Table II—Results of Fitting Model [a] to the *CV versus l/d* Data for Four Powders and Two Fillers

Powder	Estimate of A	Estimate of B_1	p-Value for H_0:$B_1 = 0$	p-Value for H_0:$B_2 = 0$	Sum of Squared Observations	Sum of Weighted Squared Deviations about the Model
Zinc acetate [b]	0.361	1.43	0.0001	0.83	145.50	4.99
Erythromycin [b]	0.277	1.40	0.0016	0.91	19.97	2.91
Pooled data from zinc acetate and erythromycin [b]	0.294	1.47	0.0001	0.76	187.96	8.09
All four [c]	0.408	0.94	0.0001	0.37	2.63	0.55
All four [d]	0.347	1.29	0.0001	0.73	195.84	10.86

[a] Model from Eq. 5. [b] Filled with Model LM-14, Perry Industries, Inc., Hicksville, N.Y. [c] Filled with Model E-1200, Perry Industries, Inc., Hicksville, N.Y. [d] Combinations of powders filled with Model LM-14 or Model E-1200, Perry Industries, Inc., Hicksville, N.Y.

The shape of the curve describes several things about the characteristics of vacuum/purge fillers. It indicates that, in most cases, a powder plug l/d ratio ≥ 1.5 will yield acceptably small fill-weight variances. It indicates, further, that as the l/d ratio decreases to <1.5, powder-filling precision rapidly becomes worse and is extremely sensitive to l/d ratio changes. This is logical since the exposed surface area becomes a much greater percentage of the total surface areas as the l/d ratio decreases. It also indicates that when the l/d ratio rises >1.5, precision approaches a nonzero limiting value. This asymptote predicts that efforts to increase weight control through port (or component) changes in this region will go unrewarded.

It could be speculated that the validity of the entire approach rests on the assumption of a constant packed powder density. A variable packed density could lead to random variation in fill weight which would confound any model. To examine this, data in Table I were used. These density data are shown in two sections: one with a constant d value and one when l is constant. When d is constant and l increases, density does not significantly change. When l is constant and d increases, density does not change either. Thus, the implicit assumption of constant density used in the model development is valid.

This provides a basis for selecting the length for a filling port of preset diameter from a design curve, thereby eliminating the necessity for large-scale experimental testing of different port sizes. Given the bulk density of a powder or a mixture of powders and the required fill weight, one may use the design curve to determine the port length yielding acceptable process weight control for any preset port diameter (l/d ratio of ~ 1.5 is a good general choice). In addition, the curve allows prediction of fill-weight variances given a fixed port length. The model has been established with a large data base, it fits the data well, and it satisfies engineering constraints.

For powders similar to those used in this work, the design curve can be used as is. For powders with significantly different characteristics, a few data points will allow the curve to be established. In any such operation, various l/d ratios producing the desired fill weight should be established, then the model (Eq. 5) fitted to the data with nonsignificant terms deleted. If very high l/d ratios are used, Ce^x should be added to the model, where C is to be estimated. A plot of the data with the fitted curve will then allow a reasonable choice of the l/d ratio.

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Antacid Effects on the Gastrointestinal Absorption of Riboflavin

STUART FELDMAN[x] and WYATT HEDRICK

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Abstract □ The effect of aluminum hydroxide, magnesium hydroxide, and a combination of aluminum–magnesium hydroxide suspensions on the oral absorption of riboflavin was examined in five subjects. Coadministration of aluminum hydroxide or magnesium hydroxide suspension with riboflavin (30 mg) resulted in an increase in time of peak urinary excretion rate of riboflavin when compared with control studies. There was no increase in the peak excretion rate or total urinary excretion of riboflavin when the antacid-treated subjects were compared to the control studies. *In vitro* experiments indicated that significant binding of riboflavin to the aluminum hydroxide and magnesium hydroxide suspensions occurred. The results of the present investigation are consistent with the reported effect of aluminum ion on GI motility and the known influence of gastric emptying on the absorption of riboflavin from the GI tract.

Keyphrases □ Absorption, GI—antacid effects on riboflavin □ Riboflavin—antacid effects on GI absorption □ Antacids—effects on the GI absorption of riboflavin

Antacids are a therapeutic class of drugs which have great potential for drug absorption interactions. Since they may be purchased over-the-counter, they are widely used by the public and may be taken concurrently with many other drugs. Antacids have been reported to alter the GI absorption of a number of drugs through the formation of

Table I—Time to Peak Riboflavin [a] Excretion Rate in Control and Antacid-Treated Subjects

Subject	Control, hr	Aluminum–Magnesium Hydroxide, hr	Aluminum Hydroxide, hr	Magnesium Hydroxide, hr
A	2.25	1.75	2.25	1.75
B	0.75	2.25	2.25	2.25
C	1.25	1.25	2.25	2.75
D	0.75	1.25	2.25	1.75
E	2.25	0.75	2.75	2.25
Mean	1.45	1.45	2.35[b]	2.15[b]
SD	0.75	0.57	0.22	0.41

[a] The riboflavin dose was 30 mg. [b] $p < 0.05$, ANOVA and Dunnett multiple comparison test (8).

Table II—Peak Excretion Rate of Riboflavin [a] in Control and Antacid-Treated Subjects

Subject	Control, μg/hr	Aluminum–Magnesium Hydroxide, μg/hr	Aluminum Hydroxide, μg/hr	Magnesium Hydroxide, μg/hr
A	2394	2811	2826	2337
B	673	1476	822	1391
C	1247	653	1301	1512
D	787	1437	1010	2176
E	631	552	968	800
Mean	1146	1386	1386	1643
SD	739	904	824	624

[a] The riboflavin dose was 30 mg.

complexes (1), alterations in gastric pH (2), and changes in the rate of gastric emptying (2, 3).

It was shown (2) that aluminum hydroxide gel delayed the GI absorption of pentobarbital sodium in the rat by retarding gastric emptying. A similar effect of aluminum hydroxide gel has been shown (4) to alter the rate of disappearance of [^{51}Cr]sodium chromate from the stomach of leukemic children. In the five patients studied, administration of aluminum hydroxide gel slowed the mean maximal emptying rate from 5.1 to 1.8%/min. Effects of other antacids or combinations of antacids on gastric emptying have not been well documented.

The present investigation examines the influence of commercially available preparations of aluminum hydroxide, magnesium hydroxide, and an aluminum–magnesium hydroxide combination on the GI absorption of riboflavin in humans. The suitability of riboflavin to study the effect of antacids on gastric emptying stems from the fact that riboflavin is absorbed by a specialized transport system (5) in the proximal portion of the small intestine, and alterations in gastric emptying can produce significant changes in the rate and extent of riboflavin absorption from the GI tract (6, 7).

EXPERIMENTAL

Subjects—Five healthy male subjects (age 22–30 years; weight, 66–81 kg) volunteered for the study and gave written, informed consent. No vitamin preparations were taken for at least 1 month prior to and during the course of the study. The study was conducted over a period of 4 consecutive weeks in a randomized, crossover manner with each subject receiving riboflavin[1] control, riboflavin with aluminum–magnesium hydroxide oral suspension[2], riboflavin with aluminum hydroxide gel[3], or riboflavin with magnesium hydroxide oral suspension[4].

Riboflavin Absorption Study—After an overnight fast, each subject ingested 50 ml of water 1 and 0.5 hr prior to the administration of the drug. At the time of riboflavin administration, the bladder was voided and 30 mg of riboflavin was suspended in water and ingested in a total volume of 100 ml. This dose of riboflavin was utilized in other studies of riboflavin absorption in humans (5) and reflected alterations in gastric emptying patterns. Total urine samples were collected in plastic bags[5] at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 16 hr after administration of riboflavin and at convenient intervals up to 36 hr after taking the drug. Food was not ingested for 4 hr following administration of the riboflavin dose. Fifty milliliters of water was ingested after each urine sample for as long as necessary to maintain adequate urinary output. Glacial acetic acid (3 ml/100 ml of urine) was added for stability purposes. The urine samples were stored in a refrigerator or freezer until assayed. Blank urinary excretion rates of riboflavin were obtained from 2- to 4-hr urine samples collected on the day prior to the experiment.

Antacid–Riboflavin Absorption Study—One hour before administration of riboflavin, 50 ml of water was ingested. One-half hour before administration of the drug, 20 ml of either aluminum hydroxide gel or aluminum–magnesium hydroxide suspension, or 10 ml of magnesium hydroxide suspension was ingested with either 30 or 40 ml of water. At the time of riboflavin ingestion, 20 ml of aluminum hydroxide or aluminum–magnesium hydroxide or 10 ml of magnesium hydroxide followed by 30 mg of riboflavin suspended in a total volume of 100 ml of water was ingested. The collection procedure was identical to that followed for the riboflavin control samples. The antacid dose was chosen to represent minimum dosages according to label directions. A lower dose of magnesium hydroxide was necessary to minimize the possibility of a laxative effect from magnesium hydroxide. At least 1 week separated each of the riboflavin absorption studies.

Assay—After suitable dilution, the urine samples were assayed using a modified USP assay for riboflavin (5), and fluorescence was measured on a filter fluorimeter[6].

Binding Studies—Various volumes of each antacid suspension were added to two different concentrations (1.6 and 4.9 μg/ml) of riboflavin in glass bottles. These concentrations reflected the low solubility of riboflavin in aqueous solution and represented only an approximation of *in vivo* levels. The resulting suspensions were shaken in a water bath[7] at 37° for at least 30 min. Equilibrium was established by repetitive sampling. The suspensions were centrifuged[8] in warm (40°) centrifuge tubes for 2 min at 3000 rpm, and the supernatant solution was assayed for riboflavin content by the described assay method.

RESULTS AND DISCUSSION

One measure of gastric emptying rate is the time to peak urinary excretion rate of an oral dose of riboflavin. Peak excretion rate data for the five subjects studied are presented in Table I. The data, when analyzed by ANOVA and the Dunnett test (8), reveal that coadministration of aluminum hydroxide gel or magnesium hydroxide suspension with the riboflavin suspension results in a significant ($p < 0.05$) increase in the time to peak excretion rate.

The data for the peak urinary excretion rate of riboflavin in the control- and antacid-treated subjects are presented in Table II. The coadministration of the antacid mixtures with the riboflavin suspension results in a slight increase in the mean peak urinary excretion rates of riboflavin, but these data were not significantly different from control values.

The percent urinary recovery of riboflavin for the control and in the presence of each antacid studied for each subject is presented in Table III. Control riboflavin urinary recovery ranged from 12.1 to 38.0% of the 30-mg dose with a mean value of 21.4 ± 9.3%. Examination of the data in Table III reveals no change in the percent of riboflavin dose excreted in urine following concomitant administration of the antacids.

Typical plots of the urinary excretion rate of riboflavin *versus* time in one subject for each experiment are presented in Fig. 1. Administration of aluminum hydroxide gel results in a significant delay in the excretion peak time rate of riboflavin when compared with control values. This is consistent with the reported activity of Al^{3+} as a smooth muscle relaxant (9). The smooth muscle relaxing effect of aluminum hydroxide would reduce the gastric emptying rate and, therefore, result in a delay in the time until riboflavin reached its absorption site in the small intestine.

[1] Eastman Kodak Co.
[2] Maalox, W.H. Rorer Co.
[3] Amphojel, Wyeth Laboratories.
[4] Milk of Magnesia, C. H. Phillips Co.
[5] Whirl-Pak, 18 oz., Nasco Co.
[6] Turner Fluorimeter, model 111, G. K. Turner Associates Inc.
[7] Precision model 25 Water Bath Shaker, Precision Scientific.
[8] IEC, model HN-S centrifuge.

Table III—Percent Dose of Riboflavin [a] Excreted in Urine in Control and Antacid-Treated Subjects [b]

Subject	Control	Aluminum–Magnesium Hydroxide	Aluminum Hydroxide	Magnesium Hydroxide
A	38.0	43.7	29.1	31.1
B	12.1	23.2	15.6	24.9
C	24.0	12.5	20.1	28.7
D	13.6	23.4	16.1	23.8
E	19.4	21.8	24.1	19.9
Mean	21.4	24.9	21.0	25.7
SD	9.3	10.2	5.1	3.9

[a] The riboflavin dose was 30 mg. [b] Cumulative amount of riboflavin excreted per dose × 100.

Under these conditions, coadministration of aluminum hydroxide gel should result in a significant increase in the peak urinary excretion rate of riboflavin, since decreased gastric emptying would lead to a decrease in the rate in which the vitamin reaches the absorption site in the small intestine and, thereby, result in an increase in peak absorption rate (5–7). If this were the case, an increase in riboflavin bioavailability in the presence of aluminum hydroxide gel would be expected. Table III indicates that this is not the case. The mean percent riboflavin urinary recovery in control studies was 21.4%, while the percent recovery in aluminum hydroxide treated subjects was 21.0%. A possible explanation for this occurrence is presented in Table IV, which lists the percent riboflavin bound as a function of antacid and riboflavin concentration in the *in vitro* studies. As can be seen from this table, in the *in vitro* experiment, riboflavin binding to the aluminum hydroxide suspension (50%) at an initial riboflavin concentration of 1.6 μg/ml was 30.9% and was 26.9% at a riboflavin concentration of 4.9 μg/ml. If binding occurs *in vivo*, it could potentially reduce the total amount of riboflavin available for absorption and result in no apparent net change in the amount of riboflavin excreted in urine in the presence of aluminum hydroxide suspension when compared with control experiments.

Administration of magnesium hydroxide suspension to the five subjects also resulted in a significant alteration in the time to peak excretion rate,

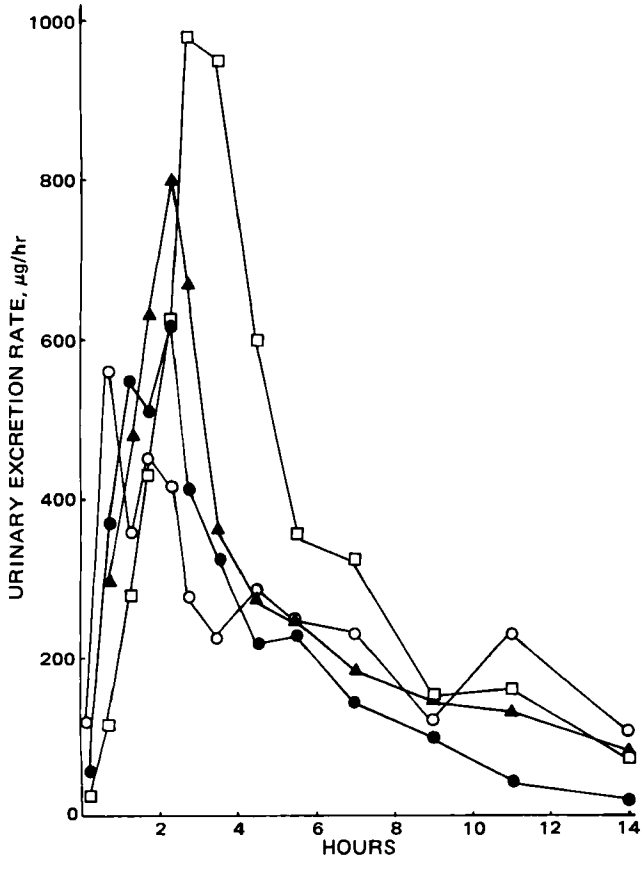

Figure 1—*Urinary excretion rate of riboflavin as a function of time in subject E for control (●), aluminum–magnesium hydroxide (○), magnesium hydroxide (▲), and aluminum hydroxide (□) treatments.*

Table IV—Percent Riboflavin Bound as a Function of Riboflavin and Antacid Concentration

Antacid [a]	Initial Concentration of Riboflavin, μg/ml 1.6	4.9
Aluminum–magnesium hydroxide (50)	10.9 ± 1.4 [b]	11.8 ± 1.0
Aluminum–magnesium hydroxide (17)	2.7 ± 0.7	2.4 ± 0.5
Aluminum hydroxide (50)	30.9 ± 0.8	26.9 ± 1.6
Aluminum hydroxide (17)	4.1 ± 0.4	5.7 ± 0.4
Magnesium hydroxide (50)	83.0 ± 0.8	80.8 ± 0.4
Magnesium hydroxide (17)	53.3 ± 1.7	68.3 ± 0.9

[a] Numbers in parentheses are the percent of v/v liquid antacid used. The total volume was 30 ml. [b] Percent riboflavin bound; mean ± *SD* of five determinations.

with no change in peak excretion rate and the amount of riboflavin excreted in the urine. However, an increase in peak rate and extent of riboflavin excretion was noted in four of the five subjects studied. It was shown in rats (3) that magnesium hydroxide suspension can decrease gastric emptying through an effect on gastric fluid volume. Of additional interest is the percent riboflavin bound to magnesium hydroxide suspension in the *in vitro* studies presented in Table IV. In a 50% magnesium hydroxide suspension, ~83% of a 1.6-μg/ml riboflavin solution was bound, while 81% of a 4.9-μg/ml solution was bound. This high percentage of binding could reduce substantially the dose of riboflavin available at the GI absorption site. Further experiments would be necessary to support this possibility.

There was no apparent effect of coadministration of the magnesium–aluminum hydroxide combination suspension on riboflavin absorption from the GI tract. This was surprising in view of the effects of both aluminum hydroxide and magnesium hydroxide on the pattern of riboflavin absorption in humans. One possible explanation is the Al^{3+} dose contained in each dosage form. The total dose of aluminum hydroxide gel administered contained 2.56 g of aluminum hydroxide (10), while the aluminum–magnesium hydroxide combination contained 1.8 g of aluminum hydroxide (10). However, the magnesium hydroxide dose was identical (1.6 g) in both the combination antacid and magnesium hydroxide suspension (10). Since no dose–effect relationship of the antacid dose to riboflavin absorption has been studied, other possibilities cannot be ruled out. However, it was shown (3) that of a series of aluminum-containing antacids studied, only aluminum hydroxide gel produced significant concentrations of aluminum ion capable of altering gastric emptying after reaction with acid. This reportedly is due to the relatively low pH (4.5) of the aluminum hydroxide antacid compared with the pH (7.2) of the aluminum–magnesium hydroxide combination. The relatively low degree of binding (~11%) of riboflavin to the combination antacid product (Table IV) should be noted.

The results of the present investigation reveal an alteration in the absorption profile of a drug that is reported to be absorbed by a specialized process in the upper portion of the small intestine when the drug is administered with aluminum hydroxide gel or magnesium hydroxide suspension. While additional work needs to be done in relation to the effect of dose and dosing regimen, it is apparent that antacids can influence the absorption pattern of a specialized transport drug, the effect being dependent upon type of antacid or product administered and the degree of drug binding.

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