Frequency of impaired mephenytoin 4'-hydroxylation in an Indian population

An increasing number of studies demonstrate that the frequency of the genetically determined poor metabolizer (PM) phenotype for the debrisoquine/sparteine-type of polymorphic drug oxidation differs according to the population being studied. A major factor for such variability appears to be differences in allelic frequency that have a racial basis. For example, the incidence in Caucasians of different ethnic backgrounds is between 3 and 10% (Eichelbaum & Gross, 1990) whereas the trait is essentially absent in Oriental populations such as Japanese (Horai *et al.*, 1989; Nakamura *et al.*, 1985) and Chinese (Horai *et al.*, 1989; Lou *et al.*, 1987). Intermediate frequencies are present in populations studied in Africa and the sub-continent of India (Eichelbaum & Gross, 1990; Idle & Smith, 1984). More limited information is available concerning the other substantiated polymorphism of carbon oxidation, namely, that characterized by the 4'-hydroxylation of S-mephenytoin (Wilkinson *et al.*, 1989). Nevertheless, it appears that Caucasians and Orientals again differ in the frequency of the PM phenotype, although in the opposite geocentric longitudinal direction to that seen with the debrisoquine/sparteine polymorphism. That is, the incidence of the PM is higher (17.4 to 22.5%) in Japanese (Horai *et al.*, 1989; Nakamura *et al.*, 1985) and Chinese (Horai *et al.*, 1989) than that observed (2.7 to 6.1%) in Caucasians (Wilkinson *et al.*, 1989). The PM trait is apparently absent in Cuna Amerindians (Inaba *et al.*, 1988) but its frequency in populations of other racial origins has not been investigated. We now report that the PM phenotype for the mephenytoin polymorphism in an Indian population residing in Bombay has a similar frequency to that in Orientals.

The study group consisted of 48 male volunteers, aged 19 to 34 years, who had not received any drugs for 2 weeks prior to the study and were in good health by history, physical examination and biochemical measurements of renal and hepatic function. The study was approved by the local institutional review board and written consent was provided by each subject. Phenotyping was performed by administering an oral dose (100 mg, 460 μ mol) of racemic mephenytoin

Figure 1 Frequency distribution of 0-8 h urinary S/R ratio of mephenytoin in 48 Indian subjects.

(Mesantoin®, Sandoz Ltd) about 2-3 h after a standard evening meal and subsequently collecting an overnight 0-8 h urine sample. After aliquoting, the urine was stored at -10°C before shipping in a frozen state to Nashville for analysis. The urinary S/R ratio and the hydroxylation index (dose of S-mephenytoin/amount of 4'-hydroxymephenytoin excreted in the 0-8 h urine) were determined as previously described (Wedlund *et al.*, 1984).

Both phenotypic trait measurements indicated bimodal distributions that were in concordance with each other and the frequency of distribution of the S/R urinary ratio is shown in Figure 1. Ten of the subjects (20.8%; 95% confidence interval, 10.8-33.0%) had urinary S/R ratios close to unity (0.91 to 1.16) and, with one exception, excreted less than 20 μ mol of 4'-hydroxymephenytoin in 0-8 h. In the remaining 38 individuals the urine S/R ratio ranged from 0.07 to 0.57 and over 10% of the S-mephenytoin dose was recovered as the hydroxylated metabolite in the urine.

Intersubject variability in drug metabolizing ability is generally ascribed to genetic, environmental or disease-state factors, but it is often difficult to assess precisely the relative contributions of these. All of the subjects were in good health. Moreover, there was no history over the previous 2 years of infectious hepatitis or other major diseases likely to affect drug metabolism.

Thus, the observed bimodal distribution probably does not have a pathophysiological explanation. No attempt was made to control the subjects' diet or other aspects of their environmental milieu. Since the 4'-hydroxylation of mephenytoin may be modulated by enzyme inducers and inhibitors (Atiba *et al.*, 1989; Zhou *et al.*, 1990) it is possible that some of the variability in metabolism can be accounted for by such factors. However, it should be noted that under experimental conditions studied neither of these types of interaction was capable of changing an individual's oxidative phenotype nor were the subjects receiving any drugs at the time of this study. Accordingly, it is likely that the differences in 4'-hydroxylating ability reflect a genetic polymorphism similar to that previously reported in Caucasians, Chinese and Japanese populations (Horai *et al.*, 1989; Nakamura *et al.*, 1985; Wedlund *et al.*, 1984). In this regard, it is interesting that despite the group being relatively small the range of phenotypic trait values of the EM and PM phenotypes in Indians were the same as those found in the other racial groups. Finally, it should be noted that an earlier study in a similar group of subjects in the same locale showed a 1–3% frequency of the PM phenotype for the debrisoquine/sparteine type of genetic polymorphism (Idle & Smith, 1984). It is considered

that Indian and European Caucasians have evolved from a common Caucasoid descendant genetically distinct from the progenitor(s) of Oriental populations (Cavalli-Sforza *et al.*, 1988). It is of interest, therefore, that the frequency of the PM phenotype of the mephenytoin polymorphism in an Indian population is closer to that in Oriental than Caucasian populations, and the reverse occurs with the debrisoquine/sparteine polymorphism. The responsible selective pressure(s) accounting for such racial divergence is unknown, but further studies in other racial and possibly ethnic groups might provide useful insights in this area.

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