Impaired Effect of Sulfonylurea Following Increased Dosage*

E. Wåhlin-Boll, G. Sartor, A. Melander, and B. Scherstén

Departments of Community Care Sciences (Dalby), Clinical Pharmacology (Malmö General Hospital) and Internal Medicine (Lund University Hospital), University of Lund; Dalby, Malmö and Lund, Sweden

Summary. Ten Type 2 diabetics were examined during long-term treatment, at two dosage levels, with chlorpropamide once daily and glipizide t.i.d. Drug concentrations were measured by gas chromatography and high-pressure liquid chromatography, respectively, plasma insulin (IRI) by radio-immunoassay, and blood glucose enzymatically. Both drugs gave continuous sulfonylurea exposure, even at the lower dosage, and the mean plasma concentrations were almost doubled after the increase in dose. Neither the IRI nor the glucose response to meals showed any therapeutic improvement following the increase in chlorpropamide dosage. The lower dosage of glipizide produced better glucose utilization than chlorpropamide. On the other hand, the increased dose of glipizide led to impairment instead of further improvement. As this was associated with enhanced rather than reduced IRI levels, the impairment might have been due to increased peripheral insulin resistance. Thus, glipizide offers a therapeutic advantage over chlorpropamide, but its effectiveness may be restricted not only by limitations set by the disease, but also by counter-regulatory mechanisms that develop during continuous exposure to sulfonylureas at high levels.

Key words: diabetics, chlorpropamide, glipizide; dosage increase, impaired effect, blood glucose, plasma insulin

It is clinical experience that long-term sulfonylurea treatment is often insufficient. This may be due to a true inefficiency of sulfonylureas, but inadequate dosage may contribute to the therapeutic failure.

Previous studies have shown very great interindividual variation in the steady state concentrations of sulfonylureas. Indeed, some patients have had undetectable or very low plasma concentrations of sulfonylureas, which may account for certain therapeutic failures [1–3]. There are also pronounced potency differences between sulfonylureas of the first (e.g. tolbutamide and chlorpropamide) and the second (e.g. glibenclamide and glipizide) generations [4]. In addition, at least glibenclamide and glipizide may improve glucose utilization not only by stimulating insulin release but also by enhancing the effects and utilization of insulin [5–7].

In order to study how changes in dosage might influence the therapeutic effects of a first- and a second-generation sulfonylurea, ten Type 2 diabetics were examined during long-term treatment with chlorpropamide and glipizide at two different dosage levels, with monitoring of the plasma concentrations of the drugs.

Material and Methods

Patients

One female and 9 male Type 2 diabetics, who were regular attenders at the Lund University Hospital, were studied after they had given informed consent to the investigation. Their ages were 47–66 years (mean ± SD 58 ± 6 years) and their mean body mass index (kg/m²) was 28.0 ± 4.9 (range 18.7–34.3). All had normal hepatic and renal function tests. None had any endocrine disease apart from diabetes. All patients were seen by the same physician and had been found to respond unequivocally to dietary regulation and sulfonylurea.

Dosage of Chlorpropamide and Glipizide

For at least one month, 5 of the patients were initially kept on chlorpropamide¹, while the other 5 were taking glipizide². The former 5 were then switched to

¹ Diabines(®), Pfizer Corp., Groton, Conn., USA
² Minid® diab®, Farmitalia Carlo Erba, Milano, Italy
glipizide, and the latter 5 to chlorpropamide. After at least another month on the second treatment, its dosage was increased (see further below). After at least one month on the third treatment, the patients on high dose chlorpropamide were switched to high dose glipizide, and vice versa.

The resulting mean daily doses were chlorpropamide 278 and 431 mg and glipizide 14.75 (5.25 + 4.75 + 4.75) and 25 (8.5 + 8.0 + 8.5) mg, respectively.

Intake of Drug and Meals on Examination Days

Each subject came in the fasting state to the Out-Patient Department of the Medical Clinic on four different occasions, after at least one month on each therapeutic regimen. An initial blood sample was taken at 8.00 a.m. A standardized breakfast was served at 8.30 a.m., a standardized lunch at 11.30 a.m., and a standardized dinner at 4.30 p.m. Both drugs were ingested at breakfast, and glipizide was also taken at lunch and dinner time.

Meal Composition

The breakfast consisted of low-fat milk (300 g), 2 slices of white bread (50 g) with butter (10 g) and cheese (35 g), and non-sweetened black coffee (150 ml). This yielded a total energy of 1800 kJ (430 kcal). The lunch comprised fried fillet of veal (100 g) with gravy, potatoes (150 g) and peas (70 g), canned peaches (150 g) and orange juice (200 g), yielding 2400 kJ (575 kcal). The dinner consisted of boiled hen (100 g) with parsley, gravy, potatoes (100 g), carrots (70 g), 1 slice of dark bread (25 g), butter (5 g) and low-fat milk (200 g), totalling 2150 kJ (510 kcal). Thus, the total energy intake per examination day was 6350 kJ (1515 kcal), as 22% protein, 33% fat and 45% carbohydrate.

Blood Sampling

Serial blood samples were taken through an indwelling antecubital venous polyethene catheter. On each occasion, 1–2 ml blood were drawn and discarded before the 10 ml samples were collected. Samples for subsequent determination of blood glucose, and plasma insulin, chlorpropamide and glipizide were collected -30, 0, 30, 60, 120, 180, 210, 240, 300, 360, 420, 480, 510, 540 and 600 min after breakfast.

Analyses

The concentration of blood glucose was determined by the hexokinase method [8] and that of plasma immunoreactive insulin (IRI) by a solid phase radioimmunoassay (Phadebas Insulin Test®; Pharmacia, Uppsala, Sweden) [9]. The plasma concentration of chlorpropamide was determined by gas chromatography [10], and that of glipizide by high-pressure liquid chromatography [11].

Statistical Analysis

The statistical significance of differences between paired data was calculated by Wilcoxon's signed-rank test.

Results

Plasma Concentrations of Chlorpropamide and Glipizide

In every patient, the concentration of chlorpropamide was significantly \((p < 0.01)\) higher at each interval during treatment with the larger than with the smaller dose (Fig. 1, middle panel). The situation was similar for glipizide, the difference reaching significance at \(0\) \((p < 0.01)\), \(60\) \((p < 0.05)\), \(120\), \(180\) \((p < 0.01)\), \(360\), \(420\) \((p < 0.05)\), \(480\) \((p < 0.01)\) and \(510\) \((p < 0.05)\) min (Fig. 2, middle panel). One patient had no detectable chlorpropamide in plasma collected before dosing during the low dosage regimen (250 mg), and another patient had an undetectable concentration of glipizide prior to the morning dose during low dose treatment (5 mg t.i.d.). The pre-dose concentrations in these patients became measurable after the dose was increased to 375 mg once daily and 10 mg t.i.d., respectively. All other patients had detectable pre-morning dose concentrations of chlorpropamide and glipizide, during both the lower and the higher dosage regimens. For both drugs the mean plasma concentration was almost doubled following the increase in dose (Figs. 1 and 2).

Plasma Immunoreactive Insulin (IRI)

The plasma IRI response to breakfast, lunch and dinner at the two chlorpropamide dose levels are shown in Fig. 1 (lower panel). The mean fasting IRI levels were almost identical: \(19 \pm 4(\text{mm} \pm \text{SEM}; \text{low dosage})\) and \(18 \pm 4(\text{high dosage})\) mIU/ml, respectively. There was no consistent difference in plasma IRI response between the two dosage regimens.

The plasma IRI response to breakfast, lunch and dinner at the two glipizide dose levels are illustrated in Fig. 2 (lower panel). The mean fasting IRI levels were identical: \(19 \pm 4(\text{low dosage})\) and \(19 \pm 5(\text{high dosage})\) mIU/ml, respectively, and were very similar to those seen during chlorpropamide treatment (see