S-mephenytoin, sparteine and debrisoquine oxidation: genetic polymorphisms in a Turkish population

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A mephenytoin test was carried out in 106 unrelated healthy Turkish volunteers. Racemic mephenytoin was coadministered with either debrisoquine or sparteine. The S/R mephenytoin ratio ranged from < 0.1 to 0.73 in 105 subjects, accordingly phenotyped as extensive metabolisers. One subject had an S/R mephenytoin ratio of 1.02, showing that he was a poor metaboliser of mephenytoin (0.94%, confidence interval 0.25% and 13.65%). In 48 subjects, the metabolic ratios of debrisoquine and sparteine were correlated significantly ($r_s = 0.61, P < 0.001$).

Keywords  mephenytoin debrisoquine sparteine genetic polymorphism Turkish population

Introduction

A previous study of polymorphic debrisoquine oxidation in 326 Turkish Caucasians [1] showed a PM frequency of 3.4%, and this was not statistically significantly different from the frequency among Europeans [2]. The present study was undertaken in order to ascertain the frequency of PMs of mephenytoin among Turkish subjects and to assess debrisoquine/sparteine co-segregation as indices of CYP2D6.

Methods

One hundred and nine unrelated healthy volunteers, one female and 108 males with an age range from 17 to 47 years (mean ± s.d. 25.9 ± 8.2), were studied. All were students or staff members in the Medical Faculty, born in Turkey with Turkish parents. None of the subjects were regular alcohol users. Routine biochemical and haematological tests were normal and subjects had no liver or kidney diseases. Informed and written consent was obtained from each subject and the study was approved by the Hacettepe University Medical Center Ethics Committee.

It has previously been shown that coadministration of debrisoquine and mephenytoin [3] or sparteine and mephenytoin does not interfere with the phenotyping test results [4]. Each subject took a 10 mg tablet of debrisoquine hemisulphate (Declinax, Hoffman-LaRoche; 63 subjects) or a 100 mg tablet of sparteine (Depasan, Giuliani; 46 subjects) together with a 100 mg tablet of racemic mephenytoin (Mesantoin, Sandoz; all subjects). At least 1 month later, 24 subjects who were given mephenytoin plus debrisoquine took sparteine alone and 24 subjects who were given mephenytoin plus sparteine took debrisoquine alone. No other drug was allowed for at least 1 week before and during the test. Drugs were given after emptying the bladder and an 8 h urine sample was collected. A 10 ml aliquot was stored at −25°C until analysis. Assays of S- and R-mephenytoin and sparteine and its metabolites were performed at the Department of Clinical Pharmacology, Institute of Medical Biology, Odense University, Denmark. Samples from Turkey were transferred over dry ice and were still frozen on receipt in Odense.

Debrisoquine and its 4-hydroxymetabolite were assayed by h.p.l.c. with fluorescence detection [5], sparteine, 2,3-dehydrosparteine and 5,6-dehydrosparteine were assayed by gas chromatography [6] and the metabolic ratios for debrisoquine and sparteine were calculated. The peak areas of S- and R-mephenytoin, measured by gas chromatography [3], were used to calculate the S/R ratios.

At low concentrations of S-mephenytoin, the assay reproducibility was poor. Therefore, all subjects having an S/R ratio of less than 0.1 were grouped as ≤ 0.1 on the histogram. In urine samples in which R-mephenytoin but not S-mephenytoin could be detected, the S/R ratio was defined as the lower level of detection (0.1). It was decided a priori that subjects with an S/R ratio above 0.8 would be phenotyped as PM [3, 4].

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Results

S- and R-mephenytoin and sparteine and dehydrosparteines were not detected in the urine from one subject who was given mephenytoin together with sparteine, and total urinary recovery of sparteine (sparteine plus de-hydrosparteines) of one subject was less than 10%. In addition, S- and R-mephenytoin could not be detected in the urine sample of one subject who was given both mephenytoin and debrisoquine. These three subjects were excluded from the data analysis. In all other subjects, total urinary recoveries of debrisoquine (debrisoquine plus 4-hydroxydebrisoquine) and sparteine (sparteine plus dehydrosparteines) were greater than 10%.

The frequency distribution histograms of S/R ratios of 106 subjects are shown in Figure 1. The S/R ratios of subjects ranged from < 0.1 to 0.73 in 105 subjects and was 1.02 in one male subject accordingly phenotyped as PM (PM frequency: 0.94%, 95% confidence interval 0.25% and 13.65%).

Using the antimode for the metabolic ratio of 12.6 for debrisoquine [7] and 20 for sparteine [8], 4 of 106 subjects were PMs for debrisoquine/sparteine (3.77%, 95% confidence interval 1.03% and 9.65%). The PM of sparteine had no detectable levels of dehydrosparteines in his 8 h urine sample. Three PMs were phenotyped with debrisoquine and one with sparteine. In 48 subjects who received both debrisoquine and sparteine, the metabolic ratios of debrisoquine and sparteine were correlated significantly ($r_s = 0.61, P < 0.001$, Figure 2).

Discussion

We only found one subject with an S/R ratio for mephenytoin above 0.8 and he was phenotyped as PM (Figure 1). The frequency of PM of mephenytoin was 0.94% (95% confidence interval 0.25% and 13.64%) and this is not statistically significantly lower than the frequency of 3.26% in 1136 Europeans [2] ($P = 0.24$, Fisher’s test).

Previous studies demonstrated that the 4-hydroxylation of debrisoquine and the N-oxidation of sparteine were both mediated by CYP2D6 [8, 9]. However, concordance between debrisoquine and sparteine oxidation phenotypes is not necessarily complete even in whites [10]. The incidence of debrisoquine PM in Ghanaians was reported as 7.1%, but no PM of sparteine were identified [11]. The results of the present study indicate that the oxidative metabolism of debrisoquine and sparteine in Turkish subjects is catalyzed by the same P450. This is in agreement with the results of a recent study, in which we showed that the oxidative metabolism of metoprolol and debrisoquine appears to be under the control of the same P450 in Turkish subjects [12], as also shown for a Japanese population [13].

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References


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