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EFFECT OF ATTAPULGITE ON THE BIOAVAILABILITY OF A MODEL LOW DOSE DRUG (RIBOFLAVINE) IN HUMANS

Saleh A.H.Khalil*, Lobna M.Mortada, M.A.Shams-Eldeen and Manal M.El-Khawas

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

ABSTRACT

In human volunteers, both the rate and extent of urinary excretion of riboflavine were significantly reduced ($p<0.05$) when attapulgite was co-administered with the drug. About 50% reduction occurred in the cumulative amount excreted following the concurrent administration of 10 mg riboflavine in a solution form and 2 g of regular attapulgite. The co-administration of the drug with a 30 ml dose of a commercial antidiarrheal suspension containing 10% activated attapulgite and 3% colloidal attapulgite produced a relatively lesser effect; the reduction in extent of absorption being 40%. No statistically-significant effect was found when the adsorbent was ingested 2 h prior to the drug. The observed reduction in drug bioavailability in the pre-

sence of attapulgite is attributed to the significant uptake of the drug by the adsorbent.

INTRODUCTION

Antacids and some components in antidiarrheal mixtures are known to be a potential source of drug interactions (1). In view of their availability over-the-counter, they are widely used by the public and may be taken concurrently with many drugs. Kaolin and attapulgite are two ingredients commonly present in antidiarrheal preparations. A number of drugs were found to interact with kaolin and consequent reduction in bioavailability was reported (2-5).

Attapulgite B.P. is a purified native aluminium magnesium silicate belonging to the palygorskite-spiolite group of mineral clays. It exists in the form of two grades: a) regular activated attapulgite and b) colloidal activated attapulgite. Both grades have been used as gastrointestinal adsorbents (6). A B.P. monograph for the activated attapulgite first appeared in the 1975 addendum. Attapulgite is a highly efficient adsorbent against toxins and alkaloids(7,8).

In-vitro adsorption studies of strychnine, atropine and quinine onto attapulgite showed that the adsorbent was more efficient than kaolin(9). The in-vitro uptake of neomycin sulphate by attapulgite was studied by McGinity and Hill (10). The extent of desorption was influenced by magnesium ions. Adsorption and desorption testing of promazine from attapulgite system demonstrated that desorption rates were rapid (11,12).

Relatively few studies have been carried out of the influence of attapulgite on drug availability. The effect of activated attapulgite on promazine absorption was studied by Sorby and Liu (11,12). Their findings suggested that the adsorbent reduced the rate of drug absorption when promazine was equilibrated with the adsorbent. In another study (13) an attapulgite-pectin mixture suppressed lincomycin absorption when both the drug and adsorbent were co-administered.

In a recent report, Khalil et al.(14) found that a regular grade of attapulgite significantly adsorbed a model of low dose drug (riboflavine) in-vitro. In the present work, we have examined the effect of attapulgite on the bioavailability of riboflavine in human volunteers. In an attempt to overcome the interaction, the effect of spacing the doses was also examined.

MATERIALS AND METHODS

Riboflavine and a regular grade of attapulgite (B.P.) were used. A batch of antidiarrheal suspension known as Quintess^{R}(batch no. 3RG78A, Eli Lilly, USA) was used. Each 30 ml of the suspension contains 3 g activated attapulgite and 0.9 g activated colloidal attapulgite.

Six healthy subjects, 3 males and 3 females (age 24-40 years; weight 62-82 Kg) volunteered for the study and gave written consent. A randomized crossover design was adopted. The volunteers were instructed not to take any drug a week before and during the trials. Food materials known of their high riboflavine contents (15) were not consumed at least one day before and during the trials. Each subject fasted for at

least 8 h prior to and 3 h after dosing. A standard breakfast consisted of toast (4 slices), butter (20 g) and jam (40 g) was given. Each subject ingested a solution of 10 mg riboflavine in 200 ml of water with or without attapulgite (or Quintess^{R} suspension) according to the following treatments:

Treatment A: The riboflavine solution: 10 mg dissolved in 200 ml of water (control).

Treatment B: Attapulgite (2 g) suspended in the riboflavine solution.

Treatment C: Attapulgite (2 g) suspended in 200 ml and 2 h later, the riboflavine solution was ingested.

Treatment D: Quintess suspension^{R} (30 ml) diluted with the riboflavine solution.

Complete urine collection was carried out hourly for 8 h, and a pooled sample was collected from 8 to 11 h after drug administration. Urine samples were collected in light - resistant bottles. Glacial acetic acid (3 ml per 100 ml of urine) was added as a stabilizer (16). The bottles were analyzed within 24 h from the first sample collection.

Assay: After suitable dilution, the urine samples were assayed using the fluorometric method described by Levy and Jusko (17). The fluorescence was measured using a a suitable spectrofluoremeter (model 204, Perkin Elmer, Hitachi, Norwalk, Connecticut).

Adsorption Testing: The uptake of riboflavine by attapulgite was examined following the procedure previously described(14). The riboflavine content in the supernatant solution, obtained after centrifugation, was determined by the fluorometric method.

RESULTS

The influence of attapulgite on the absorption of orally-administered riboflavine was examined when both the drug and adsorbent were ingested concomitantly and when the adsorbent was ingested 2 h before the drug.

The cumulative urinary excretion data are shown in Fig.1 and urinary excretion rates are shown in Fig.2 for the six subjects. It is clear that following Treatment B, all the subjects showed statistically-significant reduction in the urinary excretion data. For Treatment C no statistically-difference was found. This was confirmed following analysis of the data by Student's t-test (Table 1); when Treatment pairs A-B and A-C were compared; the parameters being the peak excretion rate and the 11 h-cumulative amount excreted.

Statistical analysis by the ANOVA method (Table 2), using the 11 h-cumulative amounts excreted as the parameter, revealed that statistically significant difference was found ($p < 0.05$) between Treatments A, B and C (due to inclusion of Treatment C in the analysis). As would be expected, inter-subject variability was significant ($p < 0.05$). This can be attributed to the fact that riboflavine is absorbed by a specialized transport system in the proximal portion of the small intestine (17). Hence, alteration in the gastric emptying can produce significant changes in the rate and extent of riboflavine absorption from the gastrointestinal tract (18,19).

Again, no statistically-significant difference was found in the urinary excretion rates following Treatments A and C.

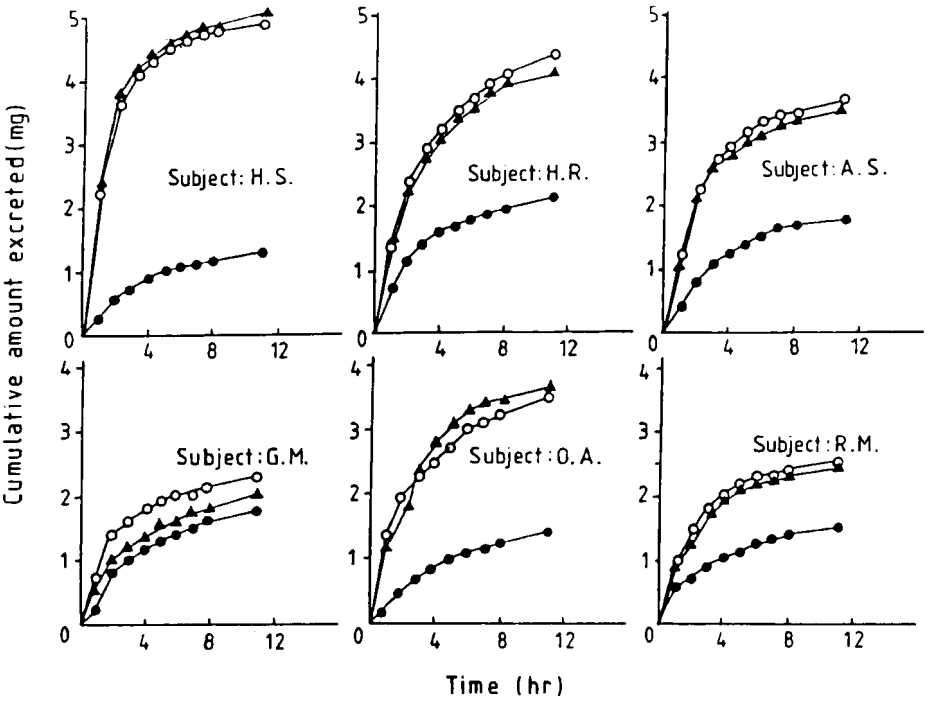

FIGURE 1

Individual cumulative amounts excreted following single dose administration(10 mg)of riboflavine after Treatment A ○ , Treatment B ● and Treatment C △ .

However, significant reduction in the rate of rise and peak excretion rate occurred following Treatment B. Intersubject variability following Treatments A and B was determined by calculating the standard error of the mean (S.E.M.) for the pharmacokinetic parameters (Table 3). In most cases, relatively low S.E.M. values were obtained following Treatment B relative to Treatment A. Figure 3 shows individual percent dose excreted following Treatments A, B and C. All the subjects showed reduced bioavailbility following Treatment B. Calculations of the relative bioavailability (Table 4) gave a range of 26.23-77.20 (mean$\pm$S.E.M. 50.4$\pm$7.2) for Treatment B.

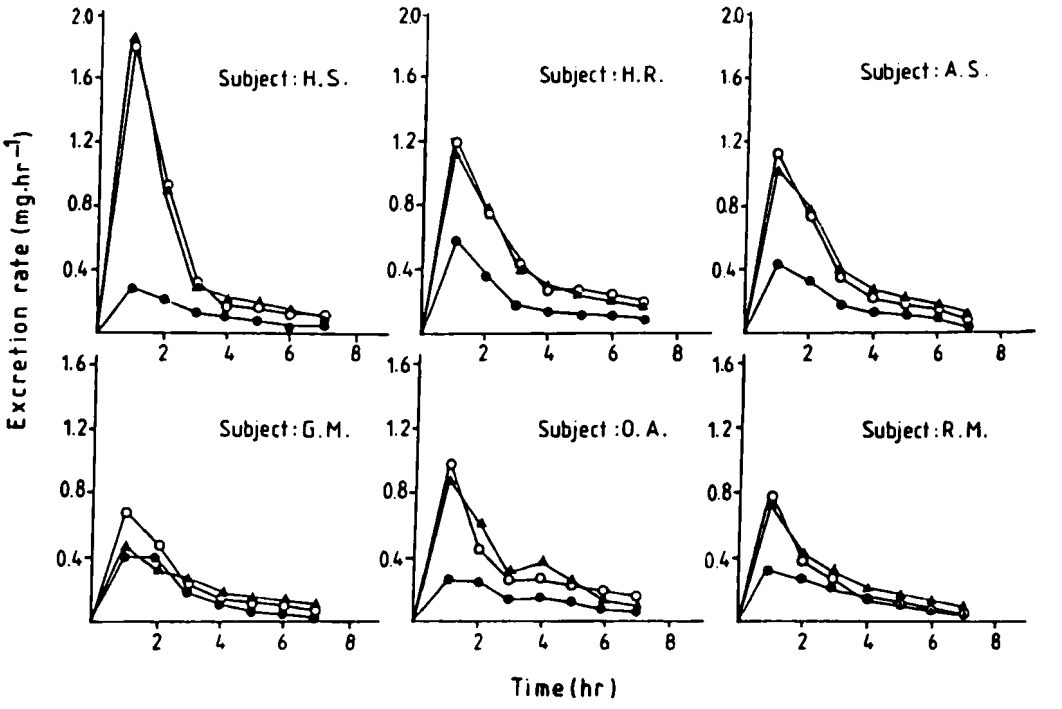

FIGURE 2

Individual urinary excretion rates following single oral dose administration(10 mg)of riboflavine after Treatment A ○ , Treatment B ● and Treatment C △ .

TABLE 1

Student t-test Applied to Excretion Data Following Oral Administration of 10 mg of Riboflavine after Treatments A, B and C (n=6).

Data Analyzed	Treatments	t-values	Significance
Peak Excretion Rate($mg.h^{-1}$)	A-B	3.91	S*
	A-C	1.69	N.S+
11 h-Cumulative Amount Excreted (mg)	A-B	4.26	S++
	A-C	1.15	N.S

*Significant ($p < 0.025$)
+Not significant
++Significant ($p < 0.001$)

TABLE 2

Analysis of Variance for the 11 h-Cumulative Excretion Data Following Oral Administration of 10 mg of Riboflavine after Treatments A, B and C.

Source	SS	dF	MS	F	Significance
Between Treatments	13.740	2	6.870	14.84	S*
Between Subjects	7.770	5	1.554	3.36	S
Error	4.629	10	0.463	--	

*S ignificant at p=0.05
Tabular F 2, 10: 4.1
Tabular F 5, 10: 3.33

TABLE 3

Effect of Treatments (A) and (B) on Intersubject Variability Following Oral Administration of 10 mg Riboflavine; (n=6).

	Intersubject Treatment Variability					
	A			B		
	High	Low	S.E.	High	Low	S.E.
C.A.E. (mg)	4.93	2.29	0.42	2.19	1.29	0.14
% Dose Excreted	49.30	22.90	4.20	21.90	12.90	1.40
P.E.T. (h)*	1.00	1.00	--	1.00	1.00	--
P.E.R. ($mg.h^{-1}$)	1.82	0.68	0.17	0.59	0.29	0.05
$t_{1/2}$, el(h)	4.95	1.74	0.51	6.30	2.17	0.62
t_p (h)**	1.88	1.01	0.14	2.31	1.61	0.10

*Approximate values, since urine samples were collected hourly.

**Time to reach peak in blood, calculated using the formula:

$$t_p = \frac{2.303 \log Ka/Kel}{Ka - Kel}$$

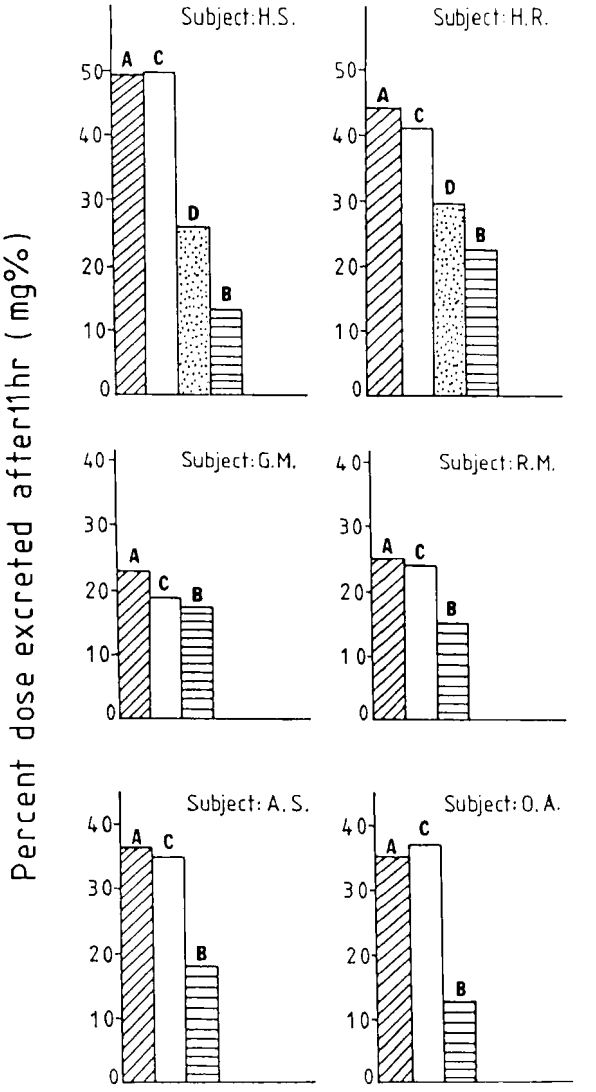

FIGURE 3

Individual percent dose excreted following single oral dose administration of riboflavine after Treatment A, Treatment B, Treatment C and Treatment D.

TABLE 4

Individual Estimates of Relative Bioavailability of Riboflavine(10 mg) Orally Administered Following Treatments A, B, C and D.

Subject	Relative Bioavailability %*		
	B/A	C/A	D/A
A.S.	49.46	96.12	N.C.**
G.M.	77.20	82.39	N.C.
H.R.	49.41	93.72	67.54
H.S.	26.23	101.89	52.94
O.A.	38.81	105.69	N.C.
R.M.	61.26	95.79	N.C.
Mean	50.40	95.93	60.24
S.E.+	7.20	3.26	4.21

* Relative to treatment A and based on 11 h-cumulative amount excreted.

** Not calculated

+ S.E.: ±standard error of the mean

The effect on riboflavine absorption of concomitant ingestion of a single dose(30 ml)of a commercial product containing attapulgite (Quintess suspension^{R}) was carried out using two subjects (Treatment D). The results obtained showed that the two subjects had reduced bioavailability. Relative to the control Treatment A, percent dose excreted were 52.94 and 67.54 in the two subjects.

Calculation of the pharmacokinetic parameters(Table 5) indicated that Treatments A-D had no effect on the parameters, and the calculated values are in good agreement with those reported by Levy et al.(17).

DISCUSSION

The observed reduction in the absorption of riboflavine in the presence of attapulgite can be discussed in the light

TABLE V

Elimination Rate Constant(Kel), Elimination Half-life($t_{1/2}$, el), Absorption Rate Constant(Ka)and Absorption Half-life ($t_{1/2}$, ab)for Riboflavine Following Treatments A, B, C and D.

Treatment	Parameter	A.S.	G.M.	H.R.	H.S.	O.S.	R.M.
A	Kel (h^{-1})	0.31	0.31	0.14	0.36	0.19	0.40
	r*	0.95	0.98	0.99	0.99	0.97	1.00
	$t_{1/2}$, el(h)	2.24	2.24	4.95	1.93	3.65	1.74
	Ka (h^{-1})	1.50	0.92	1.34	2.12	1.41	1.57
	$t_{1/2}$, ab(h)	0.46	0.75	0.52	0.33	0.49	0.44
B	Kel (h^{-1})	0.23	0.24	0.11	0.32	0.21	0.31
	r	0.93	1.00	0.94	0.98	0.97	1.00
	$t_{1/2}$, el(h)	3.01	2.89	6.30	2.17	3.30	2.24
	Ka (h^{-1})	0.88	0.88	1.11	0.83	1.38	0.65
	$t_{1/2}$, ab(h)	0.79	0.79	0.63	0.84	0.50	1.07
C	Kel (h^{-1})	0.29	0.25	0.20	0.34	0.46	0.34
	r	0.99	0.99	0.98	1.00	0.99	1.00
	$t_{1/2}$, ab(h)	2.39	2.78	3.47	2.04	1.51	2.04
	Ka (h^{-1})	1.01	1.34	0.88	1.06	0.74	1.66
	$t_{1/2}$, ab(h)	0.69	0.52	0.79	0.65	0.94	0.42
D	Kel (h^{-1})	--	--	0.22	0.22	--	--
	r	--	--	0.90	0.90	--	--
	$t_{1/2}$, el(h)	--	--	3.15	3.15	--	--
	Ka (h^{-1})	--	--	1.47	1.20	--	--
	$t_{1/2}$, ab(h)	--	--	0.47	0.58	--	--

*r= correlation coefficient for the relationship between log excretion rates versus time(Feathering technique).

TABLE 6

The In-vitro Uptake of Riboflavine by Attapulgite at pH 2 (0.01 N HCl), 37±0.2°C.

C_o^a	x/m^b	% Adsorption
0.75	0.603	80.4
1.50	1.176	78.4
2.25	1.809	80.4
5.25	3.226	74.8
6.50	4.941	76.0
7.50	5.735	76.5

[a]Initial riboflavine concentrations mg.50 ml^{-1}
[b]Amount of riboflavine adsorbed(mg)per gram of attapulgite

of the following possible mechanisms:
(a) alteration in gastric pH value, (b) alteration in gastric emptying time, (c) chelation of the drug with $Al^{+3}$and Mg^{+2}ions released from attapulgite, and (d) adsorption of the drug by attapulgite.

Alteration in gastric pH following ingestion of 2 g of attapulgite has not been reported. Although attapulgite showed weak neutralizing capacity in-vitro, it is highly unlikely that gastric pH would be significantly altered after ingestion of 2 g of attapulgite. At 37°C no appreciable decomposition occurred after digestion in 0.1 N HCl for 2 h, thus ruling out possible effect of any leachable Al^{+3}ions on gastric emptying time. The possibility of drug adsorption by attapulgite in-vivo was examined. A significant uptake of the drug occurred; the details of the adsorption data are published elsewhere (14) and representatives of the data are shown in Table 6.

Since the pharmacokinetic parameters were not significantly affected by the presence of attapulgite, it appears therefore that this type of interaction influenced only the absorption and not the disposition.

The ingestion of a dose of an attapulgite-containing suspension (Quintess suspension^{R})produced similar reduction in the rate and extent of drug excretion. Since the data of the suspension were obtained from two subjects only, it would be difficult to draw a comparison with 'pure' attapulgite. However, it was found that the suspension produced a relatively lesser effect in the same two subjects (H.S. and H.R.). Percent relative bioavailability (relative to control) were 52.9 and 67.5 (for the suspension) compared to 26.2 and 49.4 (for pure attapulgite) in the same two subjects. It is probable that the excipients added in the suspension (flavors, sweeteners and colorants) had reduced the adsorptive capacity of attapulgite present.

The data presented in this work point out to the strong adsorptive property of attapulgite toward low dose drugs such as riboflavine. This results in reduced bioavailability of the drug. Spacing the doses by 2 hours eliminated the interaction. A good correlation existed between in-vitro adsorption data and in-vivo testing of the system studied.

REFERENCES

(1) I. Stockley,"Drug Interactions" (1981), Blackwell Scientific Publications.

(2) K.S.Albert, K.A.DeSante, R.D.Welch and A.R.DiSanto, J.Pharm.Sci., 67, 1579 (1978).

(3) K.S.Albert, J.W.Ayres, A.R.DiSanto, D.J.Weidler, E.Sakmar, M.R.Hallmark, R.G.Stoll, K.A.Desante and J.G.Wagner, ibid., 67, 1582 (1978).

(4) D.D.Brown, R.P.Juhll, New Engl.J.Med., 295,1034 (1976).

(5) S.Said and H.Al-Shora, Intern.J.Pharm.Sci., 5, 223 (1980).

(6) R.P.Penna and C.Kleinfeld,"Handbook of Nonprescription Drugs", 5th Ed., American Pharmaceutical Association, Washington, D.C., p.31 (1977).

(7)M.Barr and E.S.Arnista, J.Am.Pharm.Assoc., 46, 486 (1957).

(8) J.P.Atkinson and D.L.Azarnoff, Clin.Toxicol., 4, 31 (1971).

(9) N.Evcim and M.Barr, J.Am.Pharm.Assoc., 44, 570 (1955).

(10) J.W.McGinity and J.A.Hill, J.Pharm.Sci., 64, 1566 (1975).

(11) D.L.Sorby and G.Liu, J.Pharm.Sci., 55, 504 (1966).

(12) D.L.Sorby, ibid., 54, 677 (1965).

(13) J.G.Wagner, paper presented to the Am.Pharm.Assoc,National Meeting, Dallas, Texas (1966), through Canad.J.Pharm.Sci., 7, 29 (1972); D.C.Monkhouse and J.L.Lach.

(14) S.A.H.Khalil, L.M.Mortada, M.A.Shams-Eldeen and M.M.El-Khawas, submitted to J.Pham.Sci.(1984).

(15) C.D.Hodgman, R.C.Weast, R.S.Shankland and S.M.Selby, "Handbook of Chemistry and Physics",44th Ed., The Chemical Rubber Co., USA, p.1977 (1963).

(16) S.Feldman and W.Hedrick, J.Pharm.Sci., 72, 121 (1983).

(17) G.Levy and W.J.Jusko, J.Pharm.Sci., 55, 285 (1966).

(18) G.Levy and R.R.Hewitt, Am.J.Clin.Nutr., 24, 401 (1971); through ref.(16), S.Feldman and W.Hedrick (1983).

(19) G.Levy, M.Gibaldi and J.A.Procknal, J.Pharm.Sci., 61, 798 (1972).