Bioavailability of Glipizide and its Effect on Blood Glucose and Insulin Levels in Patients with Non-insulin-dependent Diabetes

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The bioavailability of glipizide, plasma glucose, and insulin levels were measured in seven patients with non-insulin-dependent diabetes mellitus. Glucose and insulin response to three standard meals was measured at 11 identical time points on the day of placebo administration and on the first and 15th day of glipizide administration (mean dose of 8.7 mg glipizide orally per day). The bioavailability profile of glipizide was highly consistent between day 1 and day 15 of administration. On both days, the drug peaked within 1.2–1.8 h and displayed a plasma half-life of between 2.5 and 3.2 h. While insulin levels were significantly ($P < 0.05$) increased at 4 of 11 time points of day 1, significantly elevated insulin levels were found at one time point on day 15 of glipizide administration. Insulin levels were found to be increased only in the presence of plasma drug concentrations of 200 ng/ml or greater. The hypoglycemic effect of the drug was significantly greater on day 15 than on day 1 of administration, and a significant hypoglycemic effect was noted even when drug levels were undetectable in plasma. DIABETES CARE 5: 497–500, SEPTEMBER–OCTOBER 1982.

The critical issue in evaluating any drug is the ultimate efficacy of therapy compared with proven toxic effects. In the past, it was difficult to assess this efficacy/toxicity ratio in diabetes mellitus because methods of measuring effectiveness of "diabetic control" were generally unreliable. Recent studies show that many sequelae of diabetes may not only be prevented but reversed by lowering blood glucose to more normal levels.[1–4]

Although it is generally accepted that the sulfonylurea drugs lower blood glucose levels, the effectiveness of these agents in treating diabetes has been controversial since publication of the University Group Diabetes Program Study.[5] One of the important, but as yet unresolved, factors concerning this series of studies is that it failed to document adequately the degree of blood glucose control achieved in each group of patients in part because an integrator of blood glucose such as hemoglobin A_{1c} was not available. A drug that either stimulates insulin secretion or has insulin-like action may have additional effects quite distinct from those of insulin. Since new oral hypoglycemic agents may be given in dosages of less than one-hundredth that of the presently marketed sulfonylureas and since these drugs may lower glucose in ways not critically related to insulin levels, further evaluation of their efficacy in controlling glucose seems warranted.

Glipizide is a new oral hypoglycemic agent. A substituted phenylsulfonylurea, the drug effectively lowers blood glucose at considerably lower doses than most other sulfonylurea compounds.[6,7] The purpose of this study was to investigate the mechanism of action of glipizide and to determine whether its hypoglycemic effects correlated with plasma drug levels, insulin levels, or some as yet unknown property of the drug. To accomplish this goal, plasma levels of glipizide were compared with plasma glucose and insulin levels.

MATERIALS AND METHODS

Four male and three female patients with non-insulin-dependent diabetes mellitus (Table 1) were hospitalized for study at Rockefeller University Hospital. Their ages ranged from 30 to 60 yr, and all patients had fasting plasma glucose levels greater than 130 mg/dl on at least two previous outpatient visits and after a preliminary diet program. Other characteristics of these patients included a hemoglobin value greater than 12 g/dl, absence of known peripheral vascular disease, and a negative history of insulin therapy.

Before selection for study, patients underwent a thorough history, physical examination, and laboratory tests in the hospital clinic. At this time, informed consent for participation was obtained and the patients were placed on a weight-stabilization program consisting of a diet of 20–25 cal/kg

TABLE 1
Patient data

Patient	Sex	Weight	Height	Ideal body wt (%)	Duration diabetes (yr)
1	M	77.3	5'10"	106	12
2	F	56.8	4'10"	117	7
3	M	81.4	5'9"	115	15
4	F	52.3	5'2"	97	9
5	F	75.9	5'4½"	133	13
6	M	76.8	5'7"	115	8
7	F	63.6	5'5"	108	4

body wt with 40–45% of calories from carbohydrates, 20% from protein, and 35–40% from fat. Breakfast, lunch, and dinner comprised 33% of the total calories each with consistent carbohydrate content as noted above. Only those patients who maintained a fasting plasma glucose level over 130 mg/dl after 2 wk on the prescribed diet were admitted to the hospital for the drug trial.

Criteria for exclusion from the study included a history of allergy, ketoacidosis, hypersensitivity to sulfonlyurea drugs, and the presence of hepatic or renal disease (defined as a BUN greater than 20 mg/dl, a serum creatinine greater than 2 mg/dl, or a prothrombin time greater than 3 s above control). Serious or chronic disease, current infection, anticipated major surgery, known alcohol abuse, pregnancy, or the use of inadequate contraceptive techniques were also criteria for exclusion.

The hospital study took place over a 16-day period. Patients were admitted to the hospital and their glucose and insulin levels were measured before and after breakfast, lunch, and supper on day 1. On days 2–16, glipizide in a dose of 0.1 mg/kg body wt was given with breakfast. On days 2 and 15, plasma glipizide, insulin, and glucose were measured at 11 specific times after giving glipizide immediately before breakfast (0, 1, 1.5, 2.5, 4.5, 5.5, 6.5, 9.5, 10.5, 11.5, and 24.5 h). Plasma glucose levels were measured with an autoanalyzer, and insulin was measured by radioimmunoassay.[6] All meals were carefully weighed so that they were consistent on each day of the study. Statistics utilized a one-tailed test for glucose since it was assumed that glipizide did not increase glucose levels. Both one-tailed and two-tailed tests were used for insulin levels.

Plasma glipizide levels[1] were obtained using high-pressure liquid chromatography. Blood was drawn in EDTA and placed on ice. The sample was immediately spun, and the plasma was separated and frozen at −80°C until analysis was performed. For analysis, 1 ml of plasma was combined with 15 μg 10,11-dihydrocarbamazepin (Aldrich 19, 542-1) in water as an internal standard.

The sample was made basic with 0.1 ml concentrated ammonium hydroxide and extracted with 2.0 ml ethyl ether. The ether layer was discarded, and the sample was acidified with 0.2 ml concentrated hydrochloric acid and 0.5 ml of 0.2 M acetate buffer at pH 4 and extracted with 2 ml chloroform. After separation, 1.6 ml of the chloroform extract was evaporated to dryness under nitrogen and reconstituted with 100 μm of 27% acetonitrile in 0.1% acetic acid.

For chromatography, 40 μm (equivalent to 0.32 ml of the original plasma) was injected through a Rheodyne 7105 valve into a liquid chromatograph (Perkin-Elmer Series 3 with LC-65T variable wavelength uv detector/oven and Perkin-Elmer PEP-1 computer). The instrument contained a precolumn (Whatman no. 4390-403) and a Perkin-Elmer HC-ODS SIL-X 0.26 × 25-cm column. The column temperature was set at 40°C, the flow rate at 1.0 ml/min, and the wavelength at 228 nm. The retention time for glipizide was 7.8 min and for the internal standard it was 4.9 min. The method was capable of accurately detecting 5 ng of injected glipizide and the mean percent recovery for glipizide in plasma was 72.9% ± 5.2 SD for a concentration range of 100–2500 ng/ml. A standard curve was obtained daily with each run employing 8 points between 0 and 1200 ng/ml.

RESULTS

Figure 1 shows the bioavailability profile of glipizide at various times points on day 1 and day 15 of administration. Comparison of both days showed a high consistency in plasma drug levels; no statistically significant difference was observed between drug levels on day 1 and day 15. Peak plasma concentrations of glipizide occurred between 1 and 1.5 h following administration, a time when blood glucose levels following breakfast were also peaking (Figure 2).

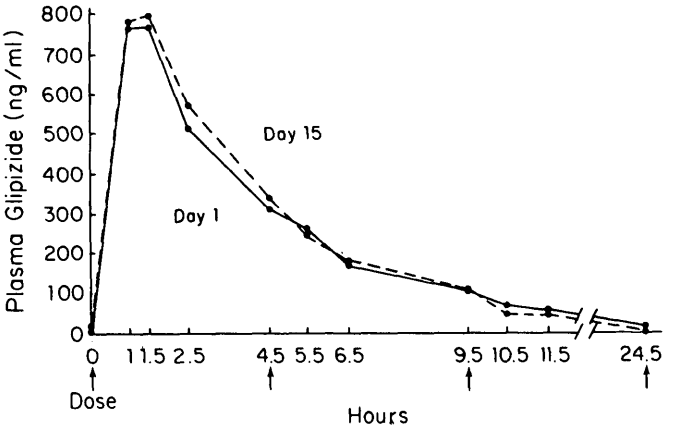

FIG. 1. Mean glipizide concentrations in plasma following oral glipizide administration at 0 h. As shown, the levels were determined for 24.5 h post-glipizide administration. Each value represents the mean of seven patients. The black line represents values from day 1 while the dashed line represents values from day 15. AUC, area under curve = 3660 day 1 and 3700 day 15 (P = NS). T_{max}, time in hours to peak drug levels = 1.8 h day 1 and 1.2 h day 15 (P = NS). C_{max}, peak concentration of drug in ng/ml = 921 day 1 and 857 day 15 (P = NS). T½, the time (h) for 50% disappearance of drug from C_{max} = 3.2 day 1 and 2.5 day 15 (P = NS).

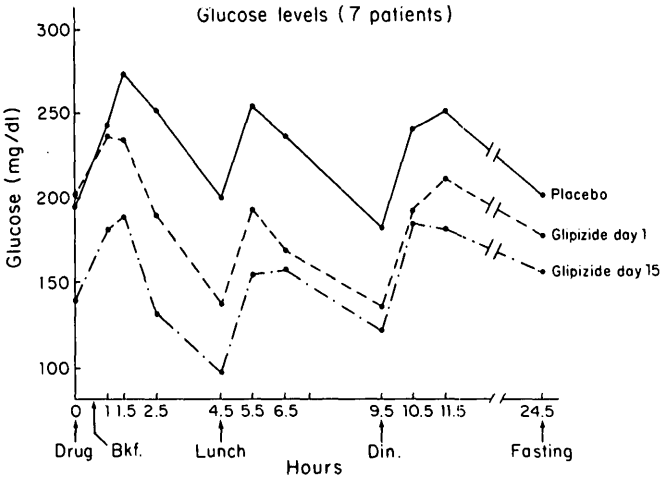

FIG. 2. Mean glucose levels (mg/dl) in the patients on the various study days. The solid lines represent the placebo period, the dashed line represents glipizide day 1, and the dotted and dashed lines day 15 of glipizide administration ($P < 0.05$ between 1.5 and 11.5 h day 1 vs. placebo and $P < 0.05$ at all time points day 15 vs. placebo).

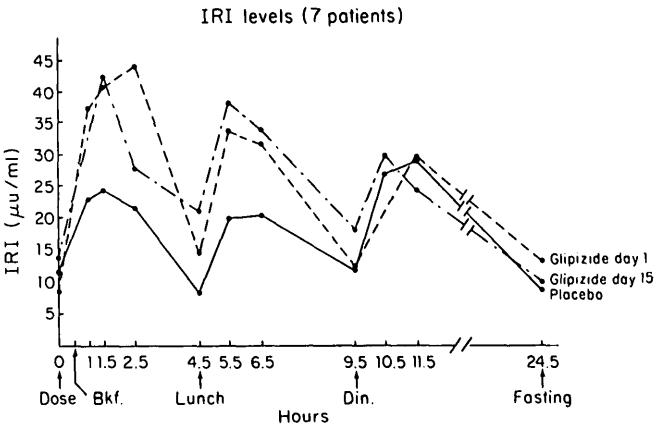

FIG. 3. Mean insulin levels in the patients on days of study. The solid lines represent the day of placebo administration, the dashed lines represent day 1 of glipizide administration, and the dashed and dotted lines represent day 15 of glipizide administration. Insulin levels were significantly ($P < 0.05$) greater than placebo at 1.5, 2.5, and 6.5 h on day 2 but only at 4.5 h on day 15 utilizing a two-tailed test.

Within 4.5 h, 50% of the drug was cleared from the plasma, and plasma clearance was 90% at 10 h.

Glucose concentrations and statistical data at various time points on day 1 and day 15 of glipizide administration are depicted in Figure 2.

On both days, glipizide lowered fasting glucose and restrained postprandial hyperglycemia when glucose levels were compared with those found when placebo was given. On day 1, differences from placebo were statistically significant between 1.5 and 11.5 h ($P < 0.05$). Differences in blood glucose levels were lower on day 15 than on day 1 of drug administration, and the differences between day 15 and placebo were statistically significant at all time points ($P < 0.05$). Differences between glipizide on day 1 and day 15 were also significant at all time points. Of note was that a hypoglycemic effect occurred at time points when the drug was no longer detectable in plasma (Figure 1).

Figure 3 shows the insulin levels at the various time points on day 1 and day 15 of glipizide administration. On day 1, there was a significant ($P < 0.05$) increase in the levels of plasma insulin placebo at 1.5, 2.5, 5.5, and 6.5 h for both one- and two-tailed tests of significance. On day 15 of glipizide administration, the difference or placebo was significant ($P < 0.05$) at 1.5, 4.5, and 5.5 h if a one-tailed test is used but only at 4.5 h if a two-tailed test is used. In contrast with plasma glucose, no significant differences were observed in plasma insulin levels on day 1 versus day 15 of glipizide administration.

It is noteworthy that plasma insulin levels were increased concomitant with detectable circulating drug levels. On day 1 of glipizide administration, drug concentrations were 200–750 ng/ml when insulin levels were significantly increased above the corresponding time points of the day of placebo administration. On day 15 of drug administration, insulin levels were significantly increased above those seen on the placebo day at 4.5 h when drug concentrations were still greater than 200 ng/ml.

DISCUSSION

The results of this study show that glipizide possesses a highly consistent bioavailability profile. The drug achieves peak plasma levels between 1.2 and 1.8 h after oral administration and has a serum half-life between 2.5 and 3.2 h. This profile is similar on both day 1 and day 15 of administration.

The study findings also support previous observations that sulfonylurea compounds exert a hypoglycemic effect independent of detectable drug levels in plasma.[7,8] Plasma insulin levels were significantly increased over placebo values on day 1 of glipizide administration, and the increase was still significant at one time point by day 15 of drug administration. Increased insulin levels were documented only in the presence of drug concentrations of 200 ng/ml or greater. In contrast, the difference in plasma glucose levels on day 15 of glipizide administration between glipizide and placebo was actually greater than that observed on day 1. While on day 1 there was a statistically significant lowering of plasma glucose at 8 of the 11 time points, all 11 time points were significantly decreased over placebo by day 15 of administration. Furthermore, plasma glucose levels were significantly lower on day 15 than on day 1 of glipizide administration at 5 of the 11 time points. The results for fasting plasma glucose on day 15 of glipizide administration are especially noteworthy. A significant decrease in plasma glucose levels was observed, despite the fact that no drug was detected and plasma insulin levels were no greater than they were during the placebo study.

Based on these findings, it appears that glipizide may exert a hypoglycemic effect by mechanisms unrelated to the drug's

plasma concentration or its effect on plasma insulin levels. Although the mechanism of this effect remains unknown, one might postulate that glipizide lowers blood glucose by increasing the number of insulin receptors.[7] Activity at the cell membrane has been observed with sulfonylurea compounds.[7,9] Moreover, as with other low-dosage sulfonylureas, the molecular structure of glipizide is characterized by the substitution of lipophilic moieties of the R1 and R2 positions. These lipophilic substitutions would not only result in greater solubility in cell membranes than that of older sulfonylurea compounds but might also explain the increased potency and duration of action of low-dosage agents.

Although further studies are needed to define the mechanisms of action of glipizide and similar agents, it appears that these compounds possess hypoglycemic properties distinct from those resulting from increased circulating insulin. It is possible that they exert additional distinguishing actions as well. Such considerations, combined with improvements in measuring control of hyperglycemia through minor hemoglobins,[10] should allow the reevaluation of the efficacy/toxicity ratio of sulfonylurea compounds in a more rational manner.

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