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PHARMACOGENETICS

Differences in the single-oral-dose pharmacokinetics and urinary excretion of paracetamol and its conjugates between Hong Kong Chinese and Caucasian subjects

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SUMMARY

Background and Objectives: **The present study was conducted to determine if ethnic differences exist for single oral dose pharmacokinetics of paracetamol and its conjugates between Hong Kong Chinese and Caucasian subjects.**

Methods: **Twenty healthy Chinese ($n = 11$) and Caucasian ($n = 9$) subjects, aged 21–44 years, 11 male and nine female, were given oral paracetamol syrup 20 mg/kg, following an overnight fast. Paracetamol and its metabolites (glucuronide, sulphate, cysteine and mercapturic acid conjugates) were measured in serial plasma samples (0·25, 0·5, 0·75, 1·0, 1·5, 2, 3,…,12, 24 h) and urine collections (0–24 h) by high-performance liquid chromatography.**

Results: **In Chinese subjects, the (mean range) peak plasma concentration of paracetamol was 23·8 μg/mL (17·9–32·3) and time to attain this peak 0·66 h (0·5–0·75). This was lower ($P < 0·015$) at 18·7 μg/mL (14·4–22·9) and achieved later ($P < 0·033$) at 1·06 h (0·5–2·0) in Caucasians. In Chinese subjects, plasma levels of glucuronide were lower, sulphate higher and cysteine conjugates significantly lower than in Caucasians ($P < 0·05$). Chinese subjects excreted 6% more sulphate and 5% less glucuronide. They also excreted significantly less mercapturic acid conjugates ($P < 0·001$).**

Discussion and Conclusion: **Chinese subjects show more rapid absorption of paracetamol, a tendency to produce less glucuronide but more sulphate conjugates and reduced production of cysteine and mercapturic acid conjugates. The latter may help to protect against hepatotoxicity following paracetamol overdose.**

***Keywords*: Chinese, conjugates, ethnics differences, paracetamol, pharmacokinetics**

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INTRODUCTION

Racial and environmental differences in the handling of many drugs (pharmacokinetics) has become increasingly relevant in recent years, especially as health-care services develop in many non-European countries. This is particularly true of Hong Kong where a high level of research and medical care is practiced in an essentially non-Caucasian population. However, much of our basic knowledge about the pharmacokinetics of different drugs comes from studies performed in Caucasian subjects. A prime example of this is paracetamol, which is an ideal drug for studying gastric emptying (1) and drug metabolism (2) in both health (3, 4) and disease (5–9). It is absorbed primarily in the small bowel and undergoes oxidative and conjugative reactions to non-toxic metabolites that are excreted in the urine. However, most of our current data on paracetamol were obtained using Caucasian subjects. Little is known about how these mechanisms differ in Hong Kong Chinese subjects, yet significant differences are know to exist between Caucasian and African (4, 10, 11), Asian (12, 13) and Thai (14) subjects. Thus, the

purpose of the present study was to define paracetamol pharmacokinetics in local Hong Kong Chinese and Caucasian subjects.

MATERIALS AND METHODS

Eleven Chinese and nine Caucasian healthy local volunteers were recruited. The study was approved by the Chinese University Clinical Research Ethics Committee. All subjects abstained from taking paracetamol-containing and other drugs for 2 weeks prior to the study. Following an overnight fast, an oral dose of paracetamol syrup 20 mg/kg (Panadol, Sterling-Winthrop, New York, NY, USA) was administered with water (100 mL). Subjects then remained sedentary for 2 h. Blood samples were taken into heparinized tubes from an intravenous canula inserted in the forearm before and at 0·25, 0·5, 0·75, 1·0, 1·5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 h following paracetamol administration. Urine was saved for 0–24 h with chloroform as preservative.

Plasma and urine concentrations of paracetamol and its metabolites (glucuronide, sulphate, cysteine and mercapturic acid conjugates) were measured by high-performance liquid chromatography (15). The concentrations of these metabolites were calculated as paracetamol equivalents (4).

Data analysis

Plasma pharmacokinetic variables were estimated using the data analysis software package Kinetica for Microsoft Windows 95 (Simed S.A., Creteil, France). A 'modified Wagner-Neslon method' was selected, which required no intravenous reference and assumed a one compartment model and first order drug elimination, to curve fit and analyse the plasma concentration profiles. Parameters estimated were peak plasma concentration (C_{max}), the time to peak (T_{max}), plasma half-life ($t_{1/2}$) and the area under the plasma concentration–time curve (AUC). For paracetamol, the AUC was calculated using data collected between 0 and 8 h and extrapolated to infinity. For metabolites, AUCs were calculated between 0–24 h and extrapolated to infinity. Renal clearances were calculated for paracetamol and its metabolities from the 24-h urinary recoveries divided by AUC (0-∞) and expressed as mL/min.

Racial differences in the major conjugative and hepatic mixed function oxidase pathways were examined by calculating their percentage compared with the total paracetamol and metabolites measured in the urine. The ratio of glucuronide to sulphate conjugate and the total cysteine plus mercapturic conjugates were also calculated.

Demographic data were compared using Student's *t*-test or the chi-squared test, as appropriate. Pharmacokinetic parameters were compared using Student's *t*-test. Results are presented as mean (SD or range) and we considered $P < 0{\cdot}05$ to be significant.

RESULTS

The Chinese subjects were smaller, with respect to weight and height, compared with their Caucasian counterparts ($P < 0{\cdot}05$) (Table 1).

Plasma pharmacokinetic data

The mean plasma paracetamol and metabolites concentration vs. time curves for both Caucasian and Chinese subjects are shown in Fig. 1. For paracetamol, peak plasma concentrations (C_{max}) were greater and times to reach these peaks (T_{max}) were less in Chinese compared with Caucasian subjects ($P < 0{\cdot}05$) (Table 2).

Chinese subjects tended to have higher sulphate and lower glucuronide plasma levels, although these differences did not reach significance (Fig. 1; Table 2). Plasma cysteine conjugate C_{max} and AUC levels were lower in Chinese subjects ($P < 0{\cdot}05$). Plasma half-lives for cysteine conjugates could not be estimated accurately form the plasma concentration vs. time curves and plasma mercapturic acid levels were not measured.

Table 1. Demographic data for Caucasian and Chinese subjects

	Caucasians ($n = 9$)	Chinese ($n = 11$)	*P*-value
Age (years)	29 (23–44)	24 (21–32)	0·07
Weight (kg)	68 (55–97)	57 (46–71)	0·03
Height (m)	175 (166–187)	163 (154–178)	0·01
Gender (M/F)	6/3	5/6	$\chi^2 = 0{\cdot}34$

Data are given as mean (range).

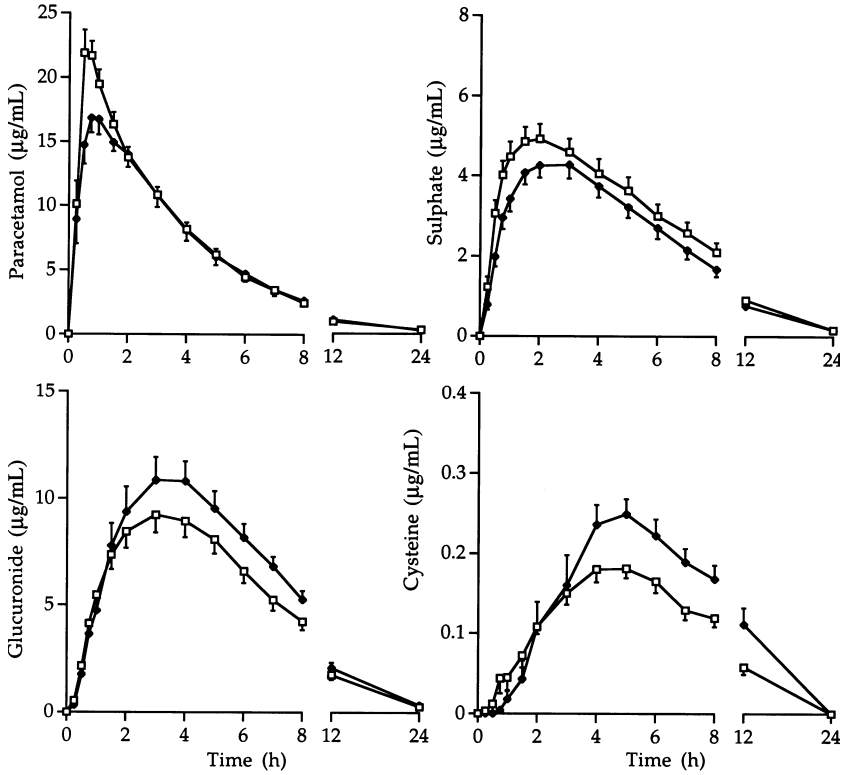

Fig. 1. Twenty-four hour plasma profiles for paracetamol and metabolites. Data presented as mean (SEM). Caucasians (n = 9) are represented by (●) and Chinese (n = 11) by (□).

Renal clearances for paracetamol and its metabolites were similar for both Caucasian and Chinese subjects (Table 2).

Urinary recovery data

The total urinary recovery of paracetamol and its metabolites was 92% (56–108%) in Caucasians and 93% (63–114%) in Chinese. Approximately 5% of the paracetamol was excreted unchanged in both groups (Table 3). Chinese subjects excreted about 6% more sulphate conjugate and 5% less glucuronide conjugate, although these differences did not reach statistical significance (Table 3). However, there was a statistically significant difference in the ratio of glucuronide to sulphate conjugate excretion (P = 0·05), which was mainly because of differences in the female subjects with high ratios in the Caucasian females (mean 2·7) and the low ratios in the Chinese females (mean 1·4). A large intersubject variability existed in the production of sulphate and glucuronide conjugates and there was a strong inverse correlation between the production of these conjugates. Chinese subjects also excreted significantly less mercapturic acid conjugates than Caucasians (P < 0·001).

DISCUSSION

The importance of ethnic and environmental factors on drug metabolism has long been recognized (16). Mucklow *et al.* (12) reported on ethnic differences in paracetamol metabolism. They measured paracetamol levels in saliva and found longer half-lives and lower clearances in Asian immigrants, when compared with Caucasians working in London. They attributed these differences to alcohol and tobacco intakes and the use of the oral contraceptive pill. However, it was unclear whether the Asians they studied were Chinese or Indian. Sommers *et al.* (10) found a greater clearance of paracetamol in Black people compared with White people, in South Africa, and Critchley *et al.* (4) found a marked reduction in the formation of cysteine and mercapturic acid conjugates in native Ghanians and Kenyans, compared with Caucasians living in Scotland. More recently Lee *et al.* (13) found a lower sulphate conjugate fraction in Chinese compared with Indian subjects living in Singapore. The present study found significant differences between Caucasian and Chinese subjects living in Hong Kong in respect to the paracetamol C_{max}, T_{max} and production of the

Table 2. Pharmacokinetic parameters for paracetamol and metabolites

Parameter	Caucasians (n = 9)	Chinese (n = 11)	P-value
Paracetamol			
C_{max} (μg/mL)	18·7 (14·4–22·9)	23·8 (17·9–32·3)	0·015
T_{max} (h)	1·06 (0·5–2·0)	0·66 (0·5–0·75)	0·033
$t_{1/2}$ (h)	2·61 (2·19–3·20)	2·62 (2·11–3·46)	ns
$AUC_{0-\infty}$ (μg/mL/h)	83·0 (56·7–117·1)	83·3 (50·8–112·6)	ns
Cl_r (mL/min)	11·9 (4·5–16·4)	11·2 (5·6–18·1)	ns
Glucuronide			
C_{max} (μg/mL)	11·2 (7·7–15·1)	9·5 (5·8–14·8)	0·21
$t_{1/2}$ (h)	4·47 (3·23–6·51)	4·33 (3·69–5·01)	ns
$AUC_{0-\infty}$ (μg/mL/h)	90·6 (60·9–119·5)	76·2 (50·9–110·5)	0·15
Cl_r (mL/min)	140 (87–185)	129 (82–187)	ns
Sulphate			
C_{max} (μg/mL)	4·43 (3·18–6·02)	5·80 (3·15–7·41)	0·28
$t_{1/2}$ (h)	5·36 (3·96–7·88)	4·96 (4·15–5·93)	ns
$AUC_{0-\infty}$ (μg/mL/h)	36·7 (24·2–50·0)	40·4 (25·2–62·0)	0·47
Cl_r (mL/min)	160 (85–217)	148 (117–196)	ns
Cysteine			
C_{max} (μg/mL)	0·26 (0·15–0·33)	0·20 (0·13–0·26)	0·034
$t_{1/2}$ (h)	n/a	n/a	n/a
$AUC_{0-\infty}$ (μg/mL/h)	1·82 (0·82–2·40)	1·37 (0·87–2·08)	0·05
Cl_r (mL/min)	416 (273–629)	401 (215–572)	ns

Data are given as mean (range). C_{max}, maximum concentration; T_{max}, time to maximum concentration; $t_{1/2}$, half-life; $AUC_{0-\infty}$, area under the curve from zero to infinity; Cl_r , renal clearance; ns, not significant; n/a, not applicable.

Table 3. Twenty-four hour urinary recoveries for paracetamol and metabolites

Parameters	Caucasians (n = 9)	Chinese (n = 11)	P-value
Paracetamol (%)	4·7 (2·4–7·6)	5·3 (3·1–9·0)	0·40
Glucuronide (%)	59·9 (47·3–68·3)	55·0 (40·7–68·6)	0·22
Sulphate (%)	27·7 (19·8–41·9)	34·2 (22·3–46·4)	0·08
Glucuronide to sulphate ratio	2·31 (1·13–3·45)	1·68 (0·93–2·69)	0·05
Cysteine (%)	3·6 (2·5–6·7)	3·2 (2·0–5·0)	0·47
Merc (%)	4·2 (1·9–6·7)	2·2 (1·0–3·1)	0·001
Cysteine plus Merc (%)	7·7 (5·2–13·5)	5·4 (3·5–8·1)	0·02

Data are given as mean (range). Percentage recovered and ratio of glucuronide to sulphate conjugates are shown. Merc, mercapturic acid.

mercapturic acid conjugate. There was also a significant difference in the ratio of the 24-h urine recovery of glucuronide and sulphate conjugates. These differences point to a more rapid absorption of paracetamol in the Chinese and reduced production of the potentially hepatotoxic metabolite. Reduced toxic metabolic activation of paracetamol has been reported previously in Chinese subjects (13). This may suggest Chinese subjects may be less susceptible than Caucasians to the hepatotoxicity of paracetamol overdose, and this is consistent with the very low incidence of liver damage following overdosage in Hong Kong (17).

The sulphate and glucuronide conjugates account for about 30 and 55%, respectively, of paracetamol elimination (2). However, saturation

of sulphate conjugation is evident within the therapeutic dose range and there may be marked individual variation in the formation of the sulphate and glucuronide conjugates (3, 4). In the present study, the findings were similar, however, recovery of sulphate conjugates tended to be less and glucuronide conjugates more in Caucasian compared with Chinese subjects (Table 3). There tended to be higher plasma sulphate and lower plasma glucuronide conjugate concentrations in Chinese subjects but the renal clearance rates for both these metabolites were similar. Lee *et al*. (13) have also shown increased urinary excretion of sulphate conjugates of paracetamol in Chinese compared with Indian subjects (36% vs. 29%) living in Singapore. Thus, Chinese subjects may have a greater capacity for sulphate conjugation or lower capacity for glucuronidation than Caucasians.

Paracetamol undergoes glucuronidation by a number of UDP-glucuronosyltransferase (UGT) isoforms in the liver, particularly UGT1A1, UGT1A6 and UGT1A9 (18) and probably UGT1A10 in the gastrointestinal tract (19). Glucuronidation has been reported to be higher in males than females (4), which appears to be related to UGT1A6 activity (18). There was a tendency ($P = 0{\cdot}16$) for glucuronide excretion to be greater in males in the present study and this might have reduced the difference between ethnic groups because of the uneven gender distribution. Polymorphisms have been reported in the genes for UGT1A1 and UGT1A6 and these are known to show extensive ethnic variations (20), which may be related to these findings. Genetic variations are also known to exist for some of the sulfotransferases.

Caucasian subjects living in Hong Kong absorbed paracetamol more slowly than Chinese subjects. There was less potentially toxic metabolite activation of paracetamol in the Chinese as shown by lower plasma concentrations of the cysteine conjugate and lower renal excretion of the mercapturic acid conjugates. The Chinese subjects also produced relatively more sulphate and less glucuronide conjugates of paracetamol than the Caucasians. These findings may suggest more rapid gastric emptying and less susceptibility to the hepatotoxicity of paracetamol following overdosage in the Chinese, but the observed differences are unlikely to be of great clinical significance. Studies with more specific phenotyping or genotyping of the metabolic pathways for paracetamol are needed to eliminate these variations.

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