Effect of Carbonated Beverages and of an Antiemetic Containing Carbohydrate and Phosphoric Acid on Riboflavin Bioavailability and Salicylamide Biotransformation in Humans

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Abstract □ Two carbohydrate–phosphoric acid solutions, one a widely used beverage (Solution C) and the other a pharmaceutical product used as an antiemetic (Solution E), administered together with riboflavin-5′-phosphate or salicylamide to healthy human adults, significantly increased the bioavailability of riboflavin and appreciably altered the metabolic fate of salicylamide (increased conversion to the sulfate and decreased formation of the glucuronide). A beverage containing phosphoric acid but no carbohydrates (Solution T) also increased the bioavailability of riboflavin but not as much as Solution C. These effects are attributed to a decrease of the gastric emptying rate caused by carbohydrates and phosphoric acid, consistent with the empirical use of Solution C syrup and Solution E as antinauseants and antiemetics. The results demonstrate also that the choice of beverage to be taken with medication can affect the bioavailability and/or metabolic fate of medicinals with saturable absorption and/or biotransformation characteristics.

Keyphrases □ Phosphoric acid and phosphoric acid–carbohydrate solutions—effect on riboflavin bioavailability and salicylamide biotransformation in humans □ Carbohydrate–phosphoric acid solutions—effect on riboflavin bioavailability and salicylamide biotransformation in humans □ Gastric emptying rates—effects of phosphoric acid and phosphoric acid–carbohydrate solutions, riboflavin bioavailability and salicylamide biotransformation in humans □ Antiemetic effect—carbohydrate–phosphoric acid solutions

A recent study in humans showed that caffeine contained in a proprietary carbonated beverage (Solution C[1]) is absorbed much more slowly from this beverage than from coffee or tea (1). Solution C contains sucrose and phosphoric acid, both of which inhibit gastric emptying (2, 3). A proprietary antinauseant and antiemetic product (Solution E[2]) also contains sugars and phosphoric acid (and no other active ingredients) and has been found to reduce the amplitude and rate of contraction of isolated strips of rabbit GI smooth muscle (4). Solution C syrup is widely used as an antiemetic, apparently on an empirical basis. Because of these findings, it was considered likely that Solution C (and other widely used beverages with similar ingredients) can inhibit significantly the rate of gastric emptying in humans and that the antiemetic properties of Solution C syrup and Solution E may be due to an inhibition of gastric motility produced by the carbohydrates and phosphoric acid.

The primary purposes of this investigation were to determine if Solution C can modify the absorption of concomitantly administered medicinal agents and to assess the relative contribution of carbohydrates and phosphoric acid to such an effect. The availability of a carbohydrate-free cola beverage, Solution T[3], otherwise practically identical to Solution C in composition (Table I), facilitated such an assessment. A secondary purpose was to obtain some indication of the mechanism whereby Solutions E and C exert an antiemetic effect; the remarkable similarity in the composition of these products (Table I) suggests that they act by an identical mechanism.

The medicinal agents utilized, riboflavin and salicylamide, were chosen because the bioavailability of the former and the metabolic fate of the latter are strongly affected by their absorption rate. Riboflavin is absorbed by a specialized, saturable process, apparently located in the proximal region of the small intestine (5–7). Large doses are almost completely recovered in the urine following parenteral injection (8, 9) and are only partially absorbed upon oral administration (5–7). Food, viscous solutions, hypothyroidism, and anticholinergic drugs increase the absorption of riboflavin, apparently by decreasing the rate of gastric emptying and thereby prolonging the residence time of riboflavin at specialized absorption sites in the proximal region of the small intestine (10–13).

Salicylamide is eliminated in humans by biotransformation to the sulfate and glucuronide and by formation of gentisamide (14). The formation of the sulfate conjugate is a saturable process of very low capacity; the fraction of a dose of salicylamide converted to salicylamide sulfate increases, therefore, with the decreasing rate of absorption (14). These pronounced nonlinear pharmacokinetic characteristics make riboflavin and salicylamide ideal agents for a safe, noninvasive, and convenient indirect determination of possible changes of the gastric emptying rate in humans. If a beverage such as Solution C can modify the bioavailability of riboflavin and the metabolic fate of salicylamide in humans, it is likely to have a similar effect on other medicinal agents with saturable absorption or biotransformation characteristics.

EXPERIMENTAL

Five healthy male volunteers, 26–38 years old, capable by education and experience to give their informed consent (research assistants and associates), participated in the study. They did not take any vitamins or drugs for 1 week before and during the experiments. They were given 41 mg of riboflavin-5′-phosphate (equivalent to 30 mg of riboflavin) in the morning on an empty stomach and did not eat for the next 4 hr. The vitamin was dissolved in 60 ml of water, 450 ml of water, 60 ml of Solution E, or 450 ml of So-

[1] Coca-Cola.
[2] Emetrol, W. H. Rorer Co., Fort Washington, Pa.
[3] Tab.

Table I—Composition of Solutions C, T, and E

Solution C[a]		Solution T[a]		Solution E[b]	
Sucrose	48.0 g	Saccharin	0.147 g	Invert sugars syrup	45.0 g
Phosphoric acid	0.25 g	Phosphoric acid	0.25 g	Phosphoric acid	0.18 g
Caffeine	0.056 g	Caffeine	0.064 g	Glycerin	7.5 g
Flavor and color		Flavor and color		Flavor, color, and preservative	
Water *q.s.*	450 ml	Water *q.s.*	450 ml	Water *q.s.*	60 ml
pH 2.5		pH 2.8		pH 1.5–1.6	

[a] Coca-Cola USA, Atlanta, Ga., personal communication. [b] Reference 4.

Table II—Effect of Solutions C and T on Riboflavin[a] Bioavailability

	Percent of Dose Excreted in Urine								
	4 hr			24 hr			36 hr		
Subject	Water	Solution C	Solution T	Water	Solution C	Solution T	Water	Solution C	Solution T
H	14.8	28.6	16.6	20.5	38.9	25.3	23.4	40.5	30.3
L	6.9	22.6	—	10.6	34.1	—	12.4	36.0	—
O	8.5	23.0	12.1	16.0	32.9	25.2	18.4	34.5	28.5
S	7.6	12.8	—	16.6	27.2	—	18.9	30.9	—
Y	4.8	21.9	11.1	10.5	32.8	19.5	11.5	35.4	23.5
Mean	8.5	21.8	13.3	14.8	33.2	23.3	16.9	35.5	27.4
SD	3.8	5.7	2.9	4.3	4.2	3.3	4.9	3.4	3.5
Statistical significance of difference from control (*p* value)[b]		<0.005	<0.05		<0.001	<0.05		<0.005	<0.025

[a] Riboflavin-5′-phosphate, 41 mg, administered orally in 450 ml of water, Solution C, or Solution T. [b] Paired *t* test.

lution C according to a modified Latin-square experimental design. The solutions were at room temperature and the container was rinsed with 10 ml of water, which was also ingested. Three of the subjects also took riboflavin in 450 ml of Solution T, the sugar-free equivalent of Solution C.

In the second part of this investigation, the five subjects were given 1 g of salicylamide in four hard gelatin capsules with 450 ml of Solution C or water, in crossover fashion, in the morning on an empty stomach. The subjects did not eat for 4 hr and collected urine according to the same protocol as was used in the riboflavin study. All experiments were carried out at 1-week intervals.

Each subject emptied his bladder immediately before vitamin or drug administration and then collected urine every 30 min for 4 hr, every hour for the next 4 hr, every 2 hr until bedtime, and then at desired intervals for up to 36 hr (riboflavin study) or 24 hr (salicylamide study). The subjects were allowed to drink 50–100 ml of water after each urine collection to facilitate urine flow, except during the first 2 hr of the Solution C and T studies and during the 1st hr of the Solution E study when no fluids were permitted.

Urine containing riboflavin was collected in brown polyethylene bottles, and 5 ml of 25% acetic acid was added. All urine samples were stored in a refrigerator. They were assayed fluorometrically for riboflavin (6, 7) and for total salicylamide, salicylamide glucuronide, salicylamide sulfate, and gentisamide as described previously (14). All data were corrected for physiological excretion rates of riboflavin (based on a 12-hr urine collection) and for apparent salicylamide blank values (based on −1 to 0-hr urine samples). A separate experiment with Solution C alone established that ingestion of this beverage did not increase the blank values of urine.

RESULTS

The results of the study of the effects of Solutions C and T on the bioavailability of riboflavin are summarized in Table II. An example of the time course of the urinary excretion rates of riboflavin in the three experiments in an individual subject is presented in Fig. 1. The bioavailability of riboflavin was increased by 110%, from 16.9 to 35.5% of the dose on the average, by administration with Solution C. Solution T caused an average increase in bioavailability of 60%, *i.e.*, from 17.8 to 27.4% of the dose.

The data for Solution E are summarized in Table III, and an individual example of the time course of riboflavin excretion rates with and without Solution E is presented in Fig. 2. The bioavailability of riboflavin was increased by 70%, from 18.0 to 30.7% of the dose. The one subject (O) who did not show an increase in bioavailability with Solution E experienced nausea after taking the solution.

Because of the difference in the volume of Solutions C and E, different controls (riboflavin-5′-phosphate in 60 and 450 ml of water, respectively) were used in the two studies. There was no statistically significant difference in bioavailability of riboflavin from the two aqueous solutions.

There was a strong ($r = -0.938$) and statistically highly significant ($p < 0.001$) negative correlation between the bioavailability of riboflavin in control experiments and the increase in bioavailability obtained with Solutions C and E. Both sets of data could be fitted to the same regression line (Fig. 3). A similar negative relationship was observed for Solution T but with a much different slope,

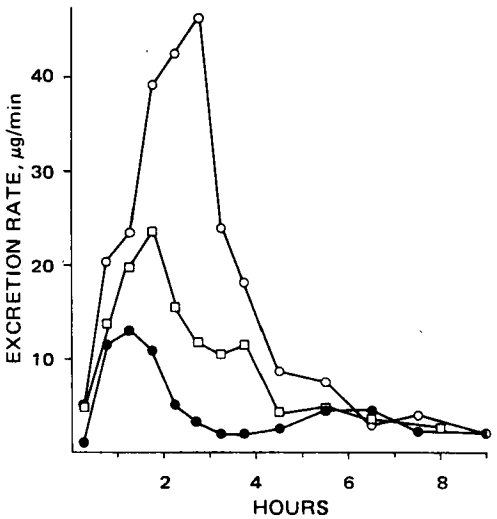

Figure 1—*Time course of urinary excretion rate of riboflavin after oral administration of 41 mg of riboflavin-5′-phosphate in 450 ml of water (●), Solution T (□), or Solution C (○). Data are for Subject Y.*

Table III—Effect of Solution E on Riboflavin[a] Bioavailability

Subject	Percent of Dose Excreted in Urine					
	4 hr		24 hr		36 hr	
	Water	Solution E	Water	Solution E	Water	Solution E
H	9.1	22.3	15.6	31.8	17.8	34.0
L	4.3	20.5	8.3	33.8	11.4	37.3
O	9.2	13.3	17.9	17.9	20.2	20.1
S	7.3	19.0	19.4	29.2	21.6	31.6
Y	10.4	17.8	16.9	26.6	19.0	30.3
Mean	8.1	18.6	15.6	27.9	18.0	30.7
SD	2.4	3.4	4.3	6.2	3.9	6.5
Statistical significance of difference from control (p value)[b]		<0.01		<0.05		<0.05

[a] Riboflavin-5′-phosphate, 41 mg, administered orally in 60 ml of water or Solution E. [b] Paired t test.

consistent with the smaller effect of this carbohydrate-free solution on riboflavin availability.

The results of the study of salicylamide biotransformation are summarized in Table IV. The total recovery of salicylamide metabolites was essentially quantitative and identical in the control and Solution C experiments. Administration of salicylamide with Solution C caused a statistically significant increase in the formation of the sulfate conjugate and a decrease in the glucuronide fraction. The change in the gentisamide fraction was not statistically significant. The maximum urinary excretion rate of salicylamide sulfate increased from 1.25 ± 0.45 mg of salicylamide equivalent/min in the control experiments to 2.11 ± 0.29 mg/min in experiments with Solution C ($p < 0.001$). The time of occurrence of maximum excretion rates of salicylamide sulfate was 1.05 ± 0.27 hr in the controls, and it was 1.65 ● 0.42 hr in experiments with Solution C ($p < 0.05$).

There was a strong ($r = -0.934$) and statistically significant ($p < 0.025$) negative correlation between the maximum excretion rate of salicylamide sulfate in control experiments and the increase in that rate with Solution C (Fig. 4). A similar negative correlation was found with respect to the fraction of the dose excreted as salicylamide sulfate ($r = -0.768$), but it was not statistically significant because of one unusual value. There was no apparent correlation between the relative increase in riboflavin bioavailability and in the fraction of salicylamide sulfate produced by concomitant administration of Solution C in the individual subjects ($r = 0.177$).

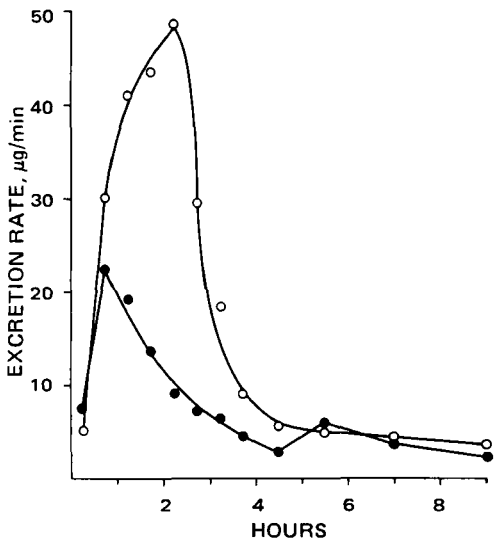

Figure 2—*Time course of urinary excretion rate of riboflavin after oral administration of 41 mg of riboflavin-5′-phosphate in 60 ml of water (●) or Solution E (○). Data are for Subject H.*

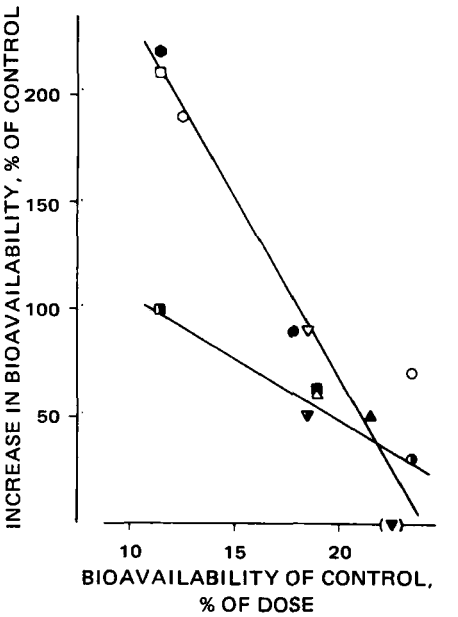

Figure 3—*Relationship between the bioavailability of riboflavin in control experiments (60 or 450 ml of water) and the increase in bioavailability upon administration of the vitamin in Solution C (open symbols), Solution E (solid symbols), and Solution T (half-open symbols). Each subject is represented by a differently shaped symbol. The symbol in parentheses was excluded in the regression analysis.*

DISCUSSION

Gastric emptying can be a major determinant of the drug absorption rate, and individual variations in the rate of drug absorption from any one dosage form may be due largely to differences in the rate of gastric emptying (15). The very slow absorption of caffeine from Solution C, relative to its absorption from coffee and tea (1), suggested that this beverage may have a pronounced inhibitory effect on gastric emptying. This supposition was strengthened by the fact that two major ingredients of Solution C, sugar and phosphoric acid, are known to inhibit gastric emptying in hu-

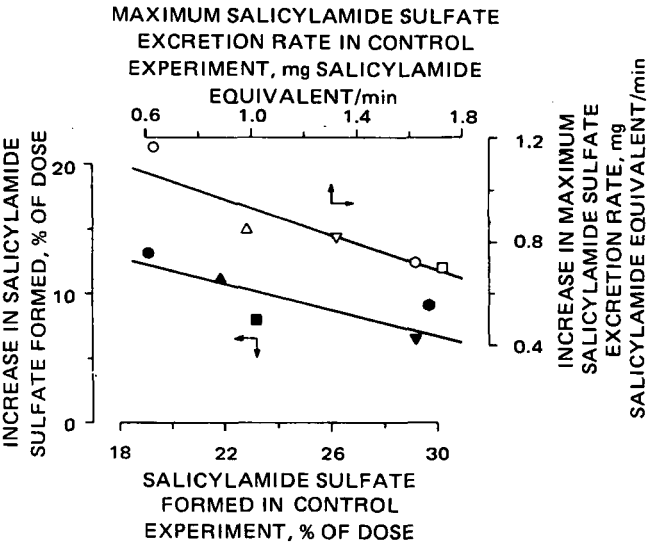

Figure 4—*Relationship between* (a) *the percent of the dose of salicylamide converted to the sulfate in control experiments and the increase in this value in the experiments with Solution C (solid symbols), and* (b) *the maximum excretion rate of salicylamide sulfate in control experiments and the increase of this rate in the experiments with Solution C (open symbols). Each subject is represented by a differently shaped symbol.*

Table IV—Effect of Solution C on the Metabolic Fate of Salicylamide[a]

	Urinary Recovery, % of Dose							
	Total Metabolites		Salicylamide Glucuronide		Salicylamide Sulfate		Gentisamide	
Subject	Control	Solution C	Control	Solution C	Control	Solution C	Control	Solution C
H	98.1	93.4	69.0	52.2	19.2	32.1	10.0	9.0
L	98.7	101.6	59.4	57.6	29.4	39.6	9.8	4.4
O	96.9	97.2	56.3	53.4	28.4	34.9	12.2	8.9
S	99.2	98.1	71.4	57.3	21.8	32.9	5.9	7.9
Y	90.6	94.9	61.3	55.6	23.2	31.1	6.1	8.1
Mean	96.7	97.0	63.5	55.2	24.4	34.1	8.8	7.7
SD	3.1	3.1	6.5	2.3	4.4	3.4	2.7	1.9
Statistical significance of difference from control (p value)[b]		N.S.		<0.05		<0.001		N.S.

[a] Salicylamide, 1 g, in gelatin capsules, followed by 450 ml of water or Solution C. [b] Paired t test.

mans (2, 3). The similarity of the composition of Solutions C and E, an antiemetic product, provided additional indirect support for this theory and suggested that the mechanism of the antiemetic effect of both products is an inhibition of gastric motility.

A change in the gastric emptying rate can, by modifying the rate of absorption, alter the time course of drug concentrations in the body. If drug biotransformation involves one or more saturable processes, changes in drug absorption kinetics can alter the metabolic fate of a drug (16). Examples of such absorption rate-dependent quantitative changes in biotransformation are the conjugation of salicylamide with sulfate (14) and the acetylation of p-aminobenzoic acid (17) and p-aminosalicylic acid (18). It is appropriate, therefore, to assess possible effects of beverages, diseases, drugs, and other modalities on the gastric emptying rate in terms of their pharmacokinetically most relevant aspects: the magnitude of change in the absorption and biotransformation of drugs with saturable absorption or biotransformation characteristics. This purpose was served by riboflavin and salicylamide in this investigation.

The results of this investigation demonstrate that the type of beverage taken with a medicinal agent may modify appreciably its absorption. This can obviously affect the onset, intensity, and time course of drug action. An additional implication, although speculative, is that the beverage taken with drug products in bioavailability studies may affect the results obtained *relative* to the standard product. It is known, for example, that a decrease in GI motility can bring about an increase in the bioavailability of incompletely absorbed digoxin tablets while having no effect on the bioavailability of a digoxin solution (19). Small differences in pH or agitation intensity can have a pronounced effect on the relative dissolution rate of a drug in different tablet formulations (20, 21). Changes in the gastric emptying rate will affect the length of time of exposure of tablets to the low pH and mild agitation conditions of the gastric environment and the much higher pH and more intensive agitation in the small intestine.

Finally, the results of this study show that both Solutions C and E inhibit gastric motility and suggest that this may be the mechanism of their antiemetic effect. The effectiveness of Solution T, which contains phosphoric acid but no sugars, and the greater effectiveness of Solution C show that both sugar and phosphoric acid contribute significantly to the inhibition of gastric emptying observed in this investigation.

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