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Stereoselective metabolism of metoprolol in Caucasians and Nigerians – relationship to debrisoquine oxidation phenotype

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The relationship between debrisoquine oxidation phenotype and the stereoselective metabolism of metoprolol was investigated in populations of British Caucasians (n = 139) and Nigerian subjects (n = 117). The 0–8 h urinary S/R-metoprolol (S/R–M) ratio was related to the ability to metabolise metoprolol and debrisoquine in both ethnic groups. The median S/R–M ratio was significantly higher in Caucasians (1.27) than in Nigerians (1.10). In the Caucasian population poor metabolisers of debrisoquine had significantly lower S/R–M ratios (median = 0.84) than extensive metabolisers (median = 1.28). Bimodality in the frequency distribution of the S/R–M ratio was not apparent in either ethnic group.

Keywords stereoselective metabolism metoprolol debrisoquine ethnic differences

Introduction

The metabolism of the β-adrenoceptor antagonist metoprolol displays genetic polymorphism of the debrisoquine-type in Caucasians (McGourty *et al.*, 1985). Furthermore, this is associated with differences in the pharmacokinetics of the enantiomers of metoprolol between extensive (EMs) and poor metabolisers (PMs) of debrisoquine (Lennard *et al.*, 1983). In contrast, we found no evidence for polymorphic control of the metabolism of metoprolol or debrisoquine in a Nigerian population (Iyun *et al.*, 1986).

As an extension to those studies, the relationships between metoprolol and debrisoquine oxidation and the stereoselective disposition of metoprolol were investigated in populations of British Caucasians and black Nigerians.

Methods

One hundred and thirty-nine Caucasians resident in the U.K. and 117 Nigerians resident in Ibadan took part in the study. One of the Nigerians had Asian Indian parents; the remainder were black Africans. After emptying the bladder each subject was given single oral doses of 100 mg metoprolol tartrate and 10 mg debrisoquine sulphate on separate occasions at least 1 week apart. In both treatment phases all urine was collected for the next 8 h and a 20 ml aliquot was stored at −20°C until assayed.

Urinary metoprolol / α - hydroxymetoprolol (M/HM) (Lennard, 1985) and debrisoquine/4-hydroxydebrisoquine (D/HD) ratios (Lennard *et al.*, 1977) were measured as described previously. The analysis of metoprolol enantiomers was based on the h.p.l.c. method of Sedman & Gal (1983), which involves derivatisation with 2, 3, 4, 6,-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (TAGIT) to form dia stereoisomeric thioureas. Urine (1.0 ml) and sodium carbonate (1.0 ml, 0.5M) were shaken gently with dichloromethane (5 ml) for 10 min. After centrifugation (900*g*, 5 min) and removal of the aqueous layer, the organic layer was evaporated to dryness at

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30°C. The residue was dissolved in acetonitrile (0.2 ml) containing TAGIT (40 μg) and allowed to stand at room temperature (20°C) for 30 min. After addition of water (0.2 ml), an aliquot (20 μl) of the solution was injected into the chromatograph. Analysis was performed using a Waters Z-Module column system containing a Nova-Pak C_{18} cartridge. The mobile phase was acetonitrile:water (60:40) (flow rate 2 ml min^{-1}) and u.v. detection was at 222 nm. Under these conditions a baseline separation of the thiourea diastereoisomers of R- and S-metoprolol was obtained in 6 min.

The statistical methods used were the Mann-Whitney U test and Spearman's rank correlation (r_s).

Results

The S/R-metoprolol (S/R–M) ratio correlated significantly with the D/HD and M/HM ratios in Caucasians (D/HD $r_s = -0.75$, $P < 0.001$; M/HM $r_s = -0.70$, $P < 0.001$) and in Nigerians (D/HD $r_s = -0.62$, $P < 0.001$; M/HM $r_s = -0.50$, $P < 0.001$) (Figure 1). The S/R–M ratio was significantly higher in Caucasians (median = 1.27; range 0.42 to 2.01) than in Nigerians (median = 1.10; range 0.73 to 1.85) ($P < 0.001$). The Asian Indian subject, whose M/HM and D/HD ratios were within the range established for Caucasian PMs (Iyun *et al.*, 1986), had the second lowest enantiomer ratio (0.76) of the Nigerian population. In the Caucasian population PMs had

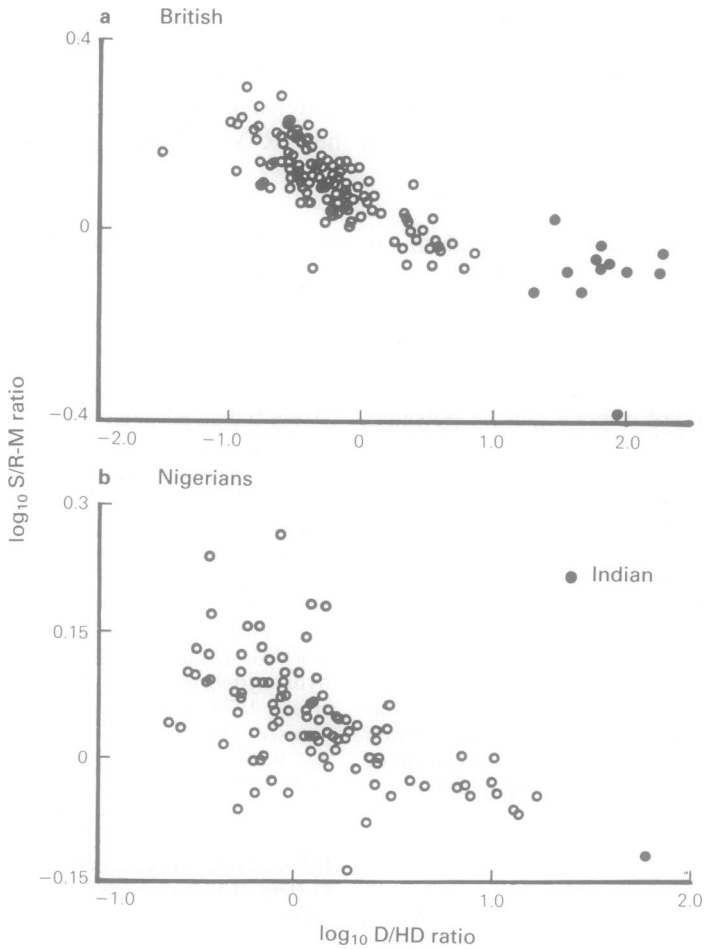

Figure 1 Relationship between the D/HD and the S/R-metoprolol (S/R–M) 0–8 h urinary ratios in a) 139 British Caucasians and b) 117 Nigerians, who were given 100 mg metoprolol tartrate and 10 mg debrisoquine sulphate p.o. at least 1 week apart. ○ EM, ● PM.

significantly lower S/R–M ratios (median = 0.84; range 0.42 to 1.07, $n = 12$) than did EMs (median = 1.28; range 0.84 to 2.01, n = 127) ($P < 0.001$). Bimodality in the frequency distribution of the $\log_{10}$ S/R–M ratio was not apparent in either ethnic group (Figure 2).

Discussion

This study has shown that the urinary R/S-metoprolol ratio is related to the ability of an individual to metabolise metoprolol and debrisoquine. In the British Caucasian population

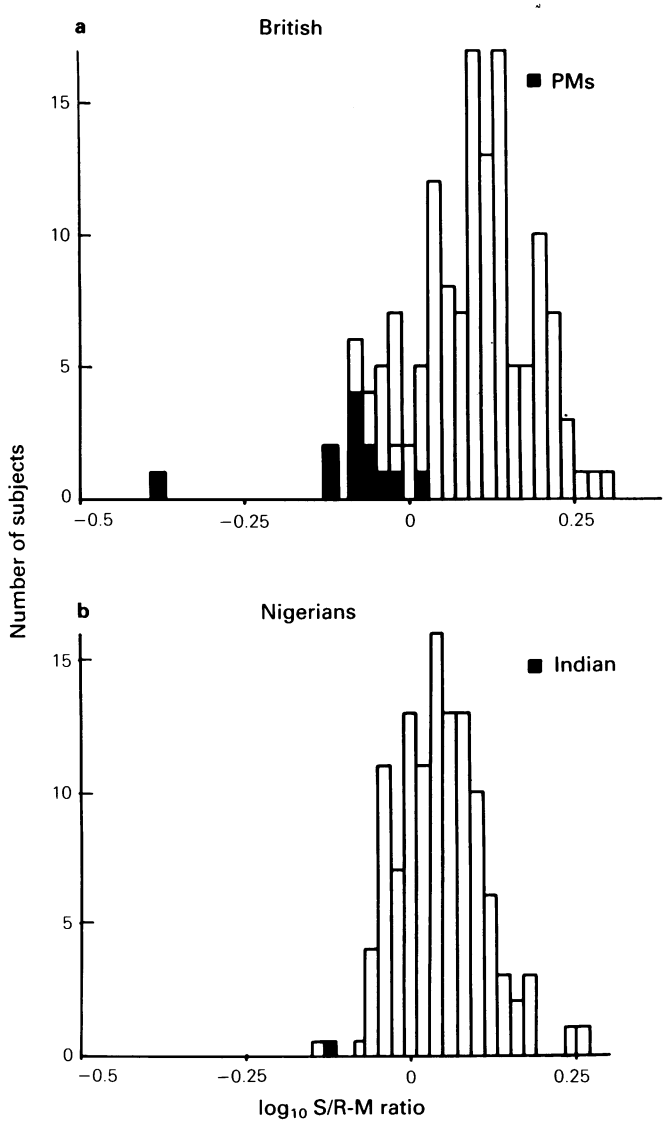

Figure 2 Frequency distributions of the $\log_{10}$ S/R-metoprolol (S/R–M) 0–8 h urinary ratio in a) 139 British Caucasians and b) 117 Nigerians, who were given 100 mg metoprolol tartrate and 10 mg debrisoquine sulphate p.o. at least 1 week apart.

EMs had a mean ratio of greater than one whereas that for PMs was less than one. This is compatible with known phenotypic differences in the plasma pharmacokinetics of the enantiomers of metoprolol. Thus, it reflects the more rapid clearance and lower urinary excretion of R–metoprolol in EMs and the faster elimination of the S–enantiomer in PMs.

Wedlund *et al.* (1984) have shown that the urinary S/R ratio of mephenytoin, the metabolism of which displays genetic polymorphism but unrelated to that of debrisoquine, discriminates between extensive and poor metabolisers of this drug. The latter group are characterised by their inability to 4-hydroxylate S-mephenytoin and they can eliminate the drug only by *N*-demethylation. This results in an absence of stereoselectivity in poor metabolisers. The S/R-mephenytoin ratio shows clear bimodality in Caucasian (Wedlund *et al.*, 1984) and Japanese (Nakamura *et al.*, 1985) populations, and a concordance with the ability to 4-hydroxylate S-mephenytoin. In contrast, we found that the distribution of the urinary S/R-metoprolol ratio, unlike that of the M/HM ratio, was not bimodal. Although a significant difference in the enantiomer ratio was observed between EMs and PMs, its distribution did not separate the phenotypes. Making some assumptions, it can be shown that the urine drug enantiomer ratio is approximately equal to the ratio of the intrinsic metabolic clearances of the enantiomers (Jackson, 1988). For a chiral drug whose metabolism is also polymorphic, elimination via non-polymorphic as well as polymorphic routes will contribute to this enantiomer ratio. Because polymorphic 4-hydroxylation contributes much more than non-polymorphic *N*-demethylation to the clearance of mephenytoin in EMs but not of course in PMs, a clear separation of the population into distinct groups can be achieved using this ratio. With metoprolol, however, the phenotypic difference in the ratio of the intrinsic clearances of the enantiomers (Lennard *et al.*, 1983) is much smaller than that for mephenytoin (Wedlund *et al.*, 1985) and clear discrimination between the phenotypic groups is not observed using the urinary S/R-metoprolol ratio.

Like Caucasian EMs, Nigerians excreted more S- than R-metoprolol in their urine. However, there was a small but statistically significant ethnic difference in the enantiomer ratio indicative of less stereoselectivity in the disposition of metoprolol in Nigerians than in British Caucasians. Differences in the urinary metoprolol/α-hydroxymetoprolol ratio between these two ethnic groups have also been observed (Iyun *et al.*, 1986).

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