Metabolic ratios of four probes of CYP2D6 in Turkish subjects: a cross-over study

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SUMMARY

The relationships among the metabolic ratios for the standard probe drugs of CYP2D6 activity, such as debrisoquine, sparteine, metoprolol and dextromethorphan, were studied in 32 Turkish subjects. All subjects were randomly selected according to their phenotypes from a group of 111 Turkish subjects whose oxidation status had been tested for debrisoquine previously. All subjects were given a 10 mg debrisoquine tablet, a 100 mg sparteine tablet, a 100 mg metoprolol tablet and a 20 mg dextromethorphan capsule orally with a wash-out period of at least 1 week between each probe administration. Metabolic ratios were calculated as percentage of dose excreted as parent drug/percentage of dose excreted as its hydroxymetabolite of parent drug in 0–8 h urine. Three poor metabolisers (PM) of debrisoquine were identified. They were also PMs of the other test probes and no misclassification by the 4 phenotyping methods was observed. All six correlations among the metabolic ratios of the 4 probe drugs assessed by Spearman’s rank test were highly significant ($P < 0.001$). The present findings indicate that the oxidative metabolism of debrisoquine, sparteine, metoprolol and dextromethorphan is catalysed by the same cytochrome P450 in the Turkish subjects.

INTRODUCTION

Debrisoquine/sparteine oxidation polymorphism has been extensively studied in various populations. The incidence of a defective liver debrisoquine 4-hydroxylase (CYP2D6) is about 3–10% in North American and European populations (1), whereas it is 0.3% in a Japanese population (2). Recently, the frequency of poor metabolizer (PM) of debrisoquine was found to be 3.4% in a Turkish population (3). However, no PMs have been found in certain populations (1). All of these studies are based on the measurement of the metabolic capacity of CYP2D6 using standard probe drugs such as debrisoquine, sparteine, metoprolol and dextromethorphan. Caucasian populations show complete concordance in their ability to metabolize these probe drugs (1). For example, PMs of debrisoquine are also PMs of both sparteine (4) and metoprolol (5). Recently, we showed close correlations between debrisoquine and metoprolol (6) and between debrisoquine and sparteine (7) in Turkish subjects. However, conflicting results are obtained in the other ethnic groups. For example, PMs of debrisoquine or phenformin are not PMs of sparteine in a Ghanaian population (8).
Fig. 1: Relationships among the urinary log metabolic ratios of the four probe drugs (MRdeb = metabolic ratio of debrisoquine/4-hydroxydebrisoquine, MRspa = metabolic ratio of sparteine/dehydrosparteine, MRmet = metabolic ratio of metoprolol/β-hydroxymetoprolol, MRdmo = metabolic ratio of dextromethorphan/dextrorphan) in 32 Turkish subjects who were given 10 mg debrisoquine hemisulfate, 100 mg sparteine sulfate, 100 mg metoprolol hemitartrate and 20 mg dextromethorphan hydrobromide at least 1 week apart. Spearman's rank correlation coefficients (rs) were calculated using data from all subjects: (A) debrisoquine and sparteine, (B) debrisoquine and metoprolol, (C) debrisoquine and dextromethorphan, (D) sparteine and metoprolol, (E) sparteine and dextromethorphan, (F) metoprolol and dextromethorphan.