Pharmacokinetics of tolbutamide in ethnic Chinese

Annette S. Gross, Simone Bridge & Gillian M. Shenfield

Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards NSW, 2065 Australia

Aims Ethnic differences in drug disposition have been described for many drugs. Despite the widespread use of tolbutamide in Asian populations, the pharmacokinetics of tolbutamide, a CYP2C9 substrate, have not been described in ethnic Chinese.

Methods The pharmacokinetics of tolbutamide (500 mg orally) were studied in 10 young, healthy volunteers (seven male/three female; age 21–29 years), each of whom had four ethnic Chinese grandparents. Plasma concentrations of tolbutamide were measured for 32 h post-dose by high performance liquid chromatography. The concentrations of hydroxytolbutamide and carboxytolbutamide were also measured in urine for 32 h post-dose. Noncompartmental pharmacokinetic parameters were calculated using standard equations and compared with those previously reported in Caucasian subjects using the Mann-Whitney U test.

Results Pharmacokinetic parameters in Chinese (mean $\pm$ s.d.) including $C_{\max}$ ($63 \pm 11 \mu\text{g ml}^{-1}$), $t_{\max}$ (median 3.3 h; range 1.6–6.0 h), V/F ($9.1 \pm 1.7 \text{ l}$) and $t_{1/2}$ (9.1 h; harmonic mean) were similar to the values in Caucasians. CL/F ($637 \pm 88 \text{ ml h}^{-1}$) was higher in Chinese than Caucasians. The urinary recoveries of hydroxytolbutamide ($13 \pm 1\%$ of dose) and carboxytolbutamide ($68 \pm 5\%$ of dose) and the partial apparent metabolic clearance ($0.15 \pm 0.02 \text{ ml min}^{-1} \text{ kg}^{-1}$) in Chinese were comparable with Caucasians.

Conclusions The pharmacokinetics of tolbutamide have been described in ethnic Chinese and the disposition is similar to that reported in Caucasians. This study suggests that there is no substantial ethnic difference in the tolbutamide hydroxylase activity of CYP2C9.

Keywords: tolbutamide, Chinese, pharmacokinetics

Introduction

Ethnic differences in pharmacokinetics and pharmacodynamics have been observed for many drugs [1, 2]. The ethnic differences in drug disposition can be attributable to both differences in drug distribution and elimination. For example drug volume of distribution can differ in Chinese and Caucasians due to variation in body composition and the plasma concentration of the drug binding protein, α_1 -acid glycoprotein. Ethnic differences in drug elimination can be a result of variation in the activity of drug metabolising enzymes, which may be a consequence of either cultural factors such as a diet incorporating enzyme inducing ingredients or the heterogeneity of the genome at regions encoding for drug metabolising enzymes. The frequencies of the genetic polymorphisms in drug metabolism can therefore vary in

different populations. For example, Chinese and Caucasians differ in the spectrum and frequency of mutant alleles of the *CYP2C19* gene and thus the frequency of poor metabolisers of mephenytoin, who inherit two mutant alleles (20% in Chinese but only 3% in Caucasians) [3].

As a consequence of altered pharmacokinetics and pharmacodynamics, the optimal dose of a drug may vary in patients from different ethnic groups. For example Oriental and Caucasian patients require different doses of warfarin and phenytoin to achieve equivalent therapeutic effects [4, 5, 6, 7]. Both phenytoin and warfarin are metabolised by the enzyme cytochrome P450 2C9 (CYP2C9) and an ethnic difference in pharmacokinetics due to a difference in the activity of CYP2C9 may be responsible for the varying dose requirements. CYP2C9 metabolises many other drugs including tolbutamide and the nonsteroidal anti-inflammatories diclofenac, ibuprofen, piroxicam and tenoxicam [8]. Recent studies have shown that there are a number of *CYP2C9* alleles and that the frequencies of mutant alleles, although low, differ

Correspondence: Professor Gillian Shenfield, Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards NSW 2065, Australia.
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in Chinese and Caucasian populations [8]. Inheriting mutant *CYP2C9* alleles can result in impaired metabolism of *CYP2C9* substrates.

Tolbutamide is a first generation oral sulphonylurea hypoglycaemic agent, used in the treatment of non-insulin dependent diabetes. Tolbutamide is eliminated principally by *CYP2C9* catalysed metabolism to hydroxy-tolbutamide, which is in turn further metabolised to carboxytolbutamide by cytosolic alcohol and aldehyde dehydrogenases [9]. Despite its declining use in the west, tolbutamide is relatively cheap and is therefore widely used in Asia [10] and its use may be predicted to increase due to the rising incidence of diabetes in Orientals [11]. The pharmacokinetics of tolbutamide have, however, not been reported in Orientals. The present study was therefore undertaken to describe the pharmacokinetics of tolbutamide in ethnic Chinese. The subjects studied lived in Australia and had a westernised lifestyle and diet. The tolbutamide pharmacokinetic parameters observed have been compared with those published previously in Caucasians [9] and therefore this study also provides insight into the *in vivo* activity of *CYP2C9* in Chinese and Caucasians.

Methods

Study protocol and subjects

The study was approved by the Medical Research Ethics Committee of Royal North Shore Hospital, Sydney (Protocol No. 9503 45M) and written informed consent was obtained from all subjects. The subjects were 10 young volunteers (seven male/three female; aged 21–29 years, weight 48–78 kg) who were considered healthy following a physical medical examination including medical history and liver and renal function tests. Each volunteer was an ethnic Chinese living in Australia but descended from four ethnic Chinese grandparents born in regions of China where the Han Chinese traditionally lived. All subjects had a balanced diet, which included some Asian dishes but was not exclusively Chinese. All females had negative pregnancy tests on the day of the study. Two male volunteers were cigarette smokers. Each subject abstained from all medication for 5 days, alcohol for 36 h and smoking for 12 h prior to, and throughout, the study. The volunteers also fasted from 22.00 h on the evening prior to study.

The pharmacokinetics of tolbutamide were studied following a 500 mg dose (Rastinon, Hoechst Australia Ltd) administered with 200 ml of water. Blood samples (10 ml) were taken via a cannula inserted into an antecubital vein predose, and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5, 6, 7, 8, 10 and 12 h post-dose. Further blood samples were taken by venepuncture at

24, 28 and 32 h post-dose. Blood glucose concentrations were monitored for 4 h post-dose, using a Reflolux IIM glucose monitor (Boehringer Mannheim, Germany) with BM-Test-Glycemic 20–80 test strips (Boehringer Mannheim, Germany). If the subjects complained of hypoglycaemic symptoms (sweating, dizziness, faintness, palpitations, nausea or anxiety) and glucose levels fell below 2.5 mmol l^{-1} , orange juice was to be given to elevate blood sugar levels. All blood samples were transferred to heparinised tubes, centrifuged at 2000 g for 4 min and the plasma separated and stored at -20°C pending analysis. All urine was collected over the following intervals: predose and 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–32 h post-dose. The volume and pH of each urine collection were measured and 10 ml aliquots were stored at -20°C prior to assay. Each subject was served the same lunch (salad sandwich, noncitrus fruit, piece of cake) 4 h post-dose and dinner 10 h post-dose.

Analysis of tolbutamide and metabolites

Tolbutamide in plasma (0.5 ml) and carboxytolbutamide and hydroxytolbutamide in urine (1 ml) were measured by reversed phase high performance liquid chromatography with ultraviolet detection [9]. Plasma calibration curves were prepared over the tolbutamide concentration range $2\text{--}100 \text{ }\mu\text{g ml}^{-1}$. The within-day and between-day reproducibilities (coefficients of variation) of the method were assessed using quality control samples and were 5.0% ([tolbutamide] = $30.6 \pm 1.5 \text{ }\mu\text{g ml}^{-1}$, $n=8$) and 5.1% ([tolbutamide] = $31.7 \pm 1.6 \text{ }\mu\text{g ml}^{-1}$, $n=8$), respectively. For hydroxytolbutamide and carboxytolbutamide in urine, calibration curves were prepared over the concentration range $10\text{--}100 \text{ }\mu\text{g ml}^{-1}$. Urine specimens with metabolite concentrations above $100 \text{ }\mu\text{g ml}^{-1}$ were reassayed after predilution (1:2 or 1:4 with drug-free urine) to ensure concentrations within the range of the calibration curve. The within-day reproducibilities of the hydroxy- and carboxy-tolbutamide assays were also assessed using quality control samples and were 2.5% ([hydroxytolbutamide] = $21.8 \pm 0.5 \text{ }\mu\text{g ml}^{-1}$, $n=10$) and 2.8% ([carboxytolbutamide] = $61.8 \pm 1.7 \text{ }\mu\text{g ml}^{-1}$, $n=10$), respectively. The between-day reproducibilities of quality controls were 5.5% ([hydroxytolbutamide] = $21.0 \pm 1.2 \text{ }\mu\text{g ml}^{-1}$, $n=6$) and 3.9% ([carboxytolbutamide] = $61.3 \pm 2.4 \text{ }\mu\text{g ml}^{-1}$, $n=6$).

Data analysis

Noncompartmental pharmacokinetic parameters were calculated using standard equations. The maximum plasma concentration (C_{max}) and the time to reach the maximum concentration (t_{max}) were determined directly from the

data. The area under the tolbutamide plasma concentration time curve to 24 and 32 h, $AUC(0,24\text{ h})$ and $AUC(0,32\text{ h})$, were calculated using the trapezoidal rule. The terminal elimination rate constant (λ_z) was calculated by estimating the slope of the log plasma concentration *vs* time curve from 10–32 h by least squares linear regression. The AUC (area under the curve extrapolated to infinity) was calculated from the relationship $AUC(0,32\text{ h}) + (\text{concentration at } 32\text{ h})/\lambda_z$. In all subjects the extrapolated area was less than 15% of the total AUC. Apparent oral clearance (CL/F) of tolbutamide was calculated as (Dose/AUC) and was also normalised for body weight in kg. The elimination half-life ($t_{1/2}$) of tolbutamide was estimated from $(\ln 2/\lambda_z)$. The area under the first moment curve (AUMC) was calculated using the trapezoidal rule. The apparent volume of distribution (V/F) was calculated using $(\text{Dose}/AUC) \times (\text{AUMC}/AUC)$ and also normalised for body weight in kg. The cumulative urinary excretion of hydroxytolbutamide and carboxytolbutamide was calculated from the amounts excreted in each urine collection interval. The total urinary recovery (0,32 h, A_e) was calculated as the sum of the molar amounts of hydroxytolbutamide and carboxytolbutamide excreted and was also expressed as a percent of the tolbutamide dose. The partial apparent tolbutamide metabolic clearance (CL_{met}/F) was calculated as $(A_e/AUC(0,32\text{ h}))$. Data are presented as mean $\pm$ s.d., except for t_{max} , which is reported as the median and range, and half-life, which is reported as the harmonic mean.

Comparison with Caucasian data

Tolbutamide pharmacokinetic parameters in the 10 ethnic Chinese subjects have been compared with those previously reported by us in 13 healthy Caucasian volunteers (six male/seven female; aged 23–44 years; weight 49–84 kg) [9]. The Caucasian subjects were somewhat heavier than the Chinese subjects ($P=0.05$; 95% CI of diff -15.3 to 1.7). Whilst the previous study also administered a 500 mg oral dose of tolbutamide following an overnight fast, blood sampling at a reduced frequency was continued for only 24 h post-dose. Tolbutamide pharmacokinetic parameters in Chinese have therefore been recalculated in the same manner as in the Caucasian subjects (based on abridged 0,24 h data) and compared to the values in Caucasians using the Mann-Whitney U test. A probability of $P<0.05$ was considered significant. Where appropriate, the 95% confidence interval for the difference in means (95% CI of difference) has also been reported. Based on the variability observed in the present study and assuming a β error of 0.20 and a two tailed α error of 0.05, a 17% difference in the apparent oral

clearance of tolbutamide between Chinese and Caucasians could be detected [12].

Results

The tolbutamide pharmacokinetic parameters calculated in the healthy Chinese subjects are given in Table 1.

The maximum tolbutamide plasma concentration in the Chinese subjects was similar to that observed in Caucasian volunteers ($53 \pm 12\text{ }\mu\text{g ml}^{-1}$) ($P>0.05$; 95% CI of difference -0.06 to 20.20). Tolbutamide t_{max} was also comparable in Chinese and Caucasians ($3.1 \pm 1.5\text{ h}$) ($P>0.05$; 95% CI of difference -0.82 to 1.61). $AUC(0,24\text{ h})$ in Caucasians ($581 \pm 176\text{ }\mu\text{g ml}^{-1}\text{ h}$) was 20% lower than in Chinese ($719 \pm 101\text{ }\mu\text{g ml}^{-1}\text{ h}$) ($P=0.009$; 95% CI of difference 9 to 268). Consequently CL/F based on $AUC(0,24\text{ h})$ differed in Chinese ($707 \pm 102\text{ l h}^{-1}$) and Caucasians ($916 \pm 208\text{ l h}^{-1}$) ($P=0.009$; 95% CI of difference -358 to -59). The weight adjusted mean apparent oral clearance was lower ($P=0.03$; 95% CI of difference -0.004 to 0.074) in Chinese ($0.19 \pm 0.02\text{ ml min}^{-1}\text{ kg}^{-1}$) than Caucasians ($0.22 \pm 0.06\text{ ml min}^{-1}\text{ kg}^{-1}$). However $CL/F/\text{kg}$ in Chinese is similar to that reported by Veronese *et al.* [13] ($0.20 \pm 0.03\text{ ml min}^{-1}\text{ kg}^{-1}$), presumably in Caucasians.

The apparent volume of distribution (V/F) of tolbutamide in the Chinese subjects was $9.1 \pm 1.7\text{ l}$. This parameter is similar ($P>0.05$; 95% CI of difference -2.75 to 0.52) to that calculated in Caucasians ($8.0 \pm 2.0\text{ l}$) [9] and reported by Toon *et al.* [14] ($8.7 \pm 1.1\text{ l}$) and Day *et al.* [15] (7.8). As the Chinese weighed less than the Caucasian subjects, the weight corrected volume of distribution was greater ($P=0.002$; 95% CI of difference -0.05 to -0.02) in Chinese ($0.15 \pm 0.02\text{ l kg}^{-1}$) than in Caucasians ($0.12 \pm 0.02\text{ l kg}^{-1}$). The elimination half-life of tolbutamide in the Chinese volunteers was 9.1 h (range 7.4 – 11.9 h). This half-life is longer ($P=0.002$; 95% CI of difference 3.8 to 6.7) than that reported in Caucasians (4.1 h ; range 2.4 – 9.0) [9]. The latter value was calculated using an abridged blood sampling protocol, which may have underestimated the true terminal half-life. Literature values for tolbutamide half-life, calculated using comparable blood sampling schedules to the present study, include 8.0 h (range 6.3 – 10.3 h) [16], 8.3 h (range 6.0 – 13.8 h) [17], 9.6 h (range 6.5 – 15.1 h) [15] and 7.2 h (range 6.0 – 8.4 h) [14], values which are similar to those observed in the Chinese.

The urinary recoveries (0,32 h) of hydroxytolbutamide and carboxytolbutamide in the 10 ethnic Chinese subjects are given in Table 2. The lowest urinary recovery was observed in subject 4 (67% of the dose). Urinary 24 h creatinine measurement (6 mmol ; normal range 9 – 17 mmol) suggested that urine collection was

Table 1 Tolbutamide pharmacokinetic parameters (mean $\pm$ s.d.) in healthy Chinese subjects.

Subject	C_{max} ($\mu\text{g ml}^{-1}$)	t_{max} (h)	λ_z (h^{-1})	$t_{1/2,z}$ (h)	AUC (0,32 h) ($\mu\text{g ml}^{-1} \text{h}$)	AUC ($\mu\text{g ml}^{-1} \text{h}$)	CL/F (ml h^{-1})	$CL/F/\text{kg}$ ($\text{ml min}^{-1} \text{kg}^{-1}$)	V/F (l)
1*	46	4.5	0.0770	9.0	567	623	803	0.21	11.0
2	59	1.6	0.0581	11.9	699	816	613	0.16	10.1
3	47	3.0	0.0659	10.5	589	667	749	0.16	11.7
4	78	3.5	0.0942	7.4	808	850	588	0.19	6.7
5	69	4.5	0.0640	10.8	768	893	560	0.15	9.6
6	77	3.1	0.0899	7.7	805	857	584	0.16	7.2
7	65	2.1	0.0792	8.8	749	813	615	0.16	7.7
8	58	3.8	0.0667	10.4	715	820	610	0.17	10.1
9*	67	2.7	0.0876	7.9	658	699	716	0.19	8.6
10	67	6.0	0.0802	8.6	850	938	533	0.19	8.0
Mean	63	3.3	0.0763	9.1 [¶]	721	798	637	0.17	9.1
$\pm$ s.d.	11	1.6–6.0 [§]	0.0122		94	102	88	0.02	1.7

*Smoker. [§]Median, Range. [¶]Harmonic mean.

Subject	Hydroxytolbutamide (mg) (% Dose)		Carboxytolbutamide (mg) (% Dose)		Recovery (% Dose)	CL_{met}/F ($\text{ml min}^{-1} \text{kg}^{-1}$)
1*	58	11	393	71	82	0.19
2	81	15	366	66	81	0.15
3	75	14	357	64	79	0.14
4	61	12	303	55	66	0.13
5	72	14	384	69	83	0.14
6	70	13	389	70	83	0.14
7	64	12	393	71	83	0.14
8	82	15	410	74	89	0.17
9*	71	13	371	67	80	0.16
10	67	13	380	68	81	0.17
Mean	70	13	375	68	81	0.15
$\pm$ s.d.	8	1	29	5	6	0.02

*Smoker.

Table 2 Urinary recoveries (0–32 h) of hydroxytolbutamide and carboxytolbutamide expressed as both absolute recovery (mg) and percent of dose (% Dose) in healthy Chinese volunteers (mean $\pm$ s.d.). The total urinary recovery and the partial apparent metabolic clearance of tolbutamide are also given.

incomplete in this subject. In all subjects cumulative urinary excretion *vs* time graphs had not plateaued at the end of the urine collection interval, indicating that the urinary excretion of the metabolites of tolbutamide was not complete at 32 h. This observation is consistent with the tolbutamide half-life observed.

In the Chinese subjects the mean 24 h urinary recoveries of hydroxytolbutamide and carboxytolbutamide (64 ± 7 mg and 346 ± 26 mg, respectively) were similar to those observed in Caucasians (69 ± 26 mg and 306 ± 69 mg, respectively) ($P > 0.05$). The weight corrected apparent metabolic clearance of tolbutamide (based on 0,24 h data) was comparable in Chinese ($0.15 \pm 0.02 \text{ ml min}^{-1} \text{kg}^{-1}$) and Caucasians ($0.17 \pm 0.06 \text{ ml min}^{-1} \text{kg}^{-1}$) ($P > 0.05$; 95% CI of difference -0.03 to 0.06).

No subject reported any symptom of hypoglycemia and no adverse effects were observed. No consistent relationship between tolbutamide plasma concentration

and blood glucose level was observed. Blood glucose concentrations fell from $3.9 \pm 0.6 \text{ mmol l}^{-1}$ prior to tolbutamide administration, to $3.2 \pm 0.6 \text{ mmol l}^{-1}$ 2 h post-dose and returned to $3.8 \pm 0.5 \text{ mmol l}^{-1}$ 4 h post-dose. The threshold plasma tolbutamide concentration measured prior to the fall in glucose levels was $20 \pm 10 \mu\text{g ml}^{-1}$ (range 10–37 $\mu\text{g ml}^{-1}$).

Discussion

Rational use of a drug requires an understanding of its pharmacokinetics in the population in which it is used. Tolbutamide is widely used in Asia, however this is the first report of its pharmacokinetics and metabolism in ethnic Chinese. The Chinese subjects were leading a westernised lifestyle in Australia and therefore only the genetic factors which may contribute to an ethnic difference in drug disposition have been examined. The parameters describing the disposition of tolbutamide are

given in Tables 1 and 2. With these data now available clinicians with Chinese diabetic patients can prescribe tolbutamide with greater confidence.

China is a multinational country with a Han majority (93.3% of the population) and 55 diverse national minorities [18]. All subjects in the present study had four grandparents born in China in regions with Han populations. Studies examining the distribution of dermatoglyphic parameters, genetic markers and anthropometric measurements of Chinese populations conclude that the Han peoples are not homogeneous but vary relative to geographic proximity. Although the process of differentiation between northern and southern Han Chinese may have begun 13 000 years ago, differentiation between Chinese and Caucasians began approximately 50 000 years ago [18]. Thus whilst there may be some ethnic diversity among the 10 Chinese subjects studied, it is minor compared with the ethnic differences between Chinese and Caucasians.

There were no differences in the indices of tolbutamide absorption ($C_{\max}$, $t_{\max}$) in the Chinese relative to the Caucasians. V/F was similar to that observed in Caucasians, however as a consequence of the difference in weight of the Chinese and Caucasian subjects, weight normalised $V/F/\text{kg}$ was 20% higher in Chinese than Caucasians. In plasma, tolbutamide is highly bound to albumin [19]. Although protein binding was not measured in this study it is not expected that any substantial difference in the plasma free fraction between Chinese and Caucasians would be observed as previous studies have not identified an ethnic difference in plasma albumin concentrations or the plasma protein binding of drugs highly bound to albumin [20, 21]. Differences in body composition and hence tissue distribution could account for the difference in weight corrected V/F .

The apparent oral clearance of tolbutamide (CL/F) was 20% lower in Caucasians than Chinese. A smaller and less highly significant difference (95% CI of difference -0.004 to 0.074) was observed when the clearance was normalised for body weight, suggesting that larger studies may be warranted to verify this observation. Indeed as the urinary recoveries of hydroxytolbutamide and carboxy-tolbutamide were similar in Chinese and Caucasians and no ethnic difference in CL_{met}/F was observed, it is likely that, at most, there is only a small ethnic difference in $\text{CL}/F/\text{kg}$ which would not be of clinical significance. This conclusion is supported by the similar tolbutamide half-life observed in Chinese and Caucasians. As half-life is a composite term and V/F is comparable in the two ethnic groups, then any difference in CL/F must be small. As CYP2C9 catalyses the rate limiting step in the formation of both hydroxytolbutamide and carboxy-tolbutamide, CL_{met}/F reflects CYP2C9 activity. Considering the low frequency of mutant CYP2C9 alleles and the

similar CL_{met}/F in Chinese and Caucasians, this study also suggests that there is no substantial ethnic difference in the tolbutamide hydroxylase activity of Chinese and Caucasian wildtype CYP2C9.

Although our Caucasian data [9] were obtained some time ago, basically the same techniques were used in both studies and we consider the historical comparison valid. The pharmacokinetics of tolbutamide have been widely reported in the literature, and although the ethnic group of the subjects investigated has often not been stated, the country of origin of most studies suggests that Caucasian volunteers were used. The pharmacokinetic parameters observed in the Chinese are similar to these literature reports [13–17, 22], supporting our conclusion that there is no clinically significant ethnic difference in tolbutamide pharmacokinetics.

A number of literature reports indicate that Oriental and Caucasian patients require different doses of drugs metabolised by CYP2C9 to attain an equivalent therapeutic effect [4–7, 23, 24]. The present study suggests that tolbutamide hydroxylase activity is similar in Chinese and Caucasians. Provided that the Chinese and Caucasian CYP2C9 wildtype proteins have comparable substrate specificity, then the differences in dose requirements reported are thus unlikely to be attributable to altered metabolism catalysed by CYP2C9. Further investigation of the pharmacokinetics and pharmacodynamics of these drugs in Oriental populations is warranted.

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