Interethnic differences in drug glucuronidation:
A comparison of paracetamol metabolism in Caucasians and Chinese

N. J. OSBORNE, A. L. TONKIN & J. O. MINERS
Department of Clinical Pharmacology, Flinders Medical Centre, Bedford Park, Adelaide, South Australia 5042

Paracetamol disposition following a single oral 1 g dose of the drug was compared in groups \( n = 12 \) of healthy young adult male Caucasians and Chinese. There was no difference between the groups in terms of paracetamol oral clearance, elimination half-life, or partial metabolic (glucuronidation, sulphation, oxidation) and renal clearances. The results demonstrate that drug glucuronidation is not universally impaired in Chinese and, together with previously published data, that paracetamol glucuronidation is minimally affected by race.

Keywords drug glucuronidation UDP-glucuronosyltransferase paracetamol interethnic differences

Introduction

It has been recognised for some time that differences may exist between certain racial groups in their ability to metabolise drugs. In particular, comparisons between Caucasian and Oriental (Chinese, Japanese) populations have demonstrated differences in the relative frequencies of the \( N \)-acetylation (Price-Evans 1989), debrisoquine 4-hydroxylation (Eichelbaum & Gross 1990) and S-mephenytoin hydroxylation (Wilkinson et al., 1989) phenotypes. Differences between Orientals and Caucasians in the activities of the enzymes involved in ethanol degradation are also known to occur (Agarwal & Goedde, 1986).

Despite the recognition of these differences between Orientals and Caucasians, the possibility of altered drug glucuronidation in Orientals has been considered only recently. In a comparison of codeine metabolism in Swedish Caucasians and Chinese resident in Sweden, it was found that the Caucasians excreted almost 50% more codeine glucuronide than the Chinese (Yue et al., 1989). However, when the results were expressed in terms of the codeine glucuronide urinary metabolic ratio, it was apparent that the Caucasians conjugated codeine more than twice as efficiently as the Chinese. UDP-glucuronosyltransferase (UDPGT), the enzyme responsible for drug glucuronidation, is known to exist as a multi-gene family with the individual isoenzymes tending to differ in terms of substrate specificity and regulation (Burchell & Coughtrie 1989; Miners & Mackenzie, 1991).

Identification of a difference between Chinese and Caucasians in the glucuronidation of one drug does not, therefore, necessarily indicate that the glucuronidation of all drugs will be impaired in Chinese. Thus, to assess the extent of differences in drug glucuronidation between Chinese and Caucasians, a study comparing paracetamol disposition in these two racial groups was performed.

Methods

Subject

Owing to a limited number of female Chinese volunteers available for study and the known effects of gender and oral contraceptive-use on paracetamol disposition (Miners et al., 1983), participation in the study was restricted to males. The study group comprised 12 Caucasians aged 20–32 years (mean 25 \( \pm \) 4 years), weight 67–88 kg (mean 77 \( \pm \) 6 kg) and 12 Chinese aged 18–31 years (mean 24 \( \pm \) 4 years), weight 56–80 kg (mean 68 \( \pm \) 6 kg). Subjects were healthy as determined by medical history, physical examination and standard biochemical and haematological parameters. They were receiving no regular drug therapy and took no medications for at least 1 week prior to the study. All subjects were non-smokers.

Correspondence: Dr J. O. Miners, Department of Clinical Pharmacology, Flinders Medical Centre, Bedford Park, South Australia 5042, Australia

765
All of the Caucasian subjects were of Anglo/Australian background; they were able to verify that their parents, grandparents or great-grandparents originated from the United Kingdom. The Caucasians all maintained a typical non-vegetarian ‘Western’ diet. Although many of the Chinese subjects were born in Asian countries other than China, the grandparents of all but one were born in China. Of the Chinese subjects, five maintained a predominantly Chinese diet, six a part ‘Western’-part Chinese diet, and one a ‘Western’ diet.

The study was approved by the Drug and Therapeutics Advisory Committee and the Clinical Investigation Committee of Flinders Medical Centre. Written informed consent was obtained from each subject prior to their participation in the study.

Protocol

After an overnight fast each subject received 2 × 500 mg paracetamol tablets (Panadol, Sterling-Winthrop) with 150 ml tap water. Food was withheld until 3 h post-dose. Blood samples (5 ml) were withdrawn via an indwelling cannula inserted in a forearm vein prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h following paracetamol administration. Urine was collected to 24 h post-dose. Plasma was separated and stored at −20°C until analysed but urine samples were assayed within a day of collection.

Sample analysis and calculation of results

Plasma paracetamol concentrations and the concentrations of unchanged paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates in urine were measured by h.p.l.c. procedures (Miners et al., 1983, 1984). Minimum quantifiable concentrations of unchanged paracetamol in plasma and of each of the urinary paracetamol metabolites were 3.3 μmol l⁻¹ (0.5 mg l⁻¹) and 50 μmol l⁻¹, respectively. Over the concentration ranges of the standard curves for each analyte, imprecision (intra- and inter-day) was < 10% while accuracy ranged from 91–108%.

Area under the plasma drug concentration-time curve (AUC) was calculated by the linear trapezoidal rule with extrapolation to infinite time. Elimination half-life ($t_{1/2}$) was determined from the slope of the linear portion of the log plasma drug concentration-time plots. Paracetamol oral clearance (CLpo) was calculated as

$$\text{CL}_{po} = \frac{D}{(AUC \times BW)},$$

where $D$ is the paracetamol dose and $BW$ is the body weight in kg. The oral clearance of a drug that is completely absorbed and heptically cleared reflects intrinsic clearance (Wilkinson & Shand, 1975). (Recovery of the dose as paracetamol and its metabolites in urine was essentially quantitative for both the Caucasian and Chinese study groups.) Partial metabolic and renal clearances of paracetamol were determined as,

$$\text{CL}_{m} = f_m \cdot \text{CL}_{po},$$

where $CL_m$ is the metabolic clearance to the glucuronide, sulphate and glutathione-derived (i.e. cysteine and mercapturic acid) conjugates or the renal clearance of unchanged paracetamol and $f_m$ is the fractional recovery of each conjugate or of unchanged paracetamol. It should be recognised that the cysteine- and mercapturic acid-conjugates arise from conjugation of a reactive, oxidised metabolite of paracetamol with glutathione. Since the initial oxidation (mediated by cytochrome P-450) is presumably rate-limiting, metabolic clearance to the glutathione-derived conjugates reflects activity of the oxidative pathway. All results are expressed as mean ± s.d. Statistical comparisons were performed using Students’ unpaired t-test following confirmation of homogeneity of variances.

Results

There was no significant difference in paracetamol oral clearance (Figure 1) or half-life between the Caucasians ($\text{CL}_{po}$ 6.04 ± 1.55 ml min⁻¹ kg⁻¹; $t_{1/2}$ 2.3 ± 0.4 h) and Chinese ($\text{CL}_{po}$ 6.15 ± 1.71 ml min⁻¹ kg⁻¹; $t_{1/2}$ 2.2 ± 0.4 h). Similarly, there was no significant difference between the groups in the urinary excretion of paracetamol and its metabolites. Respective recoveries (expressed as percentage of the recovered dose) in the Caucasians and Chinese were: glucuronide, 54.5 ± 7.3% and 52.0 ± 7.0%; sulphate, 31.7 ± 4.8% and 34.8 ± 7.2%; glutathione-derived conjugates, 10.0 ± 4.1% and 9.2 ± 2.6%; paracetamol, 3.8 ± 1.0% and 4.0 ± 1.2%. The renal and metabolic clearances of paracetamol are illustrated in Figure 1, and again there was no difference between the groups for any of the partial clearances. Respective partial clearances in the Caucasians and Chinese were: glucuronide, 3.37 ± 1.18 and 3.19 ± 0.98 ml min⁻¹ kg⁻¹; sulphate, 1.87 ± 0.46 and 2.21 ± 0.77 ml min⁻¹ kg⁻¹; glutathione-derived conjugates, 0.57 ± 0.21 and 0.58 ± 0.24 ml min⁻¹ kg⁻¹; paracetamol, 0.23 ± 0.07 and 0.24 ± 0.06 ml min⁻¹ kg⁻¹. It should be noted that the power of the study was sufficient to detect at least a 25% difference in each of the disposition parameters at the 5% significance level.

![Figure 1: Paracetamol oral clearance (CLpo) and partial metabolic and renal clearances of paracetamol in Caucasians (■) and Chinese (○): CLGL, clearance to glucuronide; CLSULPH, clearance to sulphate; CLGSH, clearance to glutathione-derived conjugates; CLR, renal clearance of unchanged paracetamol. Results presented as mean ± s.d.](image-url)
Discussion

The importance of characterising differences in drug disposition and response among patients of various racial backgrounds has been highlighted recently (Kalow, 1989). In particular, racial differences in pharmacokinetics and/or response are likely to have important consequences for determining individual drug dosage requirements. Hence, identification of interethnic variability in the activities of specific drug metabolising enzymes would assist in rationalising the drug treatment of individual racial groups.

Codeine 6-glucuronide formation in vivo is known to be lower in Chinese than in Caucasians (Yue et al. 1989), which is consistent with the lower codeine dose required to achieve analgesia in Chinese. In contrast, the present study has demonstrated that paracetamol glucuronidation does not differ between these two racial groups. Furthermore, this study has shown that there is no difference between Caucasians and Chinese in their ability to either sulphate or oxidise paracetamol. From the results presented here it is therefore apparent that xenobiotic glucuronidation is not universally impaired in Chinese. Rather it would seem that impairment of drug glucuronidation in Chinese arises from the selective effects of genetic and/or environmental factors (e.g. diet) on the various UDPGT isoenzymes involved in xenobiotic conjugation. Support for the involvement of separate UDPGT isoenzymes in the glucuronidation of codeine and paracetamol is provided by the absence of mutual inhibition when these drugs are coadministered in vivo (Bochner et al., 1990; Sonne et al., 1988) and by the lack of effect of codeine on the paracetamol UDPGT-

activity of human liver microsomes (Osborne & Miners, unpublished results). It is acknowledged that the opposing results of the codeine and paracetamol studies could arise from uncontrolled genetic or environmental factors in either of the investigations, but this is considered unlikely. In particular, the groups of Chinese and Caucasian subjects who participated in the separate studies were each considered racially homogenous and the majority of the Chinese subjects in both studies maintained wholly- or part-Chinese diets.

Although codeine glucuronidation appears to have been compared only between Caucasians and Chinese, comparisons of paracetamol disposition between Caucasians and other racial groups have been reported. The mean fractional urinary recovery of paracetamol glucuronide was reported to be higher in Africans (Kenyan and Ghanaians) than in Caucasians (Critchley et al., 1986), but the difference in excretion was very small (58% vs 54%). In a comparison of paracetamol disposition in London office and factory workers it was found that oral clearance was approximately 25% higher in Caucasians than in Asians (ethnicity not specified, but presumably predominantly from the Indian subcontinent) (Mucklow et al., 1980). The contrasting use of social drugs, such as tobacco, caffeine and the oral contraceptive, accounted for at least part of the apparent difference in paracetamol clearance in this latter study. Thus, available evidence suggests that paracetamol glucuronidation is minimally affected by race.

This work was supported by a grant from the National Health and Medical Research Council of Australia.

References


(Received 23 May 1991, accepted 13 August 1991)