The effect of cholestyramine and activated charcoal on glipizide absorption

K. T. KIVISTÖ & P. J. NEUVONEN

Department of Pharmacology, University of Turku, Turku, Finland

1 The interference of cholestyramine and activated charcoal with the absorption of glipizide was studied.

2 In a cross-over study comprising three phases, single doses of cholestyramine (8 g), activated charcoal (8 g) or water only were given to six healthy volunteers together with a single dose of glipizide.

3 The absorption of glipizide was moderately (29%, $P < 0.01$) reduced by cholestyramine and greatly reduced (81%, $P < 0.01$) by activated charcoal.

4 If cholestyramine and glipizide are used concomitantly, glipizide should be taken 1–2 h beforehand. In acute glipizide overdosage, activated charcoal can be used to reduce absorption.

Keywords cholestyramine activated charcoal glipizide absorption interactions

Introduction

Cholestyramine is an anionic-exchange resin that binds bile acids in the gastrointestinal tract. It can also interfere with the gastrointestinal absorption of several drugs. Absorption of oral anticoagulants, digitalis glycosides, and diuretics, for example, may be affected to a clinically significant degree (Hunninghake *et al.*, 1982; Jähnchen *et al.*, 1978; Neuvonen *et al.*, 1988). Many, but not all drugs, have been shown to adsorb to activated charcoal *in vitro* and *in vivo* and it is used in the treatment of acute intoxications (Neuvonen & Olkkola, 1988). Like cholestyramine, activated charcoal is also effective in lowering serum cholesterol concentration in hypercholesterolaemic patients (Neuvonen *et al.*, 1989).

Diabetic patients with hypercholesterolaemia may have to take hypolipidaemic drugs in addition to a sulphonylurea drug. Because cholestyramine impairs the absorption of certain acidic drugs and no data on its possible interference with the absorption of the 'second-generation' sulphonylureas were available, this potential inter-

action was studied using glipizide as a model drug. Activated charcoal was included as a 'positive control' and to evaluate its potential role in the treatment of acute glipizide intoxication.

Methods

Experimental design

Six male volunteers, age 28 ± 4 years (mean $\pm$ s.e. mean) and weight 76 ± 4 kg, participated in the study. They were considered to be healthy on the basis of medical history, physical examination and the results of routine laboratory tests. The study protocol was approved by the local ethics committee, and informed consent was obtained from each subject.

A cross-over design with three phases, at least 1 week apart, was employed. After an overnight fast, the subjects ingested 5 mg glipizide (Melizid, Medica, Finland) with 150 ml of water,

5 mg glipizide with 8 g cholestyramine (Questran, Lääkefarmos, Finland) as a suspension in 150 ml of water, or 10 mg glipizide with 8 g activated charcoal (Carbomix, Medica, Finland) as a suspension in 150 ml of water. A higher glipizide dose was given with charcoal to allow reliable analysis of plasma glipizide concentrations, as considerable interference with absorption was anticipated.

The subjects were under direct medical supervision, in the recumbent position, for 2 h from the beginning of the study, and no food was taken during that time. After the 2 h blood sample, the subjects were allowed to move and eat as desired. Timed blood samples for glipizide analysis were taken into heparinized tubes at 0, 0.5, 1, 2, 3, 5, 7 and 10 h after drug intake. Plasma was separated within 30 min of sampling, and the samples were stored at -20°C until analysed.

Determination of absorption

The extent of absorption was characterized by measuring the area under the plasma glipizide concentration-time curve from 0 to 10 h (AUC(0, 10 h)). In addition, peak plasma drug concentrations ($C_{\max}$) and peak times ($t_{\max}$) were observed. The AUC(0, 10 h) and $C_{\max}$ values in the charcoal phase were corrected to a dose of 5 mg of glipizide. The relative bioavailability of glipizide in the cholestyramine and charcoal phases was estimated by comparing the respective AUC values to the control value in each subject.

Glipizide assay

Plasma glipizide concentrations were measured by high-performance liquid chromatography, using tolbutamide as an internal standard (Wählin-Boll & Melander, 1979). The inter- and intra-assay coefficients of variation were 4.4% (mean 218 ng ml^{-1} , $n = 8$) and 3.7% (mean 159 ng ml^{-1} , $n = 9$), respectively.

Statistical analysis

Two-way analysis of variance was employed for analysis of the dose-normalized pharmacokinetic parameters. The pharmacokinetic parameters in the cholestyramine and charcoal phases were then compared with the control values by Student's *t*-test for paired values (two-tailed), where appropriate. Means $\pm$ s.e. means are given.

Results

Analysis of variance indicated a highly significant ($P < 0.001$) difference in the AUC(0, 10 h) and $C_{\max}$ values between the three phases. Cholestyramine and activated charcoal lowered the absorption of glipizide, measured as the area under the plasma concentration-time curve from 0 to 10 h, by 29% and 81%, respectively ($P < 0.01$, Table 1, Figure 1). Peak plasma glipizide concentration was lowered by 33% and 79%, respectively ($P < 0.01$). There was a trend for slower glipizide absorption in the cholestyramine phase.

Table 1 Effect of cholestyramine (8 g) and activated charcoal (8 g) on the absorption of glipizide, characterized by peak plasma concentration ($C_{\max}$)^a and area under the plasma concentration-time curve from 0–10 h (AUC(0, 10 h))^a, relative bioavailability, and peak time ($t_{\max}$)

	$C_{\max}$ (ng ml^{-1})	$t_{\max}$ (h)	AUC(0, 10 h) ($\text{ng ml}^{-1}\text{ h}$)	Relative bioavailability (% of control)
Control	425 ± 36	1.3 ± 0.33	1830 ± 267	100
Cholestyramine	285 ± 31^b	1.9 ± 0.41	1260 ± 145^b	71 (59–83)
Charcoal	89 ± 31^b	1.0 ± 0.22	352 ± 128^b	19 (8–37)

Relative bioavailabilities represent mean values together with ranges in six subjects. Otherwise, the values represent mean $\pm$ s.e. mean in six subjects.

^a The glipizide dose was 5 mg in the control and cholestyramine phases and 10 mg in the charcoal phase. $C_{\max}$ and AUC(0, 10 h) values are corrected to a dose of 5 mg glipizide.

^b Significantly ($P < 0.01$) different from control (Student's paired *t*-test, two-tailed).

Figure 1 The effect of cholestyramine (8 g, Δ) and activated charcoal (8 g, $\blacktriangle$) on the plasma concentration of glipizide (mean $\pm$ s.e. mean). The glipizide dose was 5 mg in the control and cholestyramine phases and 10 mg in the charcoal phase. Concentration values are corrected to a dose of 5 mg glipizide. $\circ$ control.

Mild to moderate hypoglycaemic symptoms, including palpitations, sweating and tremor in hands, were observed in the subjects during the control phase. Most subjects were symptomless during the cholestyramine phase, and no symptoms were observed during the charcoal phase. The symptoms peaked at 1–1.5 h and subsided spontaneously; no treatment was needed.

Discussion

Concomitant use of glipizide and anionic-exchange resins is common in diabetic patients. Because the resins are known to interfere with the absorption of many acidic drugs, it was surprising that no data were found in the literature concerning a possible cholestyramine-glipizide interaction. The present findings indicate that resins, at least cholestyramine, may decrease the bioavailability of glipizide and that there are considerable interindividual differences in the extent of this interaction. Although the average lowering of glipizide absorption was not more than 29%, the maximal reduction observed was 41%. Furthermore, it is possible that the extent of this interaction will be greater during prolonged use of the resins, when their concentrations in the gastrointestinal tract are higher.

In the present single-dose study, a moderate dose of 8 g cholestyramine was taken together with a 5 mg tablet of glipizide. Cholestyramine has been shown to impair the absorption of frusemide and hydrochlorothiazide by 95%

and 85%, respectively (Hunninghake *et al.*, 1982; Neuvonen *et al.*, 1988). In contrast, the extent of absorption of other acidic drugs, such as phenytoin, aspirin and tolbutamide, was found to be unaffected (Callaghan *et al.*, 1983; Hunninghake & Pollack, 1977). Thus, glipizide represents an 'intermediate' compound among drugs liable to be bound by cholestyramine. In any event, introducing cholestyramine to the drug regimen of a patient on glipizide therapy may cause clinically significant detrimental effects on blood glucose balance. Guar gum, a fibre preparation used in the treatment of diabetes mellitus, has been shown not to interfere with the absorption of glipizide (Huupponen *et al.*, 1985).

Activated charcoal was used in the present study mainly as a 'positive control'. All sulphonylureas are avidly adsorbed to activated charcoal *in vitro* and the gastrointestinal absorption of both chlorpropamide (250 mg) and tolbutamide (500 mg) is reduced by 90% by the ingestion of 50 g of activated charcoal (Neuvonen & Kärkkäinen, 1983; Neuvonen *et al.*, 1983). In the present study, the lowering of glipizide absorption by charcoal averaged 80%. According to *in vitro* data, an even more pronounced effect might have been anticipated. Thus, at a charcoal:glipizide ratio of 10:1 more than 99% of glipizide is bound *in vitro* (Kannisto & Neuvonen, 1984). In the present study, this ratio was 800:1. Consequently, it is possible that a proportion of the charcoal and cholestyramine suspensions escaped from the stomach before the dissolution of the glipizide tablets.

It has been suggested that glipizide undergoes enterohepatic circulation (Ferner & Chaplin, 1987). If this were the case, the presence of charcoal or cholestyramine in the gastrointestinal tract might enhance the elimination of glipizide by interrupting the enterohepatic circulation. Thus, the interaction would not be completely avoided by separating the administration of glipizide and the adsorbents.

In conclusion, simultaneous intake of glipizide with cholestyramine and even moderate doses of activated charcoal is best avoided. Therapeutic doses of glipizide are absorbed relatively rapidly, and taking it 1–2 h beforehand helps to minimize detrimental effects on glipizide absorption. In the case of acute glipizide overdosage, the absorption of glipizide may be prolonged and early administration of activated charcoal should be effective in lowering glipizide absorption.

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