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EFFECT OF ALUMINIUM HYDROXIDE AND GLYCOPYRRHONIUM ON THE ABSORPTION OF ETHAMBUTOL AND ALCOHOL IN MAN

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1 The effect of aluminium hydroxide and/or of glycopyrrhonium on the absorption of a single oral 50 mg/kg dose of ethambutol (EMB) was investigated on thirteen tuberculous in-patients and on two groups of healthy volunteers with six subjects each. The EMB concentrations in serum and 10+h urine were measured by colorimetry.

2 In order to assess gastric emptying the healthy volunteers ingested ethanol, either 0.5 g/kg in 10% solution or 0.8 g/kg in 20% solution, simultaneously with the drug, and breath alcohol levels were measured repetitively.

3 Aluminium hydroxide significantly lowered the serum EMB levels of the patients during the first 4 h after the EMB intake. No consistent effect was found in the first student experiment, whereas in the second experiment aluminium hydroxide and glycopyrrhonium, alone or in combination, clearly retarded the EMB absorption.

4 Repeated breath alcohol analysis proved unsuitable to indicate the time course of gastric emptying in these circumstances.

Introduction

A definite delay in the absorption of various drugs by aluminium salts has been demonstrated in animals and in man (Hurwitz, 1974) but there still is some doubt about the practical relevance of this finding (Nimmo, Heading, Tothill & Prescott, 1973). This pharmacokinetic interaction probably results from a slowed gastric emptying (Hurwitz, 1974). *In vitro,* aluminium ion antagonizes the contractile response of human and rat gastric strips to acetylcholine (Hava & Hurwitz, 1973). This effect, possibly due to the inhibition by aluminium of the calcium influx into smooth muscle cells during depolarization (Hava & Hurwitz, 1974), leads to a delay in muscle contractions (Hava & Hurwitz, 1975).

When investigating the bioavailability of an anti-tuberculosis drug ethambutol (EMB) we measured inconsistently lowered serum EMB levels after aluminium antacids. Since EMB can chelate metal ions (Shepherd, Baughn, Cantrall, Goodstein, Thomas & Wilkinson, 1966), a demonstration of altered gastric emptying is required until the Hurwitz' theory can be adopted to this particular connection. Finch, Kendall & Mitchard (1974) have elaborated a simple method of assessing gastric emptying. During the absorption of alcohol the sudden peak in blood or breath alcohol after initial slow rise indicates pyloric opening. We adopted this method to analyze our previous patient data where aluminium hydroxide delayed the EMB absorption.

Methods

Patient study

Thirteen informed tuberculosis in-patients, aged 38–56 years, and taking usual combinations of oral anti-tuberculosis drugs, volunteered for the study. Chemical pathology tests revealed no impairment of renal or hepatic function, nor did they suffer of specific gastrointestinal diseases. All medication was withdrawn for the 24 h prior to the experiment. After the night's fast a zero sample of venous blood (6–8 ml) was drawn and a urine sample collected at 08.00 h. Thereafter, the subject ingested 50 mg/kg of EMB in ordinary tablets (Myambutol®, Lederle), the blood sampling was repeated 2, 4, and 10 h later, and all urine was collected for 10 h following the drug intake. This experimental procedure was repeated after 1 week. At both tests, half of the subjects swallowed, in combination with EMB, 30 ml of gel containing 1.5 g of aluminium hydroxide (Neutragel®, Star, Tampere) and the intake of aluminium hydroxide was repeated 15 and 30 min later. A cross-over took place between the experimental treatments. The sera and aliquots of the 10 h urine were stored at −20°C for several weeks until their EMB concentrations were assayed by a colorimetric method (Fröseth, 1969). In most zero samples a blank corresponding to 0.3–1.1 μg/ml EMB was measured. This background was subtracted from the results of the later measurements.

Experiments on healthy volunteers

In a cross-over study, six healthy student volunteers ingested 50 mg/kg of EMB in combination with 0.5 g/kg of ethyl alcohol, with or without aluminium hydroxide as above. Alcohol was blended with water to yield a 10% v/v solution, and the drink was served at 4°C. Blood and urine samples were collected as described above. After the alcohol ingestion, breath alcohol levels were repetitively measured with a ASD-breath alcohol analyzer (U.S. Department of Transportation). All EMB concentrations were measured 'blind' about 2 months after the experiment.

The second cross-over study with another group of six students was conducted in order to compare the effects of aluminium hydroxide and an anticholinergic glycopyrrhonium, and to measure the alcohol absorption from higher (0.8 g/kg as 20% v/v solution) concentrations. Glycopyrrhonium bromide (3 mg in three uncoated tablets) (Gastrodyn®, Medica, Helsinki) was given 45 min before, and aluminium hydroxide (1.5 g in 30 ml of gel) was given 20 min before and 20 min after the intake of 50 mg/kg of EMB + alcohol. Treatments with aluminium hydroxide, glycopyrrhonium, both together, and without either of them were done cross-over in random order at 1 week intervals. The sampling and assay of EMB was as described above except that blood samples at 30 min and 60 min were also taken. The breath alcohol concentrations were measured with Alcolmeter (Lion Laboratories Ltd, Cardiff) device. No zero blank for EMB was found in students.

Results

Absorption of EMB

In six out of thirteen patients aluminium hydroxide definitely delayed and reduced the EMB absorption as indicated by delayed or/and lowered peak concentrations of serum EMB and by reduced excretion of EMB in 10 h urine. In four patients the EMB absorption was slightly impaired and in three patients serum EMB levels were either unchanged or actually increased after aluminium hydroxide. When the mean values of serum EMB measured with and without aluminium hydroxide (Table 1) were compared (t-test), no significant differences were found at any single time of observation. When the 2 h and 4 h levels of serum EMB were compared as a whole (two-way analysis of variance), aluminium hydroxide significantly ($F = 4.640$; $P < 0.05$) lowered serum EMB (Table 2).

When EMB was given together with 0.5 g/kg of alcohol to healthy volunteers, one subject showed elevated serum EMB levels and an increased urinary

Table 1 Mean ± s.e.mean serum levels and urinary excretion of ethambutol (EMB) after an oral dose of 50 mg/kg EMB given with and without aluminium hydroxide. Aluminium hydroxide (1.5 g in gel form) was first given together with EMB and then repeated 15 and 30 min later.

Treatment	*Serum EMB levels (μg/ml)*			*Excretion of EMB in 10 h urine (μg/10 h)*
	2 h	*4 h*	*10 h*	
Thirteen patients				
EMB alone	4.6 ± 0.5	6.8 ± 0.5	1.8 ± 0.2	894 ± 61
EMB + $Al(OH)_3$	3.6 ± 0.7	5.3 ± 0.7	1.5 ± 0.2	777 ± 66
Six student volunteers				
EMB alone	3.0 ± 0.6	3.9 ± 0.6		675 ± 41
EMB + $Al(OH)_3$	2.9 ± 0.3	3.9 ± 0.8		636 ± 87

Table 2 Serum EMB levels with and without aluminium hydroxide in thirteen patients. 2 times × 2 drugs × 13 patients = 52

Source of variance	*Sum of the squares of the differences*	*F d.f.*	s^2	*F*
Between drugs A	20.563	1	20.563	4.640
Between times B	47.120	1	47.120	10.634
Interaction AB	0.582	1		
Residual e	212.713	48	4.431	
Total	280.978	51		

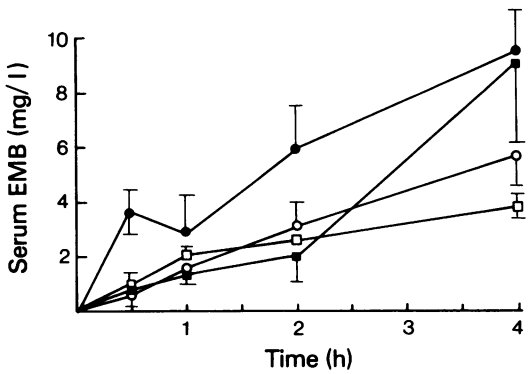

Figure 1 Serum levels of ethambutol (EMB) in healthy volunteers (mean ± s.e.mean) after an oral single dose of 50 mg/kg EMB. In each experiment EMB was given together with 0.8 g/kg alcohol. Pretreatments: ● no pretreatment; ■ aluminium hydroxide; ○ glycopyrrhonium; □ aluminium hydroxide + glycopyrrhonium.

excretion of EMB after aluminium hydroxide. The other subjects showed more or less opposite changes, but, as a whole, no significant change in the absorption of EMB by aluminium hydroxide was found (Table 1).

When EMB was given together with 0.8 g/kg of alcohol to the second group of student volunteers, treatment with aluminium hydroxide and glycopyrrhonium, separately or together, clearly delayed the EMB absorption as indicated by lowered serum EMB levels during the first few hours after its administration (Figure 1). As a whole, treatment with glycopyrrhonium, alone or together with aluminium hydroxide, significantly (two-way analysis of variance, $P<0.01$) lowered EMB serum levels during the experimental 4 h period whereas aluminium hydroxide alone did so during the first 2 h only. As regards with the urinary excretion of EMB, a broad range was found in control values (mean ± s.e.mean 1017 ± 142 mg) and the lowest excretion (712 ± 79 mg) measured after treatment with aluminium hydroxide + glycopyrrhonium, did not differ significantly from the control.

Breath alcohol levels

As seen in Table 3, no particular peak of breath alcohol was seen after 0.5 g/kg of alcohol since the concentrations quickly and steadily rose to values which can be expected after this alcohol dose. Nor did aluminium hydroxide modify the absorption pattern.

Table 3 and Figure 2 present results from the second volunteer study where 0.8 g/kg alcohol was given in 20% solution. As seen in Figure 2, high peaks were found in four out of six subjects when EMB and alcohol were given but the peak timing varied. The effect of aluminium hydroxide or/and glyco-

Table 3 Mean ± s.e. mean concentration of alcohol in breath air of six healthy volunteers after the simultaneous intake of alcohol and ethambutol (EMB) with or without aluminium hydroxide and/or glycopyrrhonium. In the first study 0.5 g/kg alcohol in 10% v/v solution was given, the dose of alcohol in the second study being 0.8 g/kg in 20% v/v solution. For more details see methods.

	Alcohol concentration in breath air (mg/ml)			
Test time (min)	*EMB + alcohol*	*EMB + alcohol + aluminium hydroxide*	*EMB + alcohol + glycopyrrhonium*	*EMB + alcohol + glycopyrrhonium + aluminium hydroxide*
First study				
10	0.27 ± 0.05	0.23 ± 0.04		
15	0.29 ± 0.03	0.28 ± 0.04		
20	0.32 ± 0.05	0.35 ± 0.03		
40	0.31 ± 0.01	0.35 ± 0.03		
60	0.30 ± 0.00	0.32 ± 0.03		
90	0.29 ± 0.00	0.32 ± 0.03		
180	0.21 ± 0.01	0.23 ± 0.03		
Second study				
10	0.40 ± 0.12	0.38 ± 0.10	0.41 ± 0.08	0.33 ± 0.02
15	0.55 ± 0.15	0.43 ± 0.09	0.51 ± 0.10	0.44 ± 0.08
20	0.64 ± 0.11	0.48 ± 0.07	0.62 ± 0.08	0.41 ± 0.07
40	0.61 ± 0.07	0.54 ± 0.10	0.53 ± 0.06	0.61 ± 0.06
60	0.68 ± 0.05	0.57 ± 0.09	0.49 ± 0.04	0.57 ± 0.08
80	0.64 ± 0.03	0.61 ± 0.04	0.52 ± 0.02	0.63 ± 0.08
180	0.52 ± 0.03	0.59 ± 0.03	0.52 ± 0.04	0.56 ± 0.02

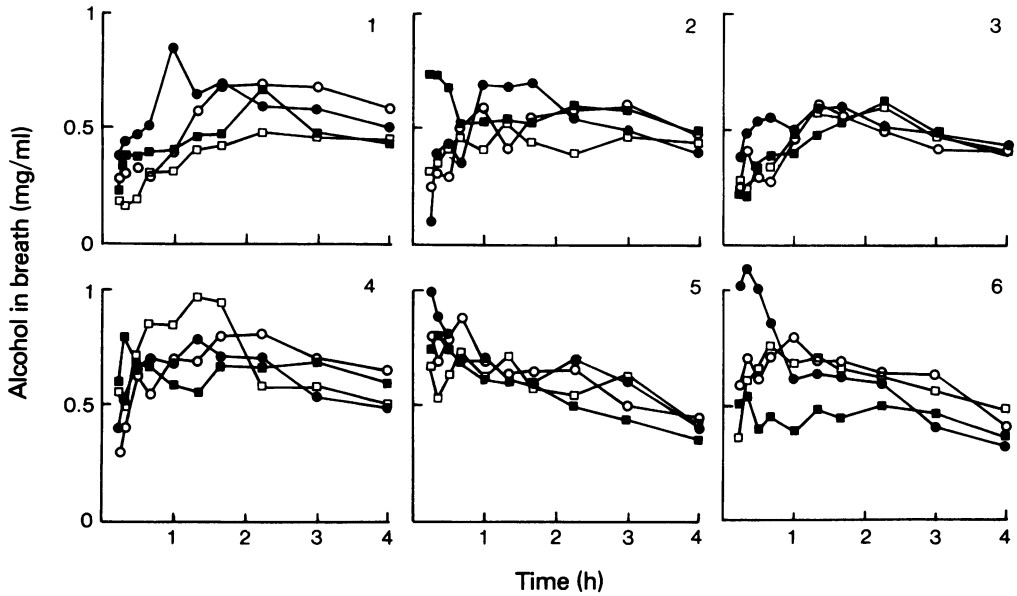

Figure 2 The alcohol concentrations in the breath air of the six healthy volunteers from one second study where 0.8 mg/kg alcohol was given in 20% solution. Pretreatments: ● no pretreatment; ■ aluminium hydroxide; ○ glycopyrrhonium; □ aluminium hydroxide + glycopyrrhonium.

pyrrhonium was inconsistent. Aluminium hydroxide and glycopyrrhonium tended to retard the alcohol absorption, but no significant differences were measured (t-test) at individual test times. When the breath alcohol concentrations after EMB + alcohol measured during the first 60 min were compared (two-way analysis of variance) with the respective levels measured after the pretreatment with aluminium hydroxide + glycopyrrhonium, no significant difference was found between the treatments (F = 2.87; $P<0.05$ (Table 4). Nor were significant differences between times (F = 1.453) whereas the drug/time interaction was highly significant (F= 24.296) reflecting the varying peak times. Only the subjects 3 and 6 in Figure 2 showed a correlation between the breath alcohol and serum EMB levels.

Discussion

Aluminium hydroxide has been demonstrated to differentially affect the absorption of drugs, even those having similar physico-chemical properties. Pseudoephedrine, a basic drug, has been demonstrated to have a faster and increased urinary excretion in man when administered in combination with aluminium hydroxide (Lucanotti, Colaizzi, Barry & Poust, 1972).

Table 4 Breath alcohol after EMB + alcohol (0.8 g/kg) with and without pretreatment with aluminium hydroxide + glycopyrrhonium in six volunteers. 2 drugs x 6 times x subjects)= 72

Sources of variance	*Sum of the square of the differences*	*d.f.*	s^2	*F*
Between drugs A	0.184	1	0.184	2.87
Between times B	0.465	5	0.093	1.453
Interaction AB	7.779	5	1.555	24.296
Residual e	−3.843	60	−0.064	
Total	4.585	71		

The urinary excretion of chlorpromazine, also a basic drug, was significantly reduced after aluminium hydroxide (Forrest, Forrest & Serra, 1970). The mixture of magnesium and aluminium hydroxides has retarded the absorption and metabolism of chlordiazepoxide (Greenblatt, Shader, Harmatz, Franke & Koch-Weser, 1976). The absorption of salicylic acid is significantly delayed from tablets buffered with aluminium hydroxide (Linnoila & Lehtola, 1977). Concomitant administration of aluminium hydroxide has not modified the absorption of corticosteroids (Galeazzi, 1973), bishydroxycoumarin, warfarin (Ambre & Fischer, 1973), and levodopa (Leon & Spiegel, 1972).

The results reviewed above demonstrate a large variation in the effect of aluminium hydroxide on the gastrointestinal absorption of different drugs. Our present results partly confirm the aluminium induced pyloric closure, but they also show a large interindividual variation in the effect of aluminium hydroxide on the absorption of EMB. A similar variation becomes evident in the effect of aluminium hydroxide on the absorption of isoniazid (Hurwitz & Scholzman, 1974). The reasons for the interindividual variation are obscure at the present time, but available information suggests avoiding the administration of aluminium hydroxide in combination with other drugs, excepting corticoids and anticoagulants.

Our findings concerning the usefulness of alcohol measured in breath as a marker of pyloric opening partly contrast those of Finch *et al.* (1974), because no abrupt peak was found after dosing alcohol 0.5 g/kg and because no clear correlation of the EMB absorption and breath alcohol peaks was found after 0.8 g/kg of alcohol, either. The probable reason for the discrepancy is that in the earlier work, the alcohol concentration of the administered drink per se was so high that it might have affected gastric emptying. Lolli & Rubin (1943) have demonstrated that diluted solutions of alcohol are absorbed faster in man than concentrated ones. Another significant factor causing pyloric spasms after alcohol ingestion is poor palatability of the drinks (Newman & Abramson, 1942). This may be the case if one has to quickly ingest a fair dose of alcohol in a 20% v/v solution, as in the study by Finch *et al.* (1973) and in our second volunteer study. We believe that our experimental conditions (aluminium hydroxide, glycopyrrhonium) have been more complex since, e.g., the alcohol induced acid secretion is compensated by antacids. But our results discourage drawing general conclusions about gastric emptying by using the Finch *et al.* (1973) method which works well in some circumstances.

The authors conclude:

1 Aluminium hydroxide generally delayed and reduced the absorption of ethambutol in tuberculous patients. However, large interindividual variations became evident in the sensitivity to the aluminium hydroxide.

2 Aluminium hydroxide gel did not significantly affect gastric emptying in healthy volunteers when assessed with 0.5 g/kg of alcohol.

3 Alcohol may not be a suitable marker of pyloric opening. Concentrated drinks which are rapidly ingested can produce pyloric spasms. Therefore, in such experiments one is measuring the effects of alcohol on pyloric muscle and its modification with drugs rather than the effects of drugs on pyloric function per se.

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