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PHARMACOKINETICS AND DISPOSITION

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Effects and pharmacokinetics of oral glibenclamide and glipizide in Caucasian and Chinese patients with type-2 diabetes

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Abstract The effects and kinetics of oral glibenclamide (Gb) and glipizide (Gz) were studied in Caucasian and Chinese patients (ten in each group) with type-2 diabetes. In randomised order, 2.5 mg Gb, 2.5 mg Gz or placebo was given orally before the administration of 75 g oral glucose. Concentrations of insulin and proinsulin were determined using radioimmunoassay (RIA) without cross-reactivities, and sulphonylurea concentrations were determined using high-performance liquid chromatography (HPLC). There were no significant interethnic differences in Gb or Gz effects whether on glucose, insulin or proinsulin/insulin ratio at any time point. Following Gz, however, Chinese patients had greater increments of serum proinsulin at 10–30 min compared with Caucasians. Apart from the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of Gz being higher among the Chinese, no significant interethnic differences in pharmacokinetics were found. It appears that the same dosage principles could be used for Caucasian and Chinese patients with type-2 diabetes when Gb or Gz are prescribed.

Key words Sulphonylurea · Proinsulin · Pharmacokinetics

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Introduction

Ethnic differences in both diabetes prevalence [1, 2] and characteristics (β-cell dysfunction versus insulin resistance) [3] have been demonstrated. Ethno-pharmacological differences regarding dynamics (e.g. β-blockers) and kinetics (e.g. mephenytoin) have also been reported [4]. However, few ethno-pharmacological studies on sulphonylurea (SU) have been carried out [5, 6].

Patients with type-2 diabetes secrete less insulin and more insulin precursors than do healthy subjects [7, 8]. However, it has not been completely clarified how SU influences the proportions of secretory β-cell products [9, 10, 11]. We have recently demonstrated that intravenous glibenclamide (i.v. Gb) augments the secretion of insulin more than that of proinsulin in diet-treated patients [6].

The aim of this study was to compare the effects (insulin and proinsulin secretion) and pharmacokinetics of orally administered Gb and glipizide (Gz) in Caucasian and Chinese patients with type-2 diabetes.

Patients and methods

Two ethnic groups of patients (ten per group) with type-2 diabetes, one Caucasian (Ca), the other Chinese (Ch), participated in the study. No patient had laboratory or clinical signs of renal or hepatic disease. All patients were diet-treated, normotensive, lean or normal-weight and had modestly increased glycosylated haemoglobin (HbA1c) levels (Table 1).

At each test an oral glucose tolerance test (OGTT, 75 g anhydrous glucose) was carried out in the fasting state. In a randomised

Table 1 Clinical characteristics [median (range)] of Caucasian and Chinese patients (ten in each group) with type-2 diabetes. *HbA1c* glycosolated haemoglobin

	Caucasians	Chinese
Gender (male/female)	7/3	5/5
Age (years)	55 (44–65)	42 (33–53)
Body mass index (kg/m^2)	24.8 (21.0–26.4)	23.4 (17.4–27.2)
Diabetes duration (years)	4 (2–9)	2 (0.5–5.0)
HbA1c (%)	5.8 (5.0–7.3, reference range 4.3–5.7)	6.8 (6.0–7.5, reference range 5.1–6.4)
Microalbuminuria	2	2
Medication	β-blockers ($n=4$), L-thyroxine ($n=1$)	None

fashion, the subjects received 2.5 mg Gb orally (p.o., Daonil, Hoechst AG, Frankfurt, Germany), 2.5 mg Gz p.o. (Mindiab, Farmitalia Carlo Erba, Milan, Italy) or placebo, each taken 30 min before the OGTT. The start of the OGTT was defined as time 0. Blood samples for measurements of serum drug levels, insulin, proinsulin and plasma glucose were collected before drug administration (–31 min), immediately before OGTT (–1 min) and then repeatedly for 4 h (all parameters) and 24 h (drug and glucose only).

Plasma glucose was determined using a glucose oxidase method. Serum insulin was measured using a radioimmunoassay without any cross-reactivities with C-peptide, human proinsulin or 32–33 split-proinsulin [12]. Serum proinsulin was measured using an immunofluorometric method with monoclonal antibodies without any cross-reactivities with insulin or C-peptide [13]. The concentrations of Gb and Gz were determined using column liquid chromatographic methods [14, 15]. The minimum detectable concentration was 1 ng/ml (Gb) and 5 ng/ml (Gz).

The glucose, insulin and proinsulin responses to the OGTT were estimated as the net areas under the curves ($AUC_{-31 \rightarrow 10, 30, 60, 120, 180, 240\ min}$) with basal values (–31 min) set as zero. The net AUC was calculated using the standard trapezoidal rule (KaleidaGraph, version 2.1.3).

Total immunoreactive insulin (IRI) was calculated from the sum of true insulin plus proinsulin. The ratio (percentage) of proinsulin to insulin molecules (RPI) was calculated by dividing proinsulin by IRI multiplied by 100.

A software product (PCNONLIN, version 4.2) was used for pharmacokinetic calculations. AUC (Gb and Gz, 0–24 h) was calculated using the standard trapezoidal rule. Non-compartmental analysis was used in all patients.

Data are presented as median and range. Mann–Whitney *U* tests were used for between-groups comparisons. A P value < 0.05 was considered as significant.

Results

Pharmacodynamics

There were no significant initial between-group differences whether in baseline plasma glucose, serum insulin, proinsulin or RPI. There were no significant interethnic differences in Gb or Gz effects whether on plasma glucose increments or on increments of serum insulin or RPI at any time point. Following Gz, the proinsulin increments were greater at 10 min (74 pmol × min/l versus 26 pmol × min/l) and 30 min (295 pmol × min/l versus 104 pmol × min/l) among the Chinese than Caucasians. Following placebo, the insulin increments were greater at 10 min (206 pmol × min/l versus –53 pmol × min/l), 30 min (1946 pmol × min/l versus 800 pmol × min/l) and 60 min (7523 pmol × min/l versus 3687 pmol × min/l) among the Chinese than Caucasians.

Pharmacokinetics

Gb was detected in serum up to 24 h in six Caucasian and five Chinese patients. Gz was detected in serum up to 24 h in four Caucasian and seven Chinese patients. There was a tendency ($P=0.0578$, Mann–Whitney) to a

Table 2 Pharmacokinetics [median (range)] of 2.5 mg glibenclamide (Gb) or glipizide (Gz) given orally during an oral glucose tolerance test (75 g anhydrous glucose) in ten Caucasian and ten Chinese patients with type-2 diabetes. t_{max} time of maximum concentration; C_{max} maximum concentration; $t_{1/2}$ elimination half-life; F fraction of administered dose that is absorbed; Cl clearance; AUC area under the plasma concentration-time curve

	Gb		Gz	
	Caucasians	Chinese	Caucasians	Chinese
t_{max} (h)	2.0 (1.0–4.5)	4.5 (1.5–6.5)	3.0 (0.75–4.5)	3.5 (0.67–4.5)
C_{max} (ng/ml)	69 (21–153)	82 (41–146)	171 (118–280)*	241 (154–495)
$t_{1/2}$ (h)[a]	7.09 (2.14–27.8)	4.63 (2.77–11.24)	4.21 (2.89–5.42)	5.00 (2.64–6.61)
F[b]	0.63 (0.18–1.00)	0.74 (0.30–1.05)	–	–
Cl (l/h)	4.42 (3.38–8.12)	4.10 (2.90–5.19)	–	–
AUC (ng × h/ml)	440 (200–684)	513 (392–661)	941 (647–1022)**	1499 (825–2515)

[a] $t_{1/2}$ of Gb calculated in nine Caucasians and seven Chinese, $t_{1/2}$ of Gz calculated in five Caucasians and nine Chinese
[b] i.v. data of Gb [6] were used for this calculation
*$P < 0.05$
**$P < 0.01$

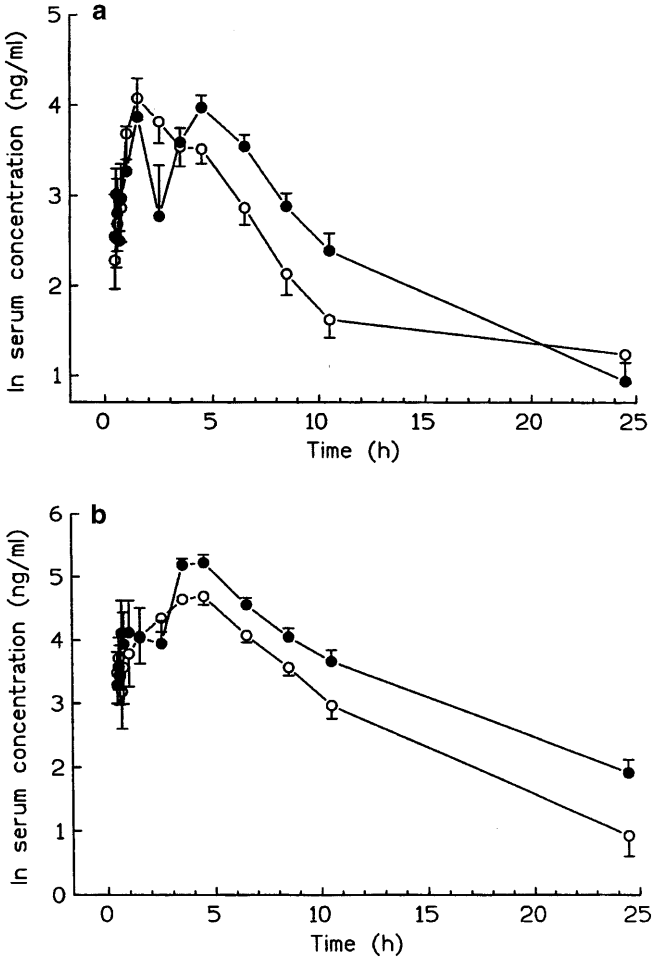

Fig. 1 Serum concentration-time curves (mean ± SEM) of 2.5 mg glibenclamide (A) and 2.5 mg glipizide (B) after a single oral dose in Caucasian (*open circles*) and Chinese (*closed circles*) patients (ten in each group) with type-2 diabetes

later time of maximum concentration (t_{max}) of Gb in the Chinese, but no significant interethnic differences in Gb pharmacokinetics were found. Apart from the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of Gz being higher among the Chinese, there were no significant interethnic differences in Gz pharmacokinetics (Table 2 and Fig. 1). In both ethnic groups, dual peak serum levels of both drugs were seen in a few patients.

Discussion

The overall glucose-lowering effects of Gb and Gz were similar in the two ethnic groups. However, minor ethnic differences in pharmacodynamics were found, which in part agrees with our findings using i.v. Gb [6]. Proinsulin secretion increased earlier and was more pronounced when Gz was administered in the Chinese than in the Caucasians; later on, the proinsulin and insulin profiles were similar. Consequently, the β-cells in the Chinese may have been more strained and hence secreted more insulin precursors than in Caucasians. Pharmacokinetic differences (vide infra) were another possibility.

No significant pharmacokinetic differences were found between Caucasians and Chinese after i.v. [6] and oral (present study) Gb administration. However, minor kinetic differences in Gz metabolism were found; C_{max} and AUC were higher in the Chinese. Variations in absorption of SU [16], as well as in the rate of absorption from different sites [17], have been demonstrated. However, it has not been clarified whether ethnic differences in gastrointestinal function influencing drug absorption do exist. As Gb metabolism in the two ethnic groups was the same after i.v. administration, genuine interethnic differences in systemic metabolism probably do not exist. Ethnic differences in the metabolism of gliclazide, an extensively metabolised SU, have been discussed [18, 19], but in accordance with our findings no significant ethno-pharmacokinetic differences were found in nine type-2 diabetic patients of different ethnic origin after oral intake of gliclazide [5].

In summary, Chinese were more hyperinsulinaemic than Caucasians during the OGTT with placebo, which might reflect higher insulin resistance. When Gz was administered, Chinese had higher C_{max} and AUC than Caucasians and they were also more hyperproinsulinaemic during the first 30 min of the OGTT. Otherwise there were no interethnic differences in pharmacokinetics and pharmacodynamics between the two ethnic groups. As the recorded differences were minute or nil, it would appear that the same dosages of Gb and Gz, respectively, can be used in Caucasian and Chinese patients with type-2 diabetes.

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