meaning as those in Equation 1.

The drug level in the body, $S_3$, was calculated both for the fast and the slow gastric emptying rate constants. The maximum value of $S_3$ ($S_{3max}$) and the time for $S_{3max}$ ($t_{max}$) were plotted as a function of $k_2$, as shown in Fig. 5. For the $k_3$ value, 0.693 ($hr^{-1}$) was used because in experimental animals many drugs have short biological half-lives of less than 2 hours.[13]

Fig. 5 indicates that in the case of fast gastric emptying of a drug, *i.e.*, $k_g$=5.2 ($hr^{-1}$) and $\alpha$=75 (%), the drug level in the body after oral administration is scarcely influenced by $k_2$ in the region where $k_2$ is greater than about 4 ($hr^{-1}$), and that in the case of slow gastric emptying, *i.e.*, $k_g$=0.24 ($hr^{-1}$) and $\alpha$=91 (%), $S_{3max}$ and $t_{max}$ are affected by $k_2$ only in the region where $k_2$ is less than 2 ($hr^{-1}$). Thus, gastric emptying of drugs should be considered as an important factor in gastrointestinal absorption before the intestinal absorption characteristics themselves are evaluated.

13) J. Watanabe, *Ann. Rept. Pharm. Nagoya City Univ.*, **23**, 1 (1975).