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PHARMACODYNAMICS

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Pharmacodynamics and pharmacokinetics of intravenous glibenclamide in Caucasian and Chinese patients with type-2 diabetes

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Abstract *Objective*: We analysed the kinetics and effects of glibenclamide (Gb) on glucose, insulin and proinsulin secretion in two ethnic groups (10 in each) of type-2 diabetic patients, one of Caucasian, the other of Chinese origin.
Background: Diabetes mellitus type 2 is a global disease affecting all ethnic groups. There are ethnic differences in both the prevalence and metabolic characteristics of the disease. Important interethnic pharmacodynamic and pharmacokinetic differences have been reported for several drugs. With few exceptions, detailed studies on sulphonylurea are lacking.
Material and methods: The patients were studied on two occasions when either no Gb (control) or 1.25 mg Gb was administered i.v., immediately before the administration of a 75-g oral glucose tolerance test. Concentrations of insulin and proinsulin were determined by means of radioimmunoassay without cross-reactivities. Gb concentration was determined using high-performance liquid chromatography. Pharmacodynamic results were calculated using net areas under the curves, with basal values set as zero. A P value less than 0.05 was considered significant.
Results: When glucose was administered orally without Gb, Chinese patients had higher plasma glucose increases at 10 min (7.6 mmol/l × min vs 2.6 mmol/l × min) and higher increases of plasma insulin levels than Caucasians at both 10 min (198 pmol/l × min vs 54 pmol/l × min) and 30 min (2286 pmol/l × min vs 1198 pmol/l × min). When Gb was administered, the plasma glucose increases were reduced, and the increases of serum insulin and proinsulin levels were greater in both ethnic groups. Compared with the basal values (−1 min), proinsulin/insulin ratios (RPI) were lowest at 10–30 min, followed by an increase. Chinese patients had higher increases of serum insulin levels at 10 min (1109 pmol/l × min vs 550 pmol/l × min) and a lower RPI at 30 min (6.0% vs 7.6%) and 240 min (15.0% vs 21.0%) relative to Caucasians. Serum Gb data were best fitted to a biexponential i.v. model. There were no interethnic differences in any of the pharmacokinetic parameters.
Conclusion: In summary, following oral glucose administration without Gb, Chinese type-2 diabetic patients had higher plasma insulin levels but also higher plasma glucose levels during the first 10 min, which might reflect reduced insulin sensitivity or more rapid glucose absorption. Gb augmented glucose-induced release of both insulin and proinsulin in both ethnic groups; the effect on insulin secretion was more pronounced. In conclusion, minor pharmacodynamic but no pharmacokinetic differences were found between the two groups. It seems appropriate to employ the same dosage principles when using Gb in Caucasians and Chinese.

Key words Glibenclamide · Insulin · Proinsulin

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Introduction

Diabetes mellitus type 2 is a major global public health problem characterised by chronic hyperglycaemia due to

impaired insulin secretion, decreased insulin sensitivity and increased hepatic glucose production [1]. The pancreatic β-cells in patients with type-2 diabetes secrete less insulin and more precursors of insulin than healthy subjects [2, 3, 4]. There are marked ethnic differences in the prevalence of type-2 diabetes [5]. The relative contributions of β-cell failure and decreased insulin sensitivity in these populations also differ [6]. Asian Indians [7, 8], Chinese [9] and Pima Indians [10] who have adopted a western lifestyle have an increased propensity to develop type-2 diabetes. At diagnosis, Asians with type-2 diabetes are often younger, less obese, have better preserved β-cell function but lower insulin sensitivity than Caucasians [11].

Glibenclamide (Gb), a potent second-generation sulphonylurea (SU), improves glucose tolerance mainly by augmenting insulin secretion [12, 13]. It reduces both fasting and post-prandial glucose levels in type-2 diabetic patients who have residual β-cell function. However, the effects of SU on the proportions of secretory β-cell products remain uncertain [2, 14, 15, 16].

Ethnic differences in pharmacokinetics of certain drugs [17], e.g. debrisoquin, β-blockers and mephenytoin, have been demonstrated. β-Blockers also display ethnic pharmacodynamic differences [17]. By contrast, there have only been a few studies examining the ethnopharmacology of SUs [18].

The aims of this study were to examine the effects of Gb on the secretion of proinsulin and insulin and to compare the pharmacodynamics and the pharmacokinetics of Gb in Caucasian and Chinese type-2 diabetic patients.

Patients and methods

Patients

Two ethnic groups of type-2 diabetic patients (2×10) – one Caucasian (Ca), living in the city of Malmö, the other Chinese (Ch), living in the city of Hong Kong – participated in the study. The patients were recruited from the diabetes out-patient clinics at the Malmö University Hospital, Sweden, and the Prince of Wales Hospital, Hong Kong, respectively. Pregnant women and patients with body mass indices of more than 28 kg/m^2, liver disease, impaired renal function, uncontrolled hypertension, peptic ulcer disease or inflammatory bowel disease were excluded. No patient had clinical signs or symptoms of renal or hepatic disease. Serum creatinine and liver enzyme levels were normal in each case. All patients were diet treated, normotensive, lean or normal weight and had slightly increased glycosylated hemoglobin (HbAIc) levels. Their medications, alcohol use and smoking habits were unchanged during the study period. Clinical findings and features of the two groups are shown in Table 1. The study was approved by the Ethics Committees of the Lund University Medical Faculty and of the Hong Kong Chinese University Medical Faculty. All patients gave written informed consent.

Methods

The patients were studied at the metabolic ward of the Department of Endocrinology at the Malmö University Hospital and at the Clinical Pharmacology Studies Unit of the Department of Clinical Pharmacology at the Prince of Wales Hospital. Each patient underwent the test twice, with an interval of 1–4 months. On the test day, the patient arrived at the ward at 0700 hours after 10 h fasting. A catheter was inserted into an antecubital vein for a slow saline infusion. An oral glucose tolerance test (75 g anhydrous glucose with 250 ml water, OGTT) was carried out. In a randomised fashion, the subject received either an intravenous (i.v.) injection of 1.25 mg Gb (Daonil, Hoechst AG, Frankfurt, Germany) or no Gb (control) immediately 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 immediately before drug administration (−1 min), and 2, 5, 10, 15 and 30 min, and 1, 2, 3, 4 h (all parameters), 6, 8 and 10 h (drug and glucose only) following the start of the OGTT. Lunch was served immediately after collection of the 4-h sample.

Blood samples were collected in plain 10-ml tubes. Serum was separated by centrifugation and kept frozen at −20 °C until analysed. Plasma glucose was determined directly at the local laboratory using a glucose oxidase method on a Greiner Multi-channel analyser. Serum insulin was measured by means of a radioimmunoassay using an antibody against human insulin (catalogue no. 1914, Linco Research, St Louis, Mo.). The lower limit of the assay was 35 pmol/l and the intra-assay coefficient of variation (CV) was less than 14% at all levels. The insulin assay did not cross-react

Table 1 Clinical characteristics [median (range)] of Caucasian and Chinese patients (ten in each group) with type-2 diabetes. Control is without glibenclamide (Gb)

Origin		Caucasian	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)
Duration of diabetes (years)		4 (2–9)	2 (0.5–5.0)
Glycosylated hemoglobin (%)		5.8 (5.0–7.3, ref. range 4.3–5.7)	6.8 (6.0–7.5, ref. range 5.1–6.4)
Microalbuminuria		2	2
Medication		β-blockers[a] (n = 4); L-thyroxine (n = 1)	None
Baseline values			
Glucose (mmol/l)	Gb	7.0 (4.7–8.7)	7.0 (5.5–9.5)
	Control	6.8 (5.4–8.5)	7.4 (4.6–9.9)
Insulin (pmol/l)	Gb	86 (51–134)	110 (65–116)
	Control	95 (50–142)	93 (64–139)
Proinsulin (pmol/l)	Gb	8 (3–23)	10 (7–30)
	Control	8 (4–24)	10 (3–39)

[a] Atenolol 25 mg; atenolol 50 mg; metoprolol 50 mg; pindolol 5 mg

with C-peptide, human proinsulin or 32–33 split-proinsulin [19]. Serum proinsulin was measured using an immunofluorometric method using monoclonal antibodies, one against insulin and one against C-peptide (PEP −001 and HUI 001, NovoNordisk, Copenhagen, Denmark). The lower limit of the assay was 1 pmol/l and the CV was less than 10%. There was a 66% cross-reactivity with 32–33 split-proinsulin in the proinsulin assay, but no cross-reactivities with insulin or C-peptide. The assay was essentially performed as described by Lindström et al. [20]. Serum insulin and proinsulin samples were analysed at Aker Diabetes Research Centre, Aker Hospital, Oslo, Norway.

The concentration of Gb in the serum was measured using a column liquid chromatographic method [21]. The minimum detectable concentration of Gb was 1 ng/ml. The precision of the assay at the 10-ng/ml and 50-ng/ml levels expressed as relative SD was 3.0% and 3.3%, respectively. The between-day precision of the chromatographic assays was followed by the variation in slopes of the standard curves during analyses of Gb. Relative standard deviations were less than 10%. Serum Gb samples were analysed at the Wallenberg Laboratory, Malmö University Hospital, Malmö, Sweden.

Calculations and statistics

To compensate for the variations in baseline values, the glucose, insulin and proinsulin responses to the OGTT were estimated as the net areas under the curves ($AUC_{-1\rightarrow10,30,120,240\ min}$), with basal values (−1 min) set as zero. The net AUC was calculated using the standard trapezoidal rule (Software, 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.

For pharmacokinetic model fitting and calculation of pharmacokinetic parameters, a software product for the statistical analysis of nonlinear models, PCNONLIN, version 4.2, was used (Statistical Consultants Inc., Lexington, Ky., 1993). The i.v. serum concentration–time data were fitted to a mono-, bi- or triexponential open i.v. model with bolus input and first-order output. Analyses and model fits of concentration–time data were made separately for each patient.

Data are presented as median and range. Wilcoxon signed-rank test was used for within-group comparisons and Mann–Whitney *U* test for between-group comparisons. A P value less than 0.05 was considered significant.

Results

Pharmacodynamics

Baseline plasma glucose, serum insulin, serum proinsulin and RPI were similar in the two groups at the start of both tests (Table 1). No serious hypoglycaemic event was reported, but some patients reached a plasma glucose concentration of around 3.0 mmol/l before lunch.

Caucasian group

When Gb was administered, the plasma glucose increase was reduced at 30 min following the OGTT and throughout (+240 min). The increases of serum insulin and proinsulin levels were higher than during control conditions at 10 min and then throughout. During the control test, RPI was decreased at 30 min and increased at 240 min relative to basal values (−1 min).

When Gb was administered, RPI was decreased at 10 min and was unchanged at 30 min; thereafter, it increased throughout the remaining study time relative to basal values. When Gb was administered, the RPI was lower at 10 min than in the control test (Table 2, Table 3, Table 4, Table 5 and Fig. 1 and Fig. 2).

Chinese group

When Gb was administered, the plasma glucose increase was reduced at 10 min following the OGTT and then throughout (+240 min). The increases of serum insulin and proinsulin levels were higher than during control conditions between 10 min and 120 min. Subsequently, there were no significant differences. During the control test, the RPI was increased at 240 min relative to basal values (−1 min). When Gb was administered, the RPI was decreased at 10 min and throughout the first 30 min; thereafter, it increased during the remaining study time relative to basal values. When Gb was administered, the RPI was lower at 10 min than in the control test (Table 2, Table 3, Table 4, Table 5 and Fig. 1 and Fig. 2).

Caucasians versus Chinese

When glucose was administered orally without Gb, Chinese patients had higher plasma glucose increases at 10 min (Table 2, Fig. 1) and higher increases of serum

Table 2 Plasma glucose levels [median (range)] expressed as net areas under curves ($AUC_{-1+10,-1+30,-1+120,-1+240\ min}$) (pmol × min × l^{-1}) during an oral glucose tolerance test (OGTT) (75 g anhydrous glucose) following administration of 1.25 mg glibenclamide (Gb) i.v. or no Gb (control) in Caucasian and Chinese patients (ten in each group) with type-2 diabetes

Time (min)	Caucasian origin		Chinese origin	
	Gb	Control	Gb	Control
+10	1.7 (−2.6–5.4)	2.4[c] (−0.6–9.2)	4.0[a] (−3.9–9.5)	7.6 (0.1–11.8)
+30	37[a] (−3–85)	54 (28–86)	44[b] (−12–95)	80 (32–102)
+120	340[b] (−88–633)	618 (456–732)	315[b] (−119–660)	587 (216–964)
+240	300[b] (−349–830)	850 (343–1518)	188[b] (−206–777)	882 (201–1386)

[a] $P < 0.05$ vs control
[b] $P < 0.01$ vs control
[c] $P < 0.05$ vs Chinese control

Table 3 Serum insulin levels [median (range)] expressed as net areas under curves ($AUC_{-1+10,-1+30,-1+120,-1+240\ min}$) (pmol × min × l^{-1}) during an oral glucose tolerance test (OGTT) (75 g anhydrous glucose) following administration of 1.25 mg glibenclamide (Gb) i.v. or no Gb (control) in Caucasian and Chinese patients (ten in each group) with type-2 diabetes

Time (min)	Caucasian origin		Chinese origin	
	Gb	Control	Gb	Control
+10	550[b,d] (268–1130)	54[c] (−31 to 178)	1109[b] (310–6401)	198 (5–1209)
+30	4176[b] (1398–7343)	1198[c] (452–2964)	7203[b] (2428–26843)	2286 (1023–6898)
+120	27482[b] (6093–62753)	13964 (3912–30544)	30754[a] (10183–118328)	25124 (6748–67783)
+240	36828[a] (9303–112343)	23245 (8772–63604)	43014 (16543–178328)	40994 (8308–110203)

[a] $P < 0.05$ vs control
[b] $P < 0.01$ vs control
[c] $P < 0.05$ vs Chinese control
[d] $P < 0.01$ vs Chinese glibenclamide

Table 4 Serum proinsulin levels [median (range)] expressed as net areas under curves ($AUC_{-1+10,-1+30,-1+120,-1+240\ min}$) (pmol × min × l^{-1}) during an oral glucose tolerance test (OGTT) (75 g anhydrous glucose) following administration of 1.25 mg glibenclamide (Gb) i.v. or no Gb (control) in Caucasian and Chinese patients (ten in each group) with type-2 diabetes

Time (min)	Caucasian origin		Chinese origin	
	Gb	Control	Gb	Control
+10	29[b] (9–123)	4 (−10 to 11)	44[b] (22–172)	12 (−9–26)
+30	259[b] (102–887)	112 (−9 to 150)	356[b] (186–814)	126 (77–252)
+120	2823[a] (1722–9057)	2690 (531–4370)	2852[a] (1674–7700)	2422 (1388–5338)
+240	5703[a] (3583–20337)	5218 (1731–9594)	5630 (2364–15800)	5856 (2372–11218)

[a] $P < 0.05$ vs control
[b] $P < 0.01$ vs control

Table 5 Proinsulin-insulin ratio [median percentage (range)] during an oral glucose tolerance test (OGTT) (75 g anhydrous glucose) following administration of 1.25 mg glibenclamide (Gb) i.v. or no Gb (control) in Caucasian and Chinese patients (ten in each group) with type-2 diabetes

Time (min)	Caucasian origin		Chinese origin	
	Gb	Control	Gb	Control
−1	10.0 (5.8–20.9)	8.8 (4.1–35.1)	8.1 (4.4–15.1)	9.0 (4.3–19.3)
+10	6.8 (4.0–17.4)[a,c]	9.0 (4.2–29.6)	5.9 (2.7–10.5)[a,c]	6.1 (3.5–14.9)
+30	7.6 (4.6–25.2)[d]	8.6 (3.4–23.4)[b]	6.0 (3.6–15.2)[b]	7.4 (4.4–12.6)
+120	13.2 (7.3–32.0)[b]	13.4 (4.9–30.1)	11.0 (8.3–19.1)[c]	11.2 (6.8–20.3)
+240	21.0 (9.8–42.7)[c,d]	16.0 (7.5–32.5)[c]	15.0 (6.2–20.0)[c]	15.6 (8.3–23.4)[c]

[a] $P < 0.05$ vs control
[b] $P < 0.05$ vs basal values (time −1)
[c] $P < 0.01$ vs basal values (time −1)
[d] $P < 0.05$ vs Chinese glibenclamide

insulin levels at 10 min and 30 min (Table 3, Fig. 2) than Caucasians. There were no differences in the serum proinsulin levels and RPI between the two groups. When Gb was administered, Chinese patients demonstrated higher increases of serum insulin levels at 10 min (Table 3, Fig. 2) and a lower RPI at 30 min and 240 min (Table 5) than Caucasians. There were no differences in the plasma glucose and serum proinsulin levels between the two groups (Table 2 and Table 4, Fig. 1).

Pharmacokinetics

Observed peak serum levels following a single i.v. 1.25-mg Gb dose ranged from 294 ng/ml to 425 ng/ml in the Caucasian group and from 226 ng/ml to 436 ng/ml in the Chinese group. Serum Gb could be detected for up to 8 h in seven patients in the Caucasian group and in five patients in the Chinese group. Serum Gb data were best fitted to a biexponential i.v. model. There were no significant differences in any of the pharmacokinetic parameters between the two groups (Table 6).

Discussion and conclusions

Intravenous administration of Gb immediately before OGTT augmented the release of both insulin and proinsulin in both Caucasians and Chinese. The effect on insulin was more pronounced during the first 10–30 min, as shown by a lower proinsulin/insulin ratio relative to baseline; thereafter, the ratio started to increase during both the control and the Gb test. The increase started earlier during the Gb test. This subsequent increase, seen both with and without Gb, might be an expression of a depletion of β-cell insulin stores or

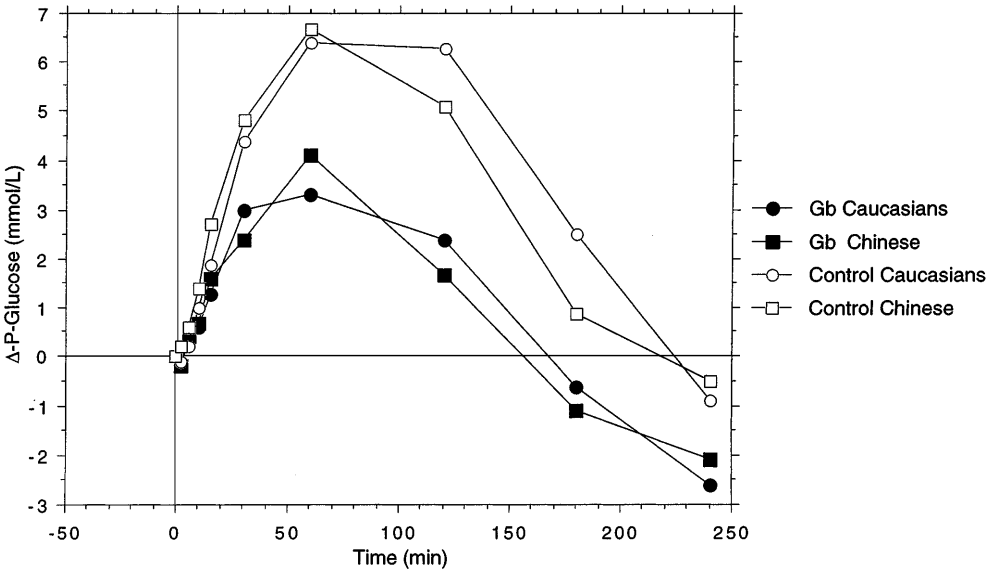

Fig. 1 Plasma concentration–time curve of Δ-glucose (mean) after a single dose of 1.25 mg glibenclamide (Gb) i.v. in type-2 diabetic patients of Caucasian and Chinese origin (ten patients in each group)

of the longer elimination half-life of proinsulin [22]. A reduced ability to convert proinsulin to insulin cannot be excluded [23].

Few other acute studies on this matter have been performed, but some studies [14, 16, 24, 25, 26] have been made during chronic SU treatment. A reduced proinsulin/insulin ratio during OGTT in patients on SU for 12 weeks has been reported [24]. Withdrawal of SU treatment for 2–4 weeks in 15 type-2 patients did not change the ratio during an i.v. glucose tolerance test [25]. SU therapy for 12 weeks in 27 newly diagnosed type-2 diabetic patients increased both insulin and proinsulin secretion without any change in the proportions of the proinsulin-like molecules [26]. The authors concluded that SU promotes release of both mature and immature insulin secretory granules.

Clinically important interethnic differences have been reported for certain drugs [17]. Chinese patients require much lower dosages of propranolol [17] due to their increased sensitivity to its β-blocking and antihypertensive actions [27]. Chinese subjects have lower plasma concentrations and higher clearance of propranolol than Caucasians [27]. The latter differences cannot account for the increased propranolol sensitivity of Chinese subjects. However, a higher free fraction of propranolol in Chinese subjects might contribute [28].

Other examples relevant to the present study are the polymorphisms of both debrisoquin [29] and mephenytoin metabolism [29]. However, Gb does not seem to be metabolised by the debrisoquin [30] or the mephenytoin system [31]. Taylor et al. [18] also found no

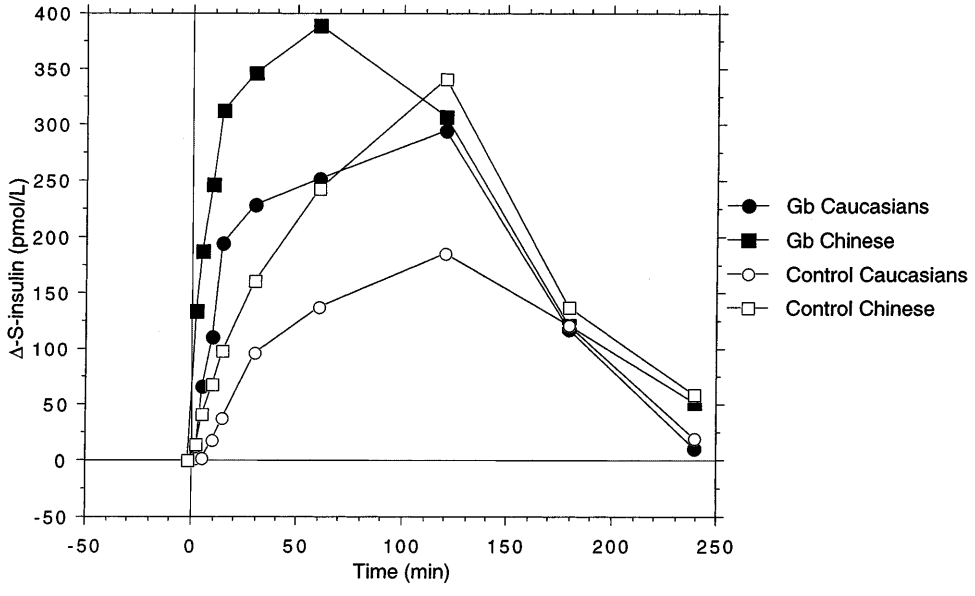

Fig. 2 Serum concentration–time curve of Δ-insulin (mean) after a single dose of 1.25 mg glibenclamide (Gb) i.v. in type-2 diabetic patients of Caucasian and Chinese origin (ten patients in each group)

Table 6 Pharmacokinetics [median (range)] of 1.25 mg glibenclamide i.v. during an oral glucose tolerance test (OGTT) (75 g anhydrous glucose) in Caucasian and Chinese patients (ten in each group) with type-2 diabetes. V_1 initial dilution volume; α fast disposition slope in a bi-exponential i.v. model; C_{max} maximal concentration; β slow disposition slope in a bi-exponential i.v. model; *Cl* clearance; *AUC* area under the plasma concentration versus time curve; *MRT* mean residence time; *k10* overall elimination rate constant; *Vss* volume of distribution at steady state; *k12* distribution rate constant for transfer from central to peripheral compartment; *k21* distribution rate constant for transfer from peripheral to central compartment

Parameter	Caucasian	Chinese
α (h^{-1})	2.1 (1.4–11.0)	1.6 (1.1–5.4)
β (h^{-1})	0.38 (0.26–1.55)	0.36 (0.15–0.82)
AUC (ng × h/ml)	283 (154–370)	305 (241–430)
k10 (h^{-1})	1.20 (0.88–2.63)	1.15 (0.78–1.64)
k12 (h^{-1})	0.59 (0.24–4.68)	0.46 (0.12–1.89)
k21 (h^{-1})	0.62 (0.34–6.12)	0.52 (0.23–2.72)
V_1 (l)	3.32 (2.98–4.04)	3.42 (2.82–5.68)
C_{max} (ng/ml)	376 (309–420)	368 (220–443)
Cl (l/h)	4.41 (3.38–8.11)	4.10 (2.91–5.18)
MRT (h)	1.40 (0.58–2.13)	1.23 (1.03–3.19)
Vss (l)	6.31 (4.68–7.68)	5.49 (4.04–9.55)

ethnopharmacokinetic difference for gliclazide, an extensively metabolised SU drug, in nine type-2 diabetic patients of different ethnic origin (two Caucasian, two Chinese, two Indian, three Afro-Caribbean). The absence of any major ethnopharmacokinetic differences in the present study is hence in agreement with preceding studies.

Small pharmacodynamic differences were found between the ethnic groups in our study; plasma glucose was more rapidly increased and was then reduced faster in the Chinese. Otherwise, the overall Gb-induced glucose responses were similar. The Chinese had a greater insulin response at 10 min and a lower proinsulin/insulin ratio at both 30 min and 240 min, suggesting more pronounced insulin release. Alternatively, it may be an expression of lower insulin sensitivity. As the interethnic pharmacodynamic difference was minor and as there were no pharmacokinetic differences, it seems appropriate to employ the same dosage principles when using Gb in Caucasians and Chinese.

In summary, following oral glucose administration without Gb, Chinese type-2 diabetic patients had higher plasma insulin levels but also higher plasma glucose levels during the first 10 min, which might reflect reduced insulin sensitivity or more rapid glucose absorption. Gb (i.v.) augmented glucose-induced release of both insulin and proinsulin in both ethnic groups; the effect on insulin secretion was more pronounced. Chinese patients had a brisker early insulin response and, subsequently, a decreased proinsulin/insulin ratio. In conclusion, minor pharmacodynamic but no pharmacokinetic differences were found between the Caucasians and the Chinese. It seems appropriate to employ the same dosage principles when using Gb in Caucasians and Chinese.

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