Relationship between Enhancement of Plasma Level of Aminopyrine by Barbital and Stomach Emptying Pattern

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Abstract □ The significantly increased plasma level of aminopyrine after simultaneous administration of barbital was recognized previously using rabbits. An increased rate of gastric emptying of aminopyrine induced by barbital could be considered as a likely reason for such a positive effect of barbital. A sample solution containing a known quantity of phenol red was given, and the total gastric content was withdrawn through a vinyl tube passed into the rabbit stomach at 0.5 and 2 hr. The calculated values from the measurement should provide precise information as to the state in the stomach. It was concluded that aminopyrine suppresses the transfer of phenol red to the duodenum, and simultaneously administered barbital can eliminate the effect of aminopyrine on the gastric emptying of phenol red and reduce the gastric emptying time of aminopyrine.

Keyphrases □ Stomach emptying pattern—relationship to aminopyrine plasma level enhancement by barbital, rabbits □ Barbital-induced enhancement of aminopyrine plasma levels—relationship to stomach emptying pattern, rabbits □ Aminopyrine plasma levels, barbital-induced enhancement—relationship to gastric emptying rates, phenol red transfer in duodenum, rabbits □ Gastric emptying rates—relationship to barbital-induced increase of aminopyrine plasma levels, rabbits

In the previous experiment (1) using rabbits, the significantly increased plasma level of aminopyrine was observed at the initial stage after oral administration of a mixture of aminopyrine and barbital as compared with the single administration of aminopyrine. To explain this phenomenon, the potentiality of complexation between aminopyrine and barbital in the process of absorption, metabolism, distribution, and excretion was checked in detail (1). Unexpectedly, it was concluded that the complexation phenomenon has no direct effect upon this process.

In the present investigation, attention was focused on the change in the gastric emptying rate of drugs induced by simultaneous administration, since the rate of transfer of a drug to the duodenum may have a remarkable influence on the overall rate and extent of drug absorption and the plasma level of the drug.

EXPERIMENTAL

Procedure—The experimental animals, three male rabbits, were fasted for 24 hr. but given water freely. A vinyl tube (5 mm. × 30 cm.) was passed into the rabbit's stomach, and 50–100 ml. of warm water (37°) was instilled. The fluid was rapidly withdrawn by suction with a syringe. This procedure was repeated five times and then the stomach content was removed as completely as possible. After washing, 100 ml. of isotonic solution containing the drugs and marker (phenol red) was instilled into the stomach through the vinyl tube as rapidly as possible. When mixing of the sample solutions in the rabbit's stomach was completed by moving the syringe vertically, 1 ml. of the sample solution was collected and the starting time of the experiment was recorded. The sample solution was analyzed, and the initial concentration of phenol red (c_0) and the initial volume of gastric content (v_0) were calculated. Then the vinyl tube was removed.

Table I—Composition of Sample Solutions Used

Number of Sample	Component: Phenol Red, mg.	Component: Aminopyrine, mg.	Component: Barbital, mg.	Preparation
1	10	—	—	Adjusted to pH 6.8 with $NaHCO_3$ and made to 100 ml. with 0.9% NaCl
2	10	900	—	
3	10	900	300	
4	10	—	300	
5	10	—	—	0.1 *N* HCl containing 0.9% NaCl added to 100 ml.
6	10	900	—	
7	10	900	300	
8	10	—	300	

After 0.5 or 2 hr., the vinyl tube was passed into the stomach again and the gastric content was withdrawn immediately (concentration of phenol red and volume of gastric content put as c_1 and v_1, respectively). One hundred milliliters of warm water was injected into the stomach through the vinyl tube to remove any residual gastric content. This washing was recovered and the volume of a residual gastric content was calculated from its phenol red concentration (c_2). The residual volume (v_2) was calculated from Eq. 1:

$$v_2 = \frac{100c_2}{c_1 - c_2} \qquad \text{(Eq. 1)}$$

The rabbits were used repeatedly at intervals of 7 days.

Administered Solution—The sample solutions used had the compositions shown in Table I.

Determination of Phenol Red—Four milliliters of 1% NaOH was added to 1 ml. of the sample solution. The color of the solution changed immediately to reddish purple; absorbance was measured at 550 nm. using a spectrophotometer[1].

Determination of Aminopyrine—The analytical method described previously was applied (1, 2).

Calculation of Values—The equations proposed by Hunt and Spurrell (3, 4) and Gloor and Heinkel (5) were used as summarized by Mizuno (6).

The residual amount of phenol red (*PR*, in mg.) at the end of the experiment:

$$PR = c_1(v_1 + v_2) \qquad \text{(Eq. 2)}$$

The residual percentage of phenol red ($PR\%$) at the end of the experiment:

$$PR\% = PR/c_0v_0 \times 100 \qquad \text{(Eq. 3)}$$

[1] Hitachi EPU-2A.

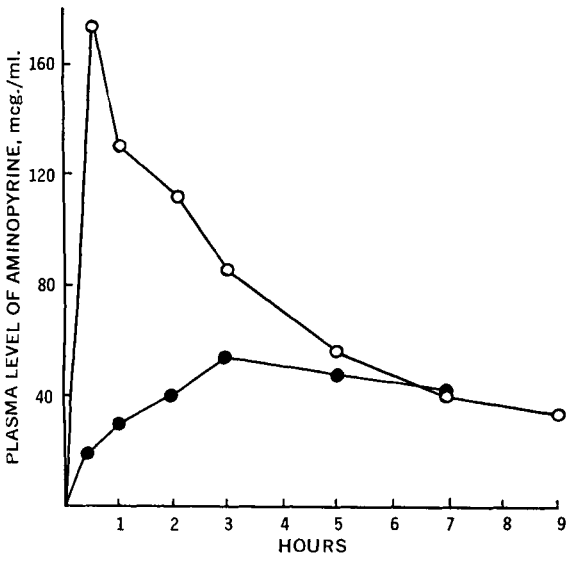

Figure 1—*Typical plasma level of aminopyrine after its oral administration in rabbits. Key: ●, 255 mg./kg. aminopyrine in solution; and ○, 255 mg./kg. aminopyrine and 85 mg./kg. barbital in solution.*

The volume of gastric content leaving the stomach during the experimental period (v_e, in ml.):

$$v_e = \frac{c_0 v_0 - PR}{(c_0 + c_1)/2} \qquad \text{(Eq. 4)}$$

The volume of gastric juice secreted during the experimental period (v_s, in ml.):

$$v_s = v_1 + v_2 + v_e - v_0 \qquad \text{(Eq. 5)}$$

Intraperitoneal Administration of Barbital—An intraperitoneal aqueous solution of barbital was prepared to contain 40 mg. of barbital in 5 ml. isotonic solution and injected intraperitoneally into rabbits. Then 100 ml. of 0.01% phenol red solution, with or without 600 mg. aminopyrine, was administered orally 20 min. after injection. The gastric contents were withdrawn after 0.5 or 2 hr. and naalyzed as previously indicated.

RESULTS AND DISCUSSION

In a previous study (1), it was demonstrated in rabbits that barbital (85 mg./kg.) given in the form of a solution significantly raised the plasma level–time curve for aminopyrine (255 mg./kg.) and also decreased the time required for attaining its maximum plasma level (Fig. 1). On the other hand, *in vitro* and *in vivo* experiments (1), consisting of an intestinal recirculation perfusion method, a circulation method using the isolated rat intestine, an everted intestine method, a ligated stomach method, and measurement of the urinary excretion rate of intact aminopyrine, revealed that

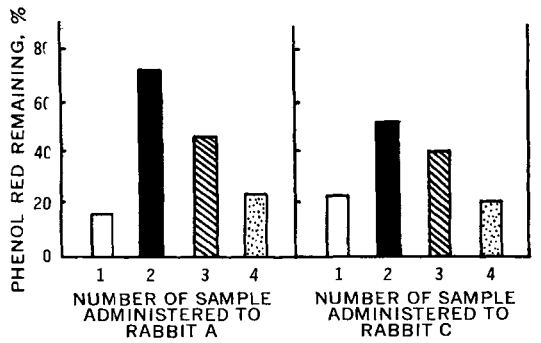

Figure 2—*Percentage of phenol red recovered from stomach 0.5 hr. after ingestion (pH 6.8). Refer to Table I for the numbers noted on the abscissa.*

Table II—Initial Volume of Gastric Content Measured Immediately after Introducing 100 ml. Phenol Red Solution

Rabbit	Rabbit Weight, kg.	Volume (ml.) of Gastric Content—No. of Experiment— 1	2	3	4	5	6	Mean
A	2.7	128	115	130	117	116	132	123
B	2.5	124.5	115.9	108.2	117.4	116	110	115.3
C	2.8	115.4	129.5	120	122.8	128	124	123.3

Table III—Transit Volume of Gastric Content to Duodenum and Secretion Volume of Gastric Juice[a] during 30 min.

Rabbit	pH of Solution	Volume (ml.) of Gastric Content or Gastric Juice—Administration with— Control	Aminopyrine	Barbital	Mixture
A	6.8	163.5 (62.5)	25.8 (5.6)	118.4 (45.5)	99.3 (26.3)
B	6.8	120.6 (41.6)	75.3 (20.0)	128.2 (27.4)	119.7 (44.4)
C	6.8	113.5 (78.7)	69.5 (22.2)	146.4 (74.2)	88.7 (39.5)
A	1.2	105.0 (46.8)	37.7 (26.2)	115.0 (52.0)	78.3 (29.3)
B	1.2	94.5 (73.4)	74.2 (8.5)	102.8 (64.0)	83.0 (30.5)

[a] Secretion volume of gastric juice is given in parentheses.

barbital hardly causes any noticeable changes in the process of absorption, metabolism, and excretion of aminopyrine. It may be reasonable to suppose that the physiological condition could be changed by simultaneously administered barbital. Particularly, barbital may in part participate in the function of the stomach. Chiou *et al.* (7) called attention to the changes in gastric emptying rates of drugs induced by additives. And Feldman *et al.* (8) reported that sodium deoxycholate decreased considerably the gastric emptying of phenol red in rats; they proposed that a large and substantial secretion of gastric juice induced by sodium deoxycholate into the gastric pouch caused the increase in gastric volume and the decrease in gastric emptying rate. The effect of additives on gastric emptying of a drug may be explained by considering several possible mechanisms. But no detailed investigation into these mechanisms was made in the present study.

Table II lists the results of an incidental experiment on the volume of the gastric content taken out and measured immediately after giving the phenol red solution and stirring the gastric content. It was found that the volume of gastric content at the initial time was almost constant; that is, the volume of solution that remained in and could not be removed from the stomach after washing was limited to 15–30 ml. in these three rabbits.

The residual percentages of phenol red in the stomach 0.5 and 2 hr. after ingestion are shown in Figs. 2 and 3. As is obvious from

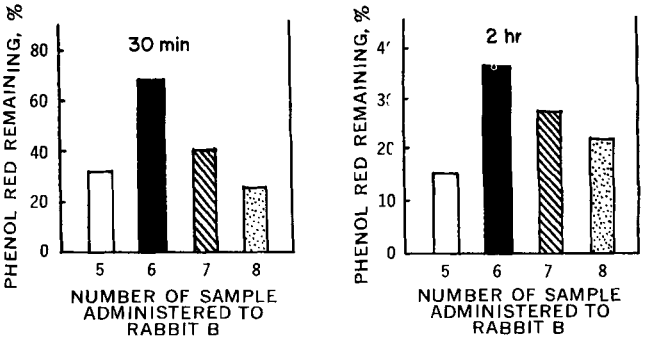

Figure 3—*Percentage of phenol red recovered from stomach 0.5 hr. and 2 hr. after ingestion (pH 1.2); these figures show the representative examples. The same trial was done repeatedly and the same tendency was observed in many experimental results. Refer to Table I for the numbers noted on the abscissa.*

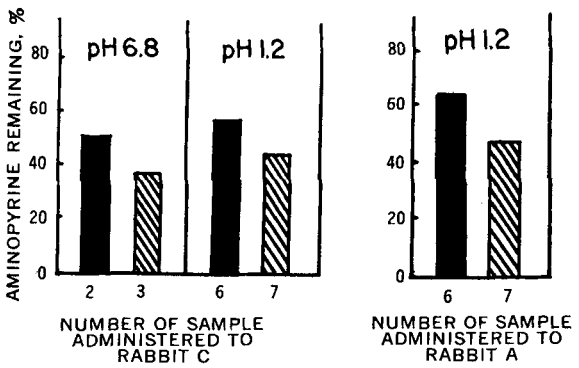

Figure 4—*Percentage of aminopyrine recovered from stomach 0.5 hr. after ingestion. Refer to Table I for the numbers noted on the abscissa.*

these graphs, aminopyrine inhibits the gastric emptying of phenol red. Barbital has almost no effect on the gastric emptying, and the residual percentage obtained after administration of a mixture of the two drugs is intermediate between those of aminopyrine and barbital. Such a tendency was also observed in the experiment using an acidic solution (pH 1.2) (Fig. 3). Since the percentage decrease of phenol red used as a marker is considered proportionate to the amount of drugs moving into the duodenum, it is suggested from the experimental results that aminopyrine inhibits the emigration of aminopyrine itself and, on the other hand, that barbital removes such an inhibiting effect of aminopyrine. The residual percentages of aminopyrine in the stomach were also determined (Fig. 4).

Since Schanker *et al.* (9) and Hogben *et al.* (10) showed that aminopyrine was not absorbed through the stomach of man and rat, the aminopyrine solution should transfer into the intestine as soon as possible to facilitate absorption. Therefore, it is advisable to administer barbital simultaneously to obtain a higher blood level of aminopyrine at the initial stage. Naito *et al.* (11) stated that caffeine could promote aminopyrine absorption. This experimental fact also may be explained in a similar manner.

If the kinetic consideration is applicable to this experiment, an exponential pattern of emptying of phenol red may be observed as reported by Hunt and Spurrell (3); a detailed discussion will follow in a later publication.

It is possible to calculate the volume of the gastric content transfered to the duodenum using Eq. 4; the values are shown in Table III. It is obvious that aminopyrine has an inhibiting effect on the emptying of the gastric content. When a mixture of two drugs had been given, the volume of the gastric content at 30 min. was intermediate between those of aminopyrine and barbital. Furthermore, the presence of aminopyrine obviously diminished the secretion of gastric juice. The values calculated from Eq. 5 are listed in Table III.

Since Chiou *et al.* (7) reported that the rabbit stomach is specific and scarcely reaches the state of empty even after fasting for 24 hr., the possibility of drug–residual food binding in the rabbit stomach will also be considered in a future report as an explanation of the previous result (1).

As an additional experiment, phenol red solution, with or without aminopyrine, was administered orally 20 min. after intraperitoneal injection of barbital (Table IV). When the administration route of barbital is different, barbital has no effect on the decrease in the gastric emptying rate to be induced by aminopyrine. Therefore, it may be proposed that the possible mechanism of barbital consists in a direct effect on the gastric mucosa or the musculature of the gastric pouch which controls the rate of gastric emptying.

Table IV—Percentages of Phenol Red Remaining in Stomach after Intraperitoneal Administration of Barbital

Rabbit	Oral Administration[a] of Phenol Red[b] with Aminopyrine	Oral Administration[a] of Phenol Red[b] without Aminopyrine	Time of Withdrawal, hr. after Oral Administration
B[c]	35.4	8.9	2
C	70.5	30.0	0.5

[a] pH of administration solution was 1.2. [b] Twenty minutes after intraperitoneal administration. [c] Refer to Fig. 3 for the percentages in case of no administration of barbital.

SUMMARY

The gastric emptying rate of a marker (phenol red) in a mixture with aminopyrine was significantly lower than in the case of the marker alone. Barbital had almost no effect on the gastric emptying of the marker. In simultaneous oral administration of two drugs, the gastric emptying rate of the marker was an intermediate between those of aminopyrine and barbital. The effect of aminopyrine and barbital on gastric emptying was also indicated in the calculation of emigration volume of the gastric content to the duodenum and the secretion volume of gastric juice during 30 min. It was concluded that the increased plasma level of aminopyrine induced by oral administration of barbital may be explained by the change in the gastric emptying rate.

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