Effect of an Anticholinergic Agent on Riboflavin Absorption in Man

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Abstract □ Oral administration of the anticholinergic drug propantheline bromide to healthy adult males 30–60 min. before an oral dose of 150 mg./m.² riboflavin (as the phosphate) delayed the absorption of the vitamin but caused a pronounced increase in the total amount absorbed. This is attributed to delayed gastric emptying and slower transit of riboflavin solution through the small intestinal lumen due to the anticholinergic effect of propantheline. It is suggested that concurrent administration of an anticholinergic agent may also have a marked effect on the bioavailability of drugs that are ordinarily not completely absorbed.

Keyphrases □ Riboflavin absorption after oral administration—effect of concurrent administration of anticholinergic agent (propantheline bromide), man □ Anticholinergic agent (propantheline bromide)—effect on riboflavin absorption, man □ Bioavailability of incompletely absorbed drugs—effect of concurrent anticholinergic administration □ Propantheline bromide—effect on riboflavin absorption after concurrent oral administration

Relatively large doses of riboflavin and riboflavin-5′-phosphate are absorbed incompletely due to the limited capacity of the specialized absorption process for this vitamin in the human small intestine (1–3). Food (2–4), bile salt (5), and a viscous vehicle (6) enhance absorption; the absence of bile due to biliary obstruction decreases the absorption of riboflavin (7). It has been suggested that these effects may be secondary to a change in gastric emptying and intestinal transit rates since the extent of absorption of riboflavin would be affected by its residence time at specialized intestinal absorption sites. To explore this possibility, the effect of an anticholinergic agent (which decreases gastric emptying and intestinal transit rates) on riboflavin absorption has now been determined.

EXPERIMENTAL

Five healthy male volunteers received 150 mg. riboflavin as riboflavin-5′-phosphate/m.² body surface area. The vitamin was dissolved in 200 ml. water and taken orally in the morning on an empty stomach. No food was permitted for 4 hr. In other experiments, the subjects received 30 mg. propantheline bromide[1] 30–60 min. before ingestion of the vitamin solution. Three of the five subjects also took 30 mg. propantheline bromide the night before. The control and propantheline experiments were carried out in crossover fashion at least 1 week apart. Urine was collected every 30 min. initially and then at longer intervals for a total of 36 hr. Total riboflavin was determined fluorometrically as described previously (2); the data were corrected for normal physiologic riboflavin excretion, which was determined from 12–24-hr. "blank" collections of urine.

The subjects did not take any drugs or vitamin preparations for at least 1 week before and during the absorption experiment. Studies were done also on one subject who had taken 15 mg. propantheline bromide three times a day for over 1 year. He took 30 mg. of the drug 30 min. before the riboflavin test. Another riboflavin absorption test was carried out in this subject 24 hr. after discontinuation of propantheline; he resumed his regular dosing schedule 24 hr. after vitamin ingestion (*i.e.*, after a total of 48 hr. without propantheline).

[1] Pro-Banthine tablets, 15 mg., Searle.

RESULTS AND DISCUSSION

The results of this study are summarized in Table I. The urinary excretion data reflect the rate and extent of riboflavin absorption, since this vitamin is recovered almost completely in the urine after parenteral administration (8, 9). The excretion of riboflavin during the first 30 min. after ingestion was significantly reduced by propantheline, but the total amount recovered in 36 hr. was considerably larger after propantheline administration. The intersubject variation in the bioavailability of riboflavin was smaller in the experiments with propantheline (Table I).

Figures 1 and 2 are representative examples of the time course of riboflavin excretion with and without prior administration of propantheline. Figure 1 shows the pronounced absorption-delaying effect of the anticholinergic agent, while Fig. 2 illustrates particularly the great difference in the duration of absorption.

A riboflavin absorption experiment in a 32-year-old male subject who had been taking 15 mg. propantheline bromide three times a day for over 1 year due to a duodenal ulcer resulted in the recovery of 11.3% of the dose in 36 hr.; the "control" experiment, 24 hr. after discontinuation of the medication, yielded 9.0% of the dose of riboflavin in the urine after 36 hr. The high recovery of riboflavin in the "control" experiment on this subject suggests that the anticholinergic effect of propantheline may last for a considerable time after discontinuation of a regular and prolonged dosage regimen.

The results of this study reflect the inhibitory effect of propantheline on gastric emptying and on intestinal transit rate. The anticholinergic action of this drug was clearly evident to all subjects;

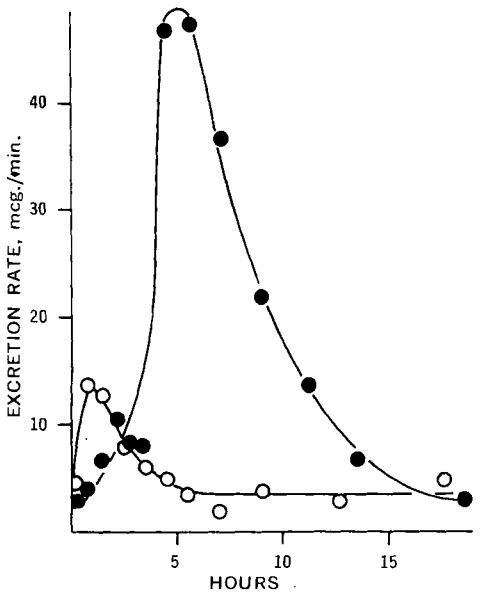

Figure 1—*Effect of propantheline on riboflavin absorption: urinary excretion rate of riboflavin as a function of time after oral administration of 150 mg./m.² riboflavin as the phosphate on an empty stomach. Key: ○, control; and ●, after propantheline; Subject O. Note the crossover of the two curves 2.5 hr. after riboflavin administration.*

Table I—Effect of Propantheline on Riboflavin Absorption in Man

Subject	Age, years	Weight, kg.	Dose of Propantheline Bromide, mg. p.m.	Dose of Propantheline Bromide, mg. a.m.	Percent of Riboflavin Dose Excreted 30 min. Control	30 min. Propantheline	24 hr. Control	24 hr. Propantheline	36 hr. Control	36 hr. Propantheline
G	22	65	30	30	0.752[a]	0.254[a]	2.21	6.07	3.43	6.44
K	26	66	—	30	0.191	0.123	2.65	6.79	3.36	7.38
L	43	85	30	30	0.054	0.023	1.28	10.6	1.48	11.2
O	27	73	30	30	0.044	0.029	2.72	6.58	5.25	8.27
S	27	81	—	30	0.047	0.012	3.49	6.0	4.69	6.75
Mean					0.084	0.047	2.47	7.21	3.64	8.01
Coefficient of variation, %					84.2	109	32.8	26.6	40.1	24.0
Statistical significance[b]					$p < 0.05$		$p < 0.02$		$p < 0.05$	

[a] Percent excreted in 2 hr., not included in the mean and in the statistical analysis. This subject was not able to void until 2 hr. after riboflavin ingestion in the control experiment. [b] By paired *t*-test.

they noted a pronounced "dry mouth" within about 30 min. which lasted usually for 4–6 hr. It is proposed that the increased absorption of riboflavin due to propantheline is the result of prolonged contact of the vitamin with specialized absorption sites in the small intestine. The decreased gastric motility and emptying rate cause the riboflavin solution to leave the stomach at a slower rate and over a longer period of time. This permits prolonged and more extensive interaction between the vitamin and its specialized absorption sites. Similar effects have been noted in certain diseases which modify GI motility (10).

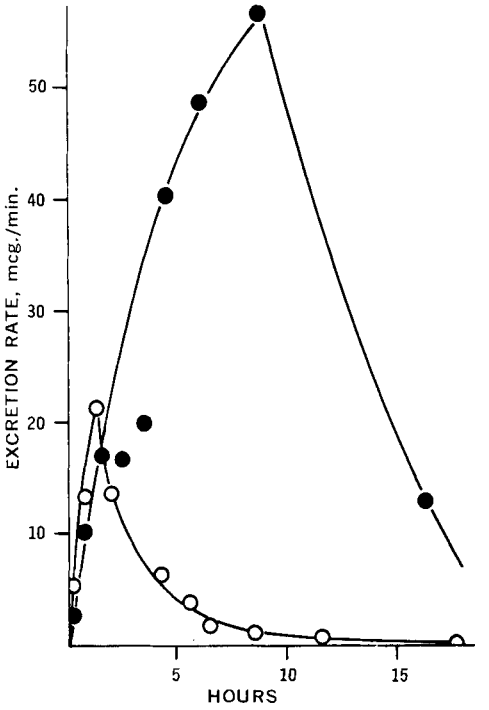

Figure 2—*Effect of propantheline on riboflavin absorption: urinary excretion rate of riboflavin as a function of time after oral administration of 150 mg./m.² riboflavin as the phosphate on an empty stomach. Key: ○, control; and ●, after propantheline; Subject L. Note the difference in the duration of absorption.*

The results of this study may apply in principle also to intrinsically poorly absorbed drugs absorbed by passive diffusion. The bioavailability of such drugs may be increased appreciably by concomitant use of an anticholinergic agent. The increased pharmacologic effect resulting from this type of drug interaction may be unanticipated and undesirable. On the other hand, the intentional combination of an intrinsically poorly absorbed drug with an anticholinergic agent may be a useful means of increasing the bioavailability of the former, provided that the anticholinergic effect is not objectionable on clinical grounds. Anticholinergic agents may also decrease bioavailability by inhibiting gastric secretions (11) or, conceivably, by decreasing the dissolution rate of drug solids due to the decreased GI motility. It may be of interest to explore the effect of anticholinergic agents on the bioavailability of such drugs as levodopa and penicillin G, which are degraded in the stomach.

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