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Effects of resins and activated charcoal on the absorption of digoxin, carbamazepine and frusemide

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1 The interference of resins and activated charcoal with the absorption of digoxin, carbamazepine and frusemide was studied.

2 In a cross-over study consisting of four phases, single doses of colestipol hydrochloride (10 g), cholestyramine (8 g), activated charcoal (8 g) or water only were given to six healthy volunteers immediately after the simultaneous ingestion of digoxin (0.25 mg), carbamazepine (400 mg) and frusemide (40 mg). Plasma and urine concentrations of the test drugs and the urine volumes were determined up to 72 h.

3 The absorption of digoxin was not reduced by colestipol, moderately (30–40 %, $P < 0.05$) reduced by cholestyramine and greatly (96 %) by charcoal.

4 The absorption of carbamazepine was not decreased by cholestyramine, slightly (10%) by colestipol and greatly (90%) by activated charcoal.

5 The absorption and the diuretic effect of frusemide were significantly diminished by all agents. The bioavailability was reduced by colestipol 80%, by cholestyramine 95% and by activated charcoal 99.5%.

6 The interference with the gastrointestinal absorption of most of the basic drugs by colestipol and cholestyramine seems to be minimal. On the other hand, the resins may seriously impair the absorption of certain acidic drugs, for example frusemide.

Keywords resins activated charcoal absorption interactions digoxin carbamazepine frusemide

Introduction

Cholestyramine and colestipol are anionic exchange resins used mainly to bind bile acids and to reduce plasma low density lipoprotein (LDL) cholesterol. Due to the increasing awareness of LDL cholesterol as a risk factor for cardiovascular mortality the use of nonabsorbable resins is increasing.

The resins may interfere with the gastrointestinal absorption of several drugs. However, many of the published data concerning the interactions are apparently inconsistent. The resins may affect the absorption of digitalis-glycosides (van Bever *et al.*, 1976; Hall *et al.*, 1977; Kuhlmann, 1984) and of some acidic (Hunninghake & Pollack, 1977) and basic drugs (Hibbard *et al.*, 1984). However, there are no data available in the literature on the possible effects of resins on the absorption of frusemide and carbamazepine, both important drugs.

Recently, activated charcoal which is generally used for the treatment of acute poisoning and adsorbs many different, but not all, drugs (Neuvonen, 1982) has been used to reduce elevated plasma LDL cholesterol concentrations (Kuusisto *et al.*, 1986).

Many of the patients who take cholestyramine, colestipol or activated charcoal will also receive other drugs concomitantly. We, therefore, con-

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sidered it important to study the effects of these drugs used to treat hyperlipidaemias on the absorption of some other important drugs, each of which had a narrow therapeutic index.

Methods

Subjects

Six healthy voluntary subjects, four males and two females, aged 22–35 years, weighing 65–75 kg, participated in the study. The results of physical examination and routine laboratory tests before and after the study were normal. Informed consent was obtained from each subject.

Study design

The study protocol was accepted by the local ethical committee. For the first 7 h after drug ingestion the volunteer subjects were under direct medical supervision in an out-patient clinic. A randomized cross-over study design with four phases was employed at intervals of 2 weeks.

The drugs employed as test drugs and their doses were: digoxin 0.25 mg (Lanoxin, Wellcome, England), carbamazepine 400 mg (Macrepan Slow, Huhtamäki Pharmaceuticals, Finland) and frusemide (furosemide) 40 mg (Lasix, Hoechst, Federal Republic of Germany). These three test drugs were always taken simultaneously by mouth at 08.00 h on an empty stomach with 50 ml of water. No food was taken for 2 h from the beginning of the study.

Colestipol hydrochloride 10 g (Lestid, Upjohn, Belgium), cholestyramine anhydrous 8 g (Questran, Lääke-Farmos, Finland) and activated charcoal 8 g (Norit A Supra, Carbomix, Huhtamäki Pharmaceuticals) were used as watery suspensions in a volume of 150 ml followed by 150 ml of water. During the control phase the subjects took 300 ml of water only. The resins and activated charcoal were ingested within 5 min after the test drugs.

Timed blood samples (5 ml) were taken into heparinized tubes at 0, 1, 2, 4, 7, 24, 48 and 72 h after drug ingestion. Plasma was separated within 30 min. Urine was collected in fractions of 0–4, 4–24, 24–48 and 48–72 h. All plasma and urine samples were stored at −20°C until analysed.

Determination of absorption

The absorption was characterized by the area under the plasma drug concentration-time curve from 0–72 h ($AUC_{0-72\ h}$) which was calculated by the trapezoidal rule. In addition, peak plasma concentrations (C_{max}), peak times (t_{max}) and the cumulative excretion of unchanged digoxin and frusemide into urine over 0–72 h were calculated.

Assay of drugs

Digoxin plasma and urine concentrations were determined by a radio-immunoassay kit (Farmos Diagnostica, Finland). Carbamazepine plasma concentrations were determined by high-performance liquid chromatography (h.p.l.c.) (Mihaly *et al.*, 1977). The concentrations of frusemide in plasma and urine were measured by h.p.l.c. with fluorimetric detection (Lovett *et al.*, 1985), using bumetanide as an internal standard. The coefficient of variation of the methods used was less than 10% for digoxin and less than 5% for carbamazepine and frusemide ($n = 10$) at the concentrations relevant to the present study.

Statistical analysis

Means ± s. e. mean are given. One-way analysis of variance for repeated measurements was employed for statistical analysis of the results. Student-Newman-Keuls' test and Student's *t*-test for paired values were applied to find the source of possible differences between various phases of the study.

Results

Digoxin

The absorption of digoxin was unaffected by colestipol. Cholestyramine reduced the absorption of digoxin by 30–40% ($P < 0.05$) and activated charcoal by 96% ($P < 0.01$). The effects of cholestyramine and activated charcoal were reflected both in the plasma digoxin concentrations and in the cumulative excretion of digoxin into urine (Table 1, Figure 1).

Carbamazepine

Cholestyramine did not reduce the absorption of carbamazepine and colestipol caused a small inhibition only (Table 1, Figure 2). Activated charcoal, however, greatly reduced the bioavailability of carbamazepine (by 90 %, $P < 0.01$).

Frusemide

The absorption of frusemide was greatly (80%) reduced by colestipol and even more (95%) by cholestyramine. Activated charcoal prevented nearly totally (99.5%) the absorption of frusemide (Table 1, Figure 3).

Table 1 Effect of colestipol hydrochloride (10 g), cholestyramine (8 g) and activated charcoal (8 g) on the absorption of digoxin (0.25 mg), carbamazepine (400 mg) and frusemide (40 mg), measured as the peak time (t_{max}), the peak plasma concentration (C_{max}), the area under the plasma concentration-time curve (AUC_{0-72h}) and the 72 h cumulative excretion of the drugs: resins and charcoal were given immediately after the test drugs

	t_{max} (h)	C_{max} ($\mu g\ l^{-1}$)	AUC_{0-72h} ($\mu g\ l^{-1}\ h$)	(% of the control)	72 h excretion (μg)	(% of the control)
Digoxin						
Control	1.2 ± 0.2 c–d	1.1 ± 0.8 c–d	14.3 ± 1.3 c–d	100	87.3 ± 5.1 c–d	100
Colestipol	1.3 ± 0.2	1.3 ± 0.09 c–d	13.8 ± 1.4 c–d	97	97.4 ± 6.9 c–d	112
Cholestyramine	1.8 ± 0.2 a	0.7 ± 0.07 a–b d	8.6 ± 0.9 a–b d	60	62.7 ± 3.4 a–b d	72
Charcoal	2.8 ± 0.9 a	0.02 ± 0.00 a–c	0.2 ± 0.1 a–c	2	3.9 ± 0.6 a–c	4
Carbamazepine		($mg\ l^{-1}$)	($mg\ l^{-1}\ h$)			
Control	24 ± 0	2.7 ± 0.11 b d	145 ± 3.7 b d	100		
Colestipol	21 ± 3	2.4 ± 0.11 a c–d	130 ± 4.7 a c d	90		
Cholestyramine	21 ± 3	3.3 ± 0.22 b d	162 ± 12.0 b d	112		
Charcoal	25 ± 12	0.28 ± 0.08 a–c	11 ± 4.7 a–c	8		
Frusemide		($mg\ l^{-1}$)	($mg\ l^{-1}\ h$)		(mg)	
Control	1.8 ± 0.2	1.2 ± 0.26 b–d	3.5 ± 0.57 b–d	100	15.4 ± 1.3 b–d	100
Colestipol	1.8 ± 0.2	0.17 ± 0.02 a c–d	0.74 ± 0.05 a c–d	21	3.0 ± 0.4 a c–d	20
Cholestyramine	2.3 ± 0.3	0.05 ± 0.01 a–b d	0.22 ± 0.12 a–b d	6	0.72 ± 0.2 a–b d	5
Charcoal	1.4 ± 0.2	0.01 ± 0.00 a–c	0.03 ± 0.02 a–c	0.9	0.07 ± 0.02 a–c	0.5

a–d: significantly ($P < 0.05$) different from: [a]control, [b]colestipol, [c]cholestyramine, [d]charcoal.
Means ± s. e. mean in six subjects.

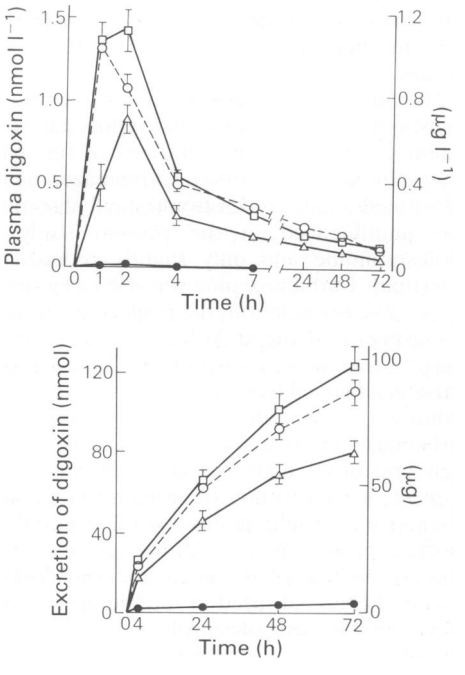

Figure 1 Effect of colestipol hydrochloride (10 g, □), cholestyramine (8 g, △) and activated charcoal (8 g, ●) on the absorption of simultaneously ingested digoxin (0.25 mg), reflected as the concentration of digoxin in plasma and as the cumulative excretion of digoxin into urine. Mean ± s. e. mean in six healthy volunteers. ○ control.

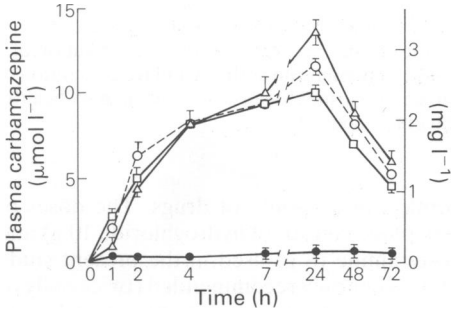

Figure 2 Effect of colestipol hydrochloride (10 g, □), cholestyramine (8 g, △) and activated charcoal (8 g, ●) on the absorption of simultaneously ingested carbamazepine (400 mg), reflected as the concentration of carbamazepine in plasma. Mean ± s. e. mean in six healthy volunteers. ○ control.

The 4 h diuretic response to frusemide was reduced from the control value of 1510 ± 200 ml to 630 ± 140 ml with colestipol, to 350 ± 90 ml with cholestyramine and to 340 ± 100 ml with charcoal.

Discussion

Colestipol is a tertiary amino polystyrene resin and cholestyramine a quaternary ammonium resin. They may alter both the rate and total

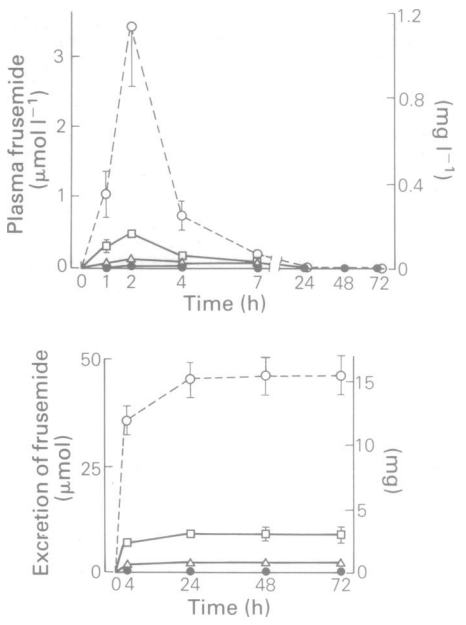

Figure 3 Effect of colestipol hydrochloride (10 g, □), cholestyramine (8 g, △) and activated charcoal (8 g, ●) on the absorption of simultaneously ingested frusemide (40 mg), reflected as the concentration of frusemide in plasma and as the cumulative excretion of frusemide into urine. Mean ± s. e. mean in six healthy volunteers. ○ control.

absorption of a variety of drugs. The doses of colestipol (as colestipol hydrochloride 10 g) and cholestyramine (8 g) used in the present study are those generally recommended (twice daily or three times daily) for the treatment of hypercholesterolaemias and their hypolipidaemic efficacy is of the same order. Also activated charcoal in a dose of 8 g three times daily has reduced serum LDL cholesterol in the patients with primary hypercholesterolaemias (Kuusisto *et al.*, 1986).

Digoxin, carbamazepine and frusemide were selected for the present study, because of their clinical importance, and on the basis of their physicochemical and pharmacokinetic properties. Digoxin is a steroid derivative, carbamazepine a substituted amide and frusemide an acid with a pKa of 3.8. Digoxin and frusemide are substantially excreted in the unchanged form into urine. This allows the exact determination of their bioavailability (even if greatly reduced).

In the present study colestipol was less likely than cholestyramine to reduce the absorption of digoxin and frusemide but this was not the case with carbamazepine. Activated charcoal had a more pronounced effect on drug absorption than either of the resins used.

The effect of resins on the gastrointestinal absorption of digitalis-glycosides has been variable (Caldwell & Greenberger, 1971; van Bever *et al.*, 1976; Hall *et al.*, 1977; Carruthers & Dujovne, 1980; Kilgore & Lehmann, 1982; Kuhlmann, 1984). In the present single-dose study colestipol had essentially no effect on the bioavailability of digoxin, and cholestyramine had a moderate effect only although the resins were ingested immediately after digoxin. The binding of frusemide by the resins served as a 'positive control' indicating that the test drugs—including digoxin—were mixed with the resins in the gastointestinal tract. On the other hand, a prolonged use of cholestyramine may have a more pronounced inhibitory effect than a single dose on digoxin absorption. The effect of activated charcoal on digoxin absorption is strong as shown earlier (Neuvonen *et al.*, 1978.) Without doubt activated charcoal is more effective than resins in preventing the gastrointestinal absorption of cardiac glycosides and in reducing their enterohepatic circulation. This property can be applied to the treatment of digitalis overdosage, but it should be kept in mind when charcoal is used in therapy concomitantly together with cardiac glycosides.

The ingestion of either cholestyramine or colestipol with propranolol has reduced to some extent the plasma concentrations of this basic drug (Hibbard *et al.*, 1984). Carbamazepine is a substituted amide. Its gastrointestinal absorption was uninfluenced in the present study by cholestyramine and only slightly reduced by colestipol. Carbamazepine was used as a slowly absorbable formulation, the peak concentration in plasma occurring at 24 h after the ingestion. Despite this slow absorption a single dose of activated charcoal (serving as a 'positive control') reduced substantially the bioavailability of carbamazepine. It has been shown earlier that in high oral doses activated charcoal can totally prevent the absorption of carbamazepine and, when given in multiple doses, oral charcoal can shorten its elimination half-life (Neuvonen & Elonen, 1980). Probably even moderate doses of activated charcoal, used in the therapy of diarrhoea and hypercholesterolaemias, may considerably reduce serum concentrations of this antiepileptic drug.

Some acidic drugs, such as warfarin and hydrochlorothiazide, show a decreased absorption (Jähnchen *et al.*, 1978; Hunninghake & King, 1978; Renowden *et al.*, 1985) while others, like aspirin and tolbutamide, have a delayed absorption when ingested with cholestyramine

(Hunninghake & Pollack, 1977). The absorption of phenytoin is unaffected both by cholestyramine and colestipol (Callaghan *et al.*, 1983). In the present study, the gastrointestinal absorption and the diuretic effect of frusemide, an acidic drug with a pKa of 3.8, was almost totally prevented by the concomitant administration of cholestyramine or colestipol. Yet, the effect of activated charcoal was even stronger. Because the absorption of frusemide is relatively rapid, its ingestion 2–3 h before the intake of non-systemic adsorbents helps to avoid this kind of interaction.

In the treatment of acute intoxications the high adsorption capacity of activated charcoal is a beneficial property. In the treatment of hyperlipidaemias the more selective action of resins may be advantageous, e.g., in the patients using digoxin or carbamazepine. In general, the resins are less liable to cause drug absorption interactions than activated charcoal. Certain systemically absorbable drugs, such as frusemide, are likely to be bound strongly by both the resins and charcoal. Such drugs should be taken 2–3 h prior to the ingestion of adsorbents to minimize the interaction.

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