Evidence for the polymorphic oxidation of debrisoquine in the Thai population

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Debrisoquine polymorphism has been studied extensively in Caucasian populations. The prevalence of the poor metaboliser phenotype is 3–10% in European and American Caucasian populations but appears to be very low in Asian populations. This study was carried out to determine the metabolic oxidation status in 173 Thai subjects. Phenotyping was performed using the metabolic ratio (MR) calculated as the 0–8 h urinary output of debrisoquine/0–8 h urinary output of 4-hydroxydebrisoquine after oral administration of 10 mg debrisoquine hemisulphate. Two subjects (1.2%) were phenotyped as poor metabolisers; they had MR values of 13.17 and 92.04. The incidence of the poor metaboliser phenotype of debrisoquine oxidation of 1.2% seems to be lower in the Thai population compared with that in various Caucasian populations.

Keywords genetic polymorphism debrisoquine pharmacogenetics oxidation phenotyping Thai

Introduction

It is well recognised that there are pronounced interindividual variations in the pharmacokinetics of many drugs. Due to these interindividual differences in pharmacokinetics, standard doses of drugs administered to a patient population result in large variations in drug response and therapeutic outcome. One major factor contributing to these differences is a marked variation in the capacity of different individuals to metabolise drugs. In several instances, genetic factors have been discovered to be important determinants of drug metabolising enzyme activity (Eichelbaum, 1982; Kalow, 1982). The importance of genetic factors in the control of oxidative drug metabolism has been appreciated only recently. Interest in the pharmacogenetics of oxidative drug metabolism gained new interest with the discovery that debrisoquine and sparteine oxidation were under monogenic control (Eichelbaum *et al.*, 1979; Mahgoub *et al.*, 1977).

Two distinct oxidation phenotypes were observed. The poor metaboliser (PM) phenotype excretes most of a dose of debrisoquine or sparteine as unchanged drug, whereas the extensive metaboliser (EM) eliminates much of the drug as metabolites.

Pronounced interethnic differences in the frequency of the PM phenotype are known to exist (Kalow, 1982). The frequency of the PM phenotype of debrisoquine in Caucasian populations averages about 7%, ranging from 3% in a Swedish population (Bertilsson *et al.*, 1981) to 10% in a Swiss population (Kupfer & Preisig, 1984). In Saudi Arabians and Egyptians the incidence of defective debrisoquine oxidation appears to be lower than that observed in Caucasian groups. The PM phenotype frequency in Saudi Arabians and Egyptians is 1.0 and 1.4%, respectively (Islam *et al.*, 1980; Mahgoub *et al.*, 1979). To our knowledge, no data are

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available for the Thai population. This study was performed to estimate the frequency of the PM phenotype in a Thai population.

Methods

Subjects

The study was performed in 173 Thai volunteers (mostly students and staff from Prince of Songkla University) aged 17 to 58 years and including 129 males and 44 females. All subjects gave their informed consent. The study was approved by the Ethics Committee, Faculty of Science, Prince of Songkla University, Thailand. All subjects were judged to be in good health as determined by medical history, physical examination, and blood pressure measurement. They were taking no medication for at least 1 week before the study and did not abuse alcohol. All subjects were Thai citizens and were born in Thailand. Classification of the Thai subjects was made on the basis of their family history to two generations and revealed no mixed marriage with Chinese or other ethnic groups. Twenty-seven percent had both parents who were Chinese.

Protocol for debrisoquine phenotyping

The subjects fasted overnight and then took a single oral dose of debrisoquine hemisulphate

10 mg (Declinax, Roche) in the morning, after emptying the bladder. All urine was collected up to 8 h after drug administration. The volume of each specimen was measured and a 10 ml aliquot was stored at -20°C until analysis. Debrisoquine and 4-hydroxydebrisoquine in urine were assayed by h.p.l.c. (Lee & Ang, 1987). The metabolic ratio (MR) was calculated as:

$$\text{MR} = \frac{\% \text{ dose eliminated as debrisoquine}}{\% \text{ dose eliminated as 4-hydroxydebrisoquine}}$$

in an 8 h urine sample. The MR was expressed as the $\log_{10}$ value. Metabolic ratios greater than 12.6 ($\log_{10}\text{MR} > 1.1$) were considered to be indicative of poor metabolisers (Price-Evans *et al.*, 1980).

Results

The distribution of $\log_{10}\text{MR}$ in the 0–8 h urine of the 173 Thai subjects is shown in Figure 1. Two phenotypes are apparent in the frequency histogram with an antimode at $\log_{10}\text{MR} = 0.78$. One hundred and seventy-one subjects (98.8%) had MR values between 0.07 and 6.08 and were classified as extensive metabolisers (EM). Two subjects were identified as poor metabolisers (PM); one male and one female. They had MR values of 13.17 and 92.04. This corresponds to a frequency of the PM pheno-

Figure 1 Frequency distribution of the $\log_{10}$ metabolic ratio of debrisoquine in 173 Thai subjects. Metabolic ratio = % dose eliminated as debrisoquine/% dose eliminated as 4-hydroxydebrisoquine in a 0–8 h urine sample. ▨ extensive metabolisers, ■ poor metabolisers.

type of 1.2% with a 95% confidence interval of 0.4 to 2.7%. The mean ($\pm$ s.d.) of the total urinary recovery of debrisoquine and 4-hydroxy-debrisoquine for the Thai population was $32.8 \pm 13.9\%$ of the dose.

Neither sex nor smoking habits affected debrisoquine oxidation phenotyping in our population. The mean ($\pm$ s.d.) of the MR for males was 2.25 ± 8.01 ($n = 129$) and for females it was 1.82 ± 2.22 ($n = 44$), $t = 0.35$, $P = 0.73$. The MR for smokers was 1.74 ± 140 (mean $\pm$ s.d., $n = 28$) and it was 2.22 ± 7.68 ($n = 145$) for non-smokers, $t = -0.33$, $P = 0.75$. There was also no correlation between MR and age ($r = -0.038$, $P > 0.5$). No side effects or any adverse drug reactions were observed.

Discussion

It is well established that there are differences between Caucasians and Asians in respect to drug responses. These include the different responsiveness to ethanol involving differences in both alcohol and aldehyde dehydrogenases, and also the different distribution of slow and fast acetylators (Kalow, 1982). Genetic variation in hepatic drug oxidation is an increasingly recognised source of interindividual differences in drug response (Eichelbaum, 1982). Debrisoquine and sparteine are the most commonly used marker drugs for the study of oxidation polymorphism. Previous studies have indicated some ethnic variation in the percentage of poor metabolisers (PM). An early study (Kalow *et al.*, 1980) reported that the frequency of debrisoquine PM was 31% in an Oriental group ($n = 13$) who were mostly first or second generation immigrants from Hong Kong. In contrast, Nakamura *et al.* (1985) found no PM in 100 Japanese subjects.

Two PM of debrisoquine were found among our 173 Thai subjects. This represented a frequency of PM in this population of 1.2%. The incidence of PM phenotype of debrisoquine oxidation in the Thai population is, therefore, lower than that observed in Caucasian populations. The low incidence of PM in the Thai population is in agreement with recent studies in Japanese (Nakamura *et al.*, 1985), Chinese (Lee *et al.*, 1988; Lou *et al.*, 1987) and Malay populations (Lee *et al.*, 1988). However, the identification of the PM in these non-Caucasian

studies and also in the present study is based on the criteria of the MR derived from Caucasian populations (MR > 12.6). Whether extrapolation of the antimode from one population to another is valid remains uncertain. The metabolic ratio is a function of factors such as renal drug clearance as well as enzyme activity. Environmental factors may modify these variables, which may give rise to differences in the antimode of the MR between ethnic groups. A sample size of several hundred would be required to demonstrate unequivocally a true bimodality in the MR for the Thai population. The possibility that the two PM found in this study could conceivably represent the tail of a skewed but unimodal distribution, cannot be discounted.

It should be noted that our study population was relatively heterogenous. This is because of the difficulty in discerning accurately the ethnic origin of Thai nationals. By direct questioning, 47 (27%) of the 173 subjects studied indicated that both parents were Chinese. None of this sub-population was identified as a debrisoquine PM. Eight hundred years ago, Thai people were known to have immigrated from the Yunnan province in the southern part of China. The ethnic origin of Thai people is, therefore, relatively close to the Chinese.

No PM of debrisoquine could be identified in 100 Japanese subjects and 97 Chinese Singaporeans (Nakamura *et al.*, 1985; Lee *et al.*, 1988). Lou *et al.* (1987) reported a frequency of the PM phenotype of 0.7% in a mainland Chinese population. The frequency of PM of debrisoquine in the Malay population was 2.1% (Lee *et al.*, 1988). Evidence of a very low incidence of defective debrisoquine oxidation among the Asian populations is also supported by recent studies in Amerindians (Arias *et al.*, 1988) and Greenlanders (Brøsen, 1986). The latter two ethnic groups are generally considered to be of Mongoloid origin and are genetically similar to many Asiatic races. Only 3.2% of the Greenlanders were phenotyped as PM. There was no evidence for the presence of PM of sparteine in the Amerindian group.

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