J. Pharm. Pharmacol. 1996, 48: 899–901
Received January 26, 1996
Accepted March 19, 1996

The Effect of pH on the In-vitro Dissolution of Three Second-generation Sulphonylurea Preparations: Mechanism of Antacid-sulphonylurea Interaction

PASI LEHTO, KARI LAINE, KARI T. KIVISTÖ* AND PERTTI J. NEUVONEN*

*Department of Pharmacology and Clinical Pharmacology, University of Turku, Turku, and *Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland*

Abstract

Simultaneously administered magnesium hydroxide or sodium bicarbonate can increase the rate and extent of absorption of non-micronized glibenclamide and glipizide. To clarify the mechanism of this interaction we have studied the effect of pH on the dissolution of two different formulations of glibenclamide (micronized and non-micronized) and one formulation of glipizide.

One tablet of each sulphonylurea preparation was placed in a dissolution chamber containing continuously mixed dissolution medium at pH 2, pH 6 or pH 9; 5 mL of the medium was replaced every 2 min. The amount of glibenclamide dissolved from the non-micronized formulation within 2 h, was 1·2, 4·5 and 76% at pH 2, pH 6 and pH 9, respectively ($P < 0.01$), whereas 21, 29 and 100% was dissolved from the micronized formulation ($P < 0.01$). The amount of glipizide dissolved within 2 h at pH 2, pH 6 and pH 9 was 3·9, 24 and 92%, respectively ($P < 0.01$).

We conclude that the elevated pH of the gastric contents is the most likely explanation for the interactions previously demonstrated between antacids and sulphonylureas after their concomitant ingestion.

The sulphonylureas glipizide and glibenclamide are weak acids (pK_a 5·9 and 5·3, respectively) only sparingly soluble in gastric juice (Marchetti & Navalesi 1989). The absorption of glibenclamide from different preparations can be highly variable, although micronized high surface-area glibenclamide preparations are more rapidly and completely absorbed (Rupp et al 1972; Neugebauer et al 1985).

Magnesium hydroxide and sodium bicarbonate, but not aluminium hydroxide, can considerably increase the rate or extent, or both, of absorption of glibenclamide and glipizide in man (Kivistö & Neuvonen 1991a, b; Neuvonen & Kivistö 1991, 1994). The bioavailability of glibenclamide from a non-micronized formulation was increased by more than 300% by concomitant ingestion of magnesium hydroxide (Neuvonen & Kivistö 1991). To clarify the role of pH in these interactions we have performed in-vitro dissolution experiments with two different formulations of glibenclamide and one formulation of glipizide.

Materials and Methods

Formulations

The tablets used contained non-micronized glibenclamide (5 mg; Gilemid, Leiras, Finland), micronized glibenclamide (1·75 mg; Semi-Euglucon, Orion, Finland) or glipizide (5 mg; Melizid, Leiras, Finland). The same formulations were used in our earlier studies on healthy subjects.

Correspondence: K. Laine, Department of Pharmacology and Clinical Pharmacology, University of Turku, Kiinamyllynkatu 10, SF-20520 Turku, Finland.

In-vitro dissolution

The in-vitro dissolution experiments were performed in the Sartorius dissolution simulator (Sartorius Solubility Simulator SM 16751; Sartorius GmbH, Göttingen, Germany) at room temperature. The tablet was placed in the dissolution chamber containing 100 mL (simulating the volume of gastric juice) of continuously mixed dissolution medium at pH 2 (0·1 M hydrochloric acid), pH 6 (0·05 M phosphate buffer) or pH 9 (0·05 M phosphate buffer). A 5-mL sample was drawn from the chamber through filters every 2 min and replaced with equal volume of fresh medium. The samples were analysed spectrophotometrically (Perkin-Elmer Lambda 2 UV/Vis Spectrophotometer; Perkin-Elmer Corporation, Uberlingen, Germany), glibenclamide at 300 nm and glipizide at 274 nm. The dissolution of all formulations was measured for up to 2 h in three separate runs for each formulation at each pH.

Statistics

The results are given as mean ± s.d. Parameters were analysed statistically by one-way analysis of variance. When significant differences were found, the Tukey test was applied to find the sources of the differences.

Results

At higher pH the drug dissolution was more rapid and complete for all three sulphonylurea formulations. The particle size of the two glibenclamide formulations had a significant effect on their dissolution. The effect of pH on the dissolution of non-micronized and micronized formulations of glibenclamide and the one formulation of glipizide are presented in Fig. 1.

The amounts of non-micronized glibenclamide dissolved

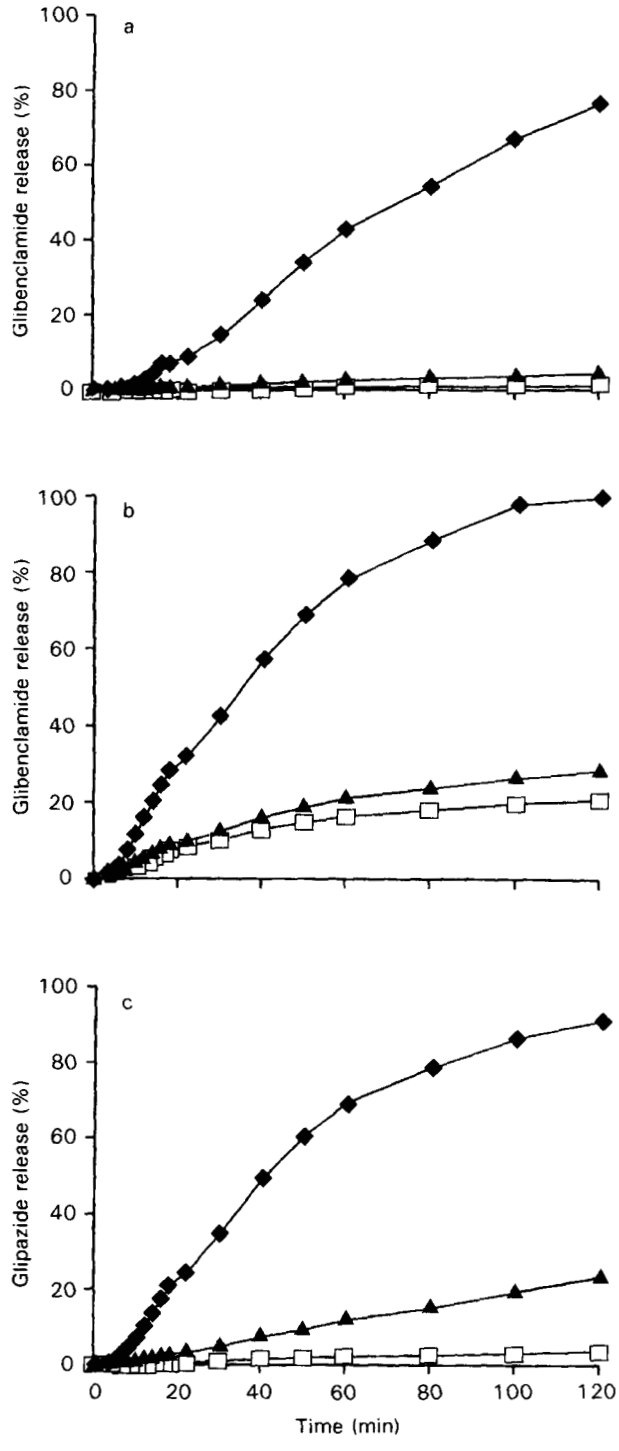

FIG. 1. In-vitro dissolution of non-micronized glibenclamide (a), micronized glibenclamide (b) and glipizide (c), given as percentage of the dose (mean of three experiments). □ pH 2, ▲ pH 6, ◆ pH 9.

within 2 h at pH 2, pH 6 and pH 9 were $1{\cdot}2 \pm 0{\cdot}3$ (mean ± s.d.), $4{\cdot}5 \pm 1{\cdot}8$ and $76 \pm 1{\cdot}0\%$, respectively ($P < 0{\cdot}01$). The micronized glibenclamide formulation dissolved better than the non-micronized, $21 \pm 1{\cdot}8$, $29 \pm 6{\cdot}3$ and $100 \pm 6{\cdot}7\%$ being dissolved at pH 2, pH 6 and pH 9, respectively ($P < 0{\cdot}01$). The amounts of glipizide dissolved at pH 2, pH 6 and pH 9 were $3{\cdot}9 \pm 3{\cdot}2$, $24 \pm 1{\cdot}1$ and $92 \pm 0{\cdot}5\%$, respectively ($P < 0{\cdot}01$).

Discussion

The higher the pH of the dissolution medium, the faster was the dissolution of all three sulphonylurea preparations studied. The magnitude of the effect of pH on the dissolution of these sulphonylureas differed markedly, however. At pH 6 only 5% of non-micronized glibenclamide was dissolved, whereas 29% was dissolved from the micronized preparation at the same pH. As expected, the micronized preparation dissolved better at every pH studied. At pH 9, 24% of the non-micronized preparation of glibenclamide remained undissolved, whereas the micronized preparation and glipizide were almost completely dissolved. Similarly to the micronized glibenclamide preparation only about 25% of glipizide was dissolved at pH 6.

The results of this in-vitro study are in good agreement with our previous in-vivo studies. In healthy volunteers, sodium bicarbonate (3 g) increased the area under the curve of glipizide from 0 to 2 h (AUC_{0-2} by 100% (Kivistö & Neuvonen 1991b). This increase in the early bioavailability of glipizide also resulted in increased insulin and glucose responses. In contrast, aluminium hydroxide (1 g) had no significant effect on the absorption of glipizide (Kivistö & Neuvonen 1991b). The 1·0- and 3·0-g doses of sodium bicarbonate increased the AUC_{0-2} of plasma glibenclamide (non-micronized formulation) approximately 3-fold (Kivistö et al 1993). The total bioavailability of glibenclamide was not, however, affected. Co-administration of magnesium hydroxide (0·85 g) with the non-micronized glibenclamide preparation increased the AUC_{0-10} 3-fold and resulted in an increased hypoglycaemic effect (Neuvonen & Kivistö 1991). On the other hand, only the initial absorption, but neither the extent of absorption nor the hypoglycaemic activity, of micronized glibenclamide was altered (Neuvonen & Kivistö 1991). Thus the non-micronized preparation of glibenclamide is likely to be more susceptible to pH-dependent changes in dissolution than the micronized preparation of glibenclamide or glipizide.

The effect of magnesium hydroxide on the absorption of sulphonylureas is, in general, greater than that of sodium bicarbonate or aluminium hydroxide; aluminium hydroxide does not increase the absorption of sulphonylureas. Magnesium hydroxide can increase gastric pH more than other antacids (Tuderman et al 1979). In-vitro, 0·85 g magnesium hydroxide elevated the pH of simulated gastric contents (100 mL 0·1 N HCl) to > 9, whereas 1 g and 3 g sodium bicarbonate elevated it to 6 and 7, respectively (Tuderman et al 1979). Aluminium hydroxide increases the pH of the gastric contents in-vitro and in-vivo only to about 4–5, i.e. much less than magnesium hydroxide (Tuderman et al 1979). Aluminium hydroxide can, moreover, adsorb many substances on its surface thus preventing their absorption.

Sulphonylureas are weakly acidic drugs with pK_a values of approximately 5; they are, therefore, non-ionized and sparingly soluble in water at gastric pH. Accordingly, an increase in gastric pH can enhance their solubility and, hence improve the dissolution of sulphonylurea formulations. We conclude, that the accelerated absorption of sulphonylureas and their enhanced effect, observed in our previous studies in healthy

subjects, are likely to be a result of accelerated dissolution of these drugs at higher pH.

References

Kivistö, K. T., Neuvonen, P. J. (1991a) Enhancement of absorption and effect of glipizide by magnesium hydroxide. Clin. Pharmacol. Ther. 49: 39–43

Kivistö, K. T., Neuvonen, P. J. (1991b) Differential effects of sodium bicarbonate and aluminium hydroxide on the absorption and activity of glipizide. Eur. J. Clin. Pharmacol. 40: 383–386

Kivistö, K. T., Lehto, P., Neuvonen, P. J. (1993) The effects of different doses of sodium bicarbonate on the absorption and activity of non-micronized glibenclamide. Int. J. Clin. Pharmacol. Ther. Toxicol. 31: 236–240

Marchetti, P., Navalesi, R. (1989) Pharmacokinetic-pharmacodynamic relationships of oral hypoglycaemic agents. Clin. Pharmacokinet. 16: 100–128

Neugebauer, G., Betzien, G., Hrstka, V., Kaufmann, B., von Möllendorf, E., Abshagen, U. (1985) Absolute bioavailability and bioequivalence of glibenclamide (Semi-Euglucon N). Int. J. Clin. Pharmacol. Ther. Toxicol. 23: 453–460

Neuvonen, P. J., Kivistö, K. (1991) The effects of magnesium hydroxide on the absorption and efficacy of two glibenclamide preparations. Br. J. Clin. Pharmacol. 32: 215–220

Neuvonen, P. J., Kivistö, K. (1994) Enhancement of absorption by antacids-an unrecognized drug interaction. Clin. Pharmacokinet. 27: 120–128

Rupp, W., Christ, O., Fülberth, W. (1972) Untersuchungen zur Bioavailability von Glibenclamid. Arzn. Forsch. 22: 471–473

Tuderman, V., Klinge, E., Lind, H. (1979) In vitro evaluations of antacid suspensions marketed in Finland. Acta Pharm. Fenn. 88: 63–72