The effects of magnesium hydroxide on the absorption and efficacy of two glibenclamide preparations

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- 1 The effect of magnesium hydroxide on the absorption and efficacy of two glibenclamide preparations was investigated in healthy volunteers in two separate studies, using a randomized cross-over design with two phases.
- 2 A single dose of magnesium hydroxide (850 mg) or water only (150 ml) was given immediately after the ingestion of a micronised (1.75 mg, seven subjects) or a non-micronised (2.5 mg, six subjects) preparation of glibenclamide. Plasma concentrations of glibenclamide, insulin and glucose were measured.
- 3 Magnesium hydroxide accelerated ($P < 0.05$) the absorption of glibenclamide from the micronised preparation to a small extent but the extent of absorption and the insulin and glucose responses were unaltered.
- 4 Coadministration of magnesium hydroxide with the non-micronised glibenclamide preparation increased the area under the plasma glibenclamide concentration-time curve from 0 to 3 h, five-fold ($P < 0.05$), the total area three-fold ($P < 0.05$) and the peak drug concentration three-fold ($P < 0.05$). The incremental insulin area from 0 to 3 h was increased 35-fold ($P < 0.05$) and the maximum insulin response 10-fold ($P < 0.05$) by magnesium hydroxide.
- 5 Concomitant ingestion of magnesium hydroxide and non-micronised glibenclamide may greatly enhance the absorption and efficacy of glibenclamide. The absorption of micronised glibenclamide appears to be only slightly influenced by magnesium hydroxide.

Keywords glibenclamide magnesium hydroxide absorption interactions
insulin glucose

Introduction

Glibenclamide, a second-generation sulphonylurea is widely used in the management of non-insulin dependent diabetes mellitus. Different glibenclamide preparations can, however, have quite different rates and extents of absorption, and, consequently, their effects on blood glucose are not identical (Haupt *et al.*, 1984; Karttunen *et al.*, 1985). The non-micronised preparations are slowly and incompletely absorbed, and display large inter-individual variation in their absorption (Ikegami *et al.*, 1986; Neugebauer *et al.*, 1985). Micronised formulations with a higher surface area have therefore been developed to improve the pharmacokinetic properties of glibenclamide. Autonomic neuropathy, resulting in delayed gastric emptying, may cause additional variability in the absorption of glibenclamide in diabetic patients (Ikegami *et al.*, 1986).

Many drug-antacid interactions have been described in the literature (Gugler & Allgayer, 1990; Hurwitz, 1977); most studies indicate reduced bioavailability or delayed absorption of the drug affected. On the other hand, magnesium hydroxide can increase the rate of absorption of the weakly acidic drugs, tolifenamic and mefenamic acids (Neuvonen & Kivistö, 1988). Recently, magnesium hydroxide and sodium bicarbonate were shown to accelerate the absorption and increase the glucose-lowering effect of glipizide (Kivistö & Neuvonen, 1991a,b). These findings prompted us to study whether the absorption of two different glibenclamide formulations could be influenced by magnesium hydroxide and also to determine the effects of the possible interaction on insulin and glucose responses.

Methods

Experimental design

The present investigation comprised two separate studies. Four male and three female volunteers, with a mean ($\pm$ s.e. mean) age of 23 ± 2 years and weight of 65 ± 3.5 kg, participated in Study 1, and four male and two female volunteers, with a mean age of 25 ± 1 years and weight of 71 ± 3.8 kg, in Study 2. 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 ethics committee of the Turku University Medical School. The subjects were thoroughly informed, and verbal consent was obtained.

A randomized cross-over design with two phases, at least 1 week apart, was employed in both studies. After an overnight fast, the subjects ingested a single dose of glibenclamide with 150 ml water or with 150 ml water containing 850 mg magnesium hydroxide (Milk of Magnesia, Winthrop Laboratories, England). Glibenclamide was administered as a micronised preparation (1.75 mg; Semi-Euglucon, Orion Pharmaceutica, Finland) in Study 1 and as a non-micronised preparation (2.5 mg; half a tablet of Gilemid 5 mg, Star, Finland) in Study 2.

The subjects were under direct medical supervision, in the recumbent position, for 3 h from the beginning of the study, and no food was taken during that time. After the 3 h blood sample, breakfast was given and the subjects were allowed to move and eat as desired. Hypoglycaemic symptoms were monitored during the study days, and glucose for both oral and intravenous use was available in case of severe hypoglycaemia (it was not needed). Timed blood samples for glibenclamide analysis were taken from an indwelling catheter into heparinized tubes, chilled on ice both before and after sample collection, at 0, 20, 30 and 45 min, and at 1, 1.5, 2, 3, 4, 5, 7 and 10 h after drug intake. Plasma insulin and glucose were measured in these samples from 0 to 3 h. Plasma was separated within 30 min of sampling at $+4^{\circ}\text{C}$, and the samples were stored at -20°C until analysed.

Analytical methods

Plasma glibenclamide concentrations were measured by high-performance reversed phase liquid chromatography, using a modified version of two previously published methods (Emilsson, 1987; Wählin-Boll & Melander, 1979). To 1 ml plasma was added 0.2 ml 0.5 M hydrochloric acid and 200 ng glipizide, the internal standard. The sample was then extracted with 5 ml of a mixture of dichloromethane and hexane (1:1), by shaking for 4 min. After centrifugation, the organic phase was evaporated to dryness under a stream of nitrogen at 40°C . The residue was redissolved in 70 μl of the mobile phase, and an aliquot of 20 μl was chromatographed on a LiChrosorb RP-18 column (5 μm particle size; E. Merck, Darmstadt, Germany). The mobile phase consisted of a mixture of methanol and 0.01 M phosphate buffer at pH 3.5 (65:35), and the flow-rate was 1.2 ml min^{-1} . The u.v. detector was set at 229 nm, and the sensitivity was kept

at 0.02 a.u.f.s. The assay limit for glibenclamide and the interassay coefficient of variation were 10 ng ml^{-1} and 6.6%, respectively.

Plasma insulin was measured by radioimmunoassay (Phadeseph Insulin RIA, Pharmacia Diagnostics AB, Uppsala, Sweden) and glucose by the glucose oxidase method (Reflotron, Boehringer Mannheim GmbH, Germany). The interassay coefficients of variation were 6.0% and 3.3%, respectively.

Pharmacokinetic analysis

In Study 1, the plasma concentration-time data for glibenclamide were fitted by an open one-compartment model by weighted least squares analysis with the SIPHAR programme (SIMED, Creteil, France), using the reciprocal of the concentrations as weighting factor. The rate and extent of glibenclamide absorption was characterized by the peak time (t_{max}), apparent half-life of absorption ($t_{1/2\text{abs}}$), peak plasma drug concentration (C_{max}) and the areas under the plasma drug concentration-time curve from 0 to 1 h (AUC(0, 1h)), 0 to 2 h (AUC(0, 2h)), 0 to 3 h (AUC(0, 3h)) and from 0 to 10 h (AUC(0, 10h)). The areas were calculated with the linear trapezoidal method. Glibenclamide was not detectable in any of the 10 h plasma samples. C_{max} and t_{max} values were obtained directly from the plasma drug-time profile for each subject. In addition, estimates of mean residence time (MRT) and terminal plasma half-life ($t_{1/2\text{z}}$) were obtained. In the data from Study 2 (non-micronised glibenclamide preparation) a linear elimination phase was not always discernible. Thus, data fitting was not carried out and only the C_{max} , t_{max} and AUC values were determined, as described above. Plasma glibenclamide could not be measured in one of the six subjects because of interfering peaks in the chromatograms.

Insulin and glucose responses

Insulin response was characterized by the incremental area under the plasma insulin concentration-time curve (the area above baseline) from 0 to 3 h measured using the linear trapezoidal method. In addition, the maximum rise in insulin concentration together with the peak time were determined. For glucose data, the decremental area under the plasma concentration-time curve (the area below baseline) from 0 to 3 h and the maximum fall in concentration, together with the time at which this occurred, were determined.

Statistical methods

The Wilcoxon paired-sample test (two-tailed) was used to compare the calculated parameters in the antacid phase with the control values. Plasma concentrations of glibenclamide, insulin and glucose were subjected to analysis of variance for repeated measurements, followed by Student's *t*-test for paired values (two-tailed) where appropriate. *P* values < 0.05 were considered to be statistically significant. Means $\pm$ s.e. means are given.

Results

Study 1—The effect of magnesium hydroxide on the absorption and efficacy of micronised glibenclamide

The apparent absorption half-life was shorter ($P < 0.05$) and the peak time occurred earlier ($P < 0.05$) in the antacid phase compared with the control phase (Table 1). The early fractional AUC values were increased by 20 to 90% in the antacid phase but these changes did not approach statistical significance. No significant changes were found in the peak plasma drug concentration, AUC(0, 10 h), MRT and elimination half-life. Analysis of variance for repeated measurements indicated a significant trials interaction ($P = 0.04$), i.e. there was a significant overall difference in the plasma glibenclamide concentration-time curve between the phases; the concentrations did not, however, differ at any time point (Figure 1). Insulin and glucose responses were unaffected by the concomitant administration of glibenclamide and magnesium hydroxide (Table 1, Figure 2).

Figure 1 Effect of magnesium hydroxide (850 mg, ●—●) on the absorption of micronised glibenclamide (1.75 mg), reflected in plasma glibenclamide concentrations (mean $\pm$ s.e. mean) in seven subjects. Control (○—○).

Figure 2 Plasma insulin and glucose levels (mean $\pm$ s.e. mean) in seven subjects after intake of 1.75 mg of micronised glibenclamide with water only (○—○) or with magnesium hydroxide (850 mg, ●—●).

Study 2—The effect of magnesium hydroxide on the absorption and efficacy of non-micronised glibenclamide

The extent of absorption, as measured by AUC(0, 10 h), and peak plasma drug concentration were increased approximately three-fold ($P < 0.05$) by magnesium hydroxide (Table 2). The AUC(0, 2 h) and AUC(0, 3 h) were increased six- and five-fold, respectively ($P < 0.05$); the nine-fold increase in the AUC(0, 1 h) and the

Table 1 Influence of magnesium hydroxide (850 mg) on the absorption and efficacy of micronised glibenclamide (1.75 mg)

	Control	Mg (OH) ₂	P
Glibenclamide			
<i>C</i> _{max} (ng ml ⁻¹)	117 $\pm$ 12.2	144 $\pm$ 24.7	NS
<i>t</i> _{max} (h)	1.8 $\pm$ 0.46	1.1 $\pm$ 0.31	< 0.05
<i>t</i> _{1/2abs} (h)	0.78 $\pm$ 0.17	0.41 $\pm$ 0.18	< 0.05
AUC(0, 1 h) (ng ml ⁻¹ h)	36.7 $\pm$ 16.9	68.4 $\pm$ 19.7	NS
AUC(0, 2 h) (ng ml ⁻¹ h)	118 $\pm$ 31.7	169 $\pm$ 44.0	NS
AUC(0, 3 h) (ng ml ⁻¹ h)	201 $\pm$ 32.6	245 $\pm$ 51.4	NS
AUC(0, 10 h) (ng ml ⁻¹ h)	372 $\pm$ 42.4	402 $\pm$ 61.9	NS
<i>t</i> _{1/2,z} (h)	1.5 $\pm$ 0.23	1.5 $\pm$ 0.15	NS
MRT (h)	3.1 $\pm$ 0.46	2.9 $\pm$ 0.34	NS
Insulin			
Incremental area (0, 3 h) (mu l ⁻¹ min)	673 $\pm$ 136	643 $\pm$ 132	NS
Maximum response (mu l ⁻¹)	10.3 $\pm$ 1.8	11.7 $\pm$ 2.5	NS
Time to maximum response (h)	1.4 $\pm$ 0.19	1.1 $\pm$ 0.14	NS
Glucose			
Decremental area (0, 3 h) (mmol l ⁻¹ min)	166 $\pm$ 14.6	179 $\pm$ 23.6	NS
Maximum response (mmol l ⁻¹)	2.2 $\pm$ 0.19	2.0 $\pm$ 0.16	NS
Time to maximum response (h)	2.1 $\pm$ 0.25	1.7 $\pm$ 0.26	NS

The values represent mean $\pm$ s.e. mean in seven subjects.

Table 2 Influence of magnesium hydroxide (850 mg) on the absorption and efficacy of non-micronised glibenclamide (2.5 mg)

	Control	Mg (OH) ₂	P
<i>Glibenclamide</i>			
C _{max} (ng ml ⁻¹)	34.2 ± 4.6	123 ± 21.4	< 0.05
t _{max} (h)	3.8 ± 0.86	2.3 ± 0.44	NS
AUC(0, 1 h) (ng ml ⁻¹ h)	2.40 ± 2.1	22.7 ± 10.1	NS
AUC(0, 2 h) (ng ml ⁻¹ h)	15.9 ± 10.9	95.9 ± 31.9	< 0.05
AUC(0, 3 h) (ng ml ⁻¹ h)	38.8 ± 17.8	194 ± 39.9	< 0.05
AUC(0, 10 h) (ng ml ⁻¹ h)	144 ± 19.8	390 ± 45.9	< 0.05
<i>Insulin</i>			
Incremental area (0, 3 h) (μU l ⁻¹ min)	15.7 ± 15.7	558 ± 260	< 0.05
Maximum response (μU l ⁻¹)	0.85 ± 0.50	9.8 ± 5.2	< 0.05
Time to maximum response ^a (h)	—	1.5 ± 0.22	
<i>Glucose</i>			
Decremental area (0, 3 h) (mmol l ⁻¹ min)	87.5 ± 31.2	137 ± 21.4	NS
Maximum response (mmol l ⁻¹)	1.4 ± 0.24	1.8 ± 0.22	NS
Time to maximum response (h)	2.8 ± 0.17	2.3 ± 0.25	NS

Glibenclamide parameters represent mean ± s.e. mean in five subjects (see text).

Otherwise, values represent mean ± s.e. mean in six subjects.

^a This was not determined in the control phase because the insulin concentration did not rise above baseline in most subjects.

Figure 3 Effect of magnesium hydroxide (850 mg, ●—●) on the absorption of non-micronised glibenclamide (2.5 mg), reflected in plasma glibenclamide concentrations (mean ± s.e. mean) in five subjects. * $P < 0.05$ compared with control (○—○).

earlier peak time (2.3 vs 3.8 h) failed to reach statistical significance. Analysis of variance for repeated measurements indicated a significant trials interaction ($P = 0.002$), and plasma glibenclamide concentrations were significantly higher at 2, 3 and 4 h in the antacid phase compared with the control phase (Figure 3).

A 35-fold increase in the incremental area under the plasma insulin concentration-time curve from 0 to 3 h was observed in the antacid phase ($P < 0.05$) (Table 2, Figure 4). In addition, a 10-fold enhancement of the maximum insulin response was noted ($P < 0.05$). The maximum fall in plasma glucose concentration and the corresponding time were not significantly changed by magnesium hydroxide (Table 2, Figure 4). However, a tendency towards enhanced glucose response was observed in the antacid phase, as reflected in the 57% larger decremental area under the plasma glucose concentration-time curve from 0 to 3 h. In addition, analysis of variance for repeated measurements indicated an enhanced glucose response during the antacid phase ($P = 0.003$).

Figure 4 Plasma insulin and glucose levels (mean ± s.e. mean) in six subjects after intake of 2.5 mg of non-micronised glibenclamide with water only (○—○) or with magnesium hydroxide (850 mg, ●—●). *Significant ($P < 0.05$) difference in change from baseline between treatments.

Discussion

Magnesium hydroxide increased the extent of glibenclamide absorption from the non-micronised preparation almost three-fold. This was associated with significantly enhanced insulin secretion and a moderate increase in glucose response. On the other hand, simultaneous intake of micronised glibenclamide with magnesium hydroxide resulted mainly in an increased rate of gliben-

clamide absorption; total bioavailability and insulin and glucose responses were unchanged. These findings are consistent with those found in a similar study with glipizide. Acceleration of the absorption of glipizide by magnesium hydroxide was accompanied by an earlier insulin response and a greater plasma glucose-lowering effect (Kivistö & Neuvonen, 1991a); similar results were obtained when sodium bicarbonate, but not aluminium hydroxide, was taken together with glipizide (Kivistö & Neuvonen, 1991b). The relationship between plasma sulphonylurea concentration and therapeutic effect is complex (Marchetti & Navalesi, 1989). However, the increased rate and extent of glibenclamide absorption, especially from the non-micronised formulation, appear to be of potential clinical importance. In diabetic patients, drug absorption may be delayed owing to autonomic neuropathy (Ikegami *et al.*, 1986). Therefore, there is a possibility that magnesium hydroxide could have a more pronounced effect in diabetic patients with gastroparesis, even affecting the absorption of micronised glibenclamide.

The absorption from non-micronised preparations is probably dissolution rate-limited and incomplete. Accordingly, improved dissolution of glibenclamide resulting from an elevated gastric pH is the most plausible mechanism of the observed interaction. Both glibenclamide and glipizide are weakly acidic drugs that are non-ionized but sparingly soluble in water at gastric pH. Although the observed absorption interactions may solely reflect an enhanced solubility of these drugs, elevated gastric pH and magnesium ions can also increase gastric emptying rate, and this might also account for improved absorption. Furthermore, various antacids differ in many respects and may contribute by different mechanisms to absorption interactions. Aluminium hydroxide does not share the interactions observed with magnesium hydroxide and sodium bicarbonate (Kivistö & Neuvonen, 1991b); apart from elevating gastric pH, aluminium compounds have adsorptive properties and can delay gastric emptying.

Advice is often given to take glibenclamide and other sulphonylureas half an hour before meals in order to attain an effective drug concentration by the time the meal has its greatest metabolic impact (Gerich, 1989); however, all studies do not support this concept. Significantly greater lowering of blood glucose was reported by Sartor *et al.* (1982), while no beneficial effects on blood glucose utilisation were observed in the recent study of Coppack *et al.* (1990). Bruce *et al.* (1988) presented evidence in support of the importance of the timing of insulin secretion in relation to meal intake. These investigators corrected the deficiency in early prandial insulin secretion with intravenous insulin in patients with non-insulin-dependent diabetes, and observed a

substantial improvement in prandial hyperglycaemia, while the same dose of insulin delayed by 30 min was of little benefit. In the present study, the mean plasma insulin concentration started to rise earlier and reached a higher level after the coadministration of magnesium hydroxide with glibenclamide, even when the micronised formulation was used.

Certain diabetic patients appear to have delayed absorption of sulphonylureas, as shown for both glipizide and glibenclamide (Ikegami *et al.*, 1986; Kradjan *et al.*, 1989). It has been suggested that this may lead to unexpected hypoglycaemia because of the time discrepancy between drug effect and food intake (Ikegami *et al.*, 1986). Glibenclamide seems to be more likely to provoke long-lasting and sometimes even fatal hypoglycaemia than other sulphonylureas (Ferner & Neil, 1989). Apart from alterations in gastrointestinal motility secondary to autonomic neuropathy, formulation factors may affect bioavailability of the drug. Slow and erratic absorption may increase the risk of late hypoglycaemias e.g. during the night. Chalk *et al.* (1986) found that the bioavailability of glibenclamide from three tablet preparations ranged from 0.24 to 0.69, relative to an oral solution. The non-micronised formulation is still used in many countries, e.g. the United States of America. The present study was not designed to compare the bioavailabilities of the two formulations used. It is obvious, however, that these formulations display markedly different absorption characteristics and that their effects on blood glucose differ accordingly. The extent of absorption of the micronised formulation appeared to be 3–4 times higher than that of the non-micronised formulation, when administered without the antacid. Our data suggest that a comparable enhancement of glibenclamide absorption can be achieved either by elevating the gastric pH or by using a micronised formulation.

Although our findings in healthy subjects cannot be applied directly to the treatment of diabetic patients, it should be realized that antacids may modify the response to glibenclamide. Inadequate response to drug therapy is often a problem in the treatment of diabetes, and, therefore, increasing the effect of glibenclamide by means of magnesium hydroxide, for example, might be beneficial. On the other hand, as the therapeutic range of hypoglycaemic drugs is narrow, an unexpected increase in the rate or extent of glibenclamide absorption, due to e.g. concomitant intake of magnesium hydroxide, might result in hypoglycaemia in a patient whose blood glucose has previously been normal.

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