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DEFECTIVE METABOLISM OF METOPROLOL IN POOR HYDROXYLATORS OF DEBRISOQUINE

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Eight healthy volunteers received oral metoprolol 200 mg once daily for a week. The AUC, half-life and duration of β-adrenoceptor blockade on day 7 was much greater in two subjects than in the remaining six. This suggested that the metabolism of metoprolol was impaired in two and the effect was therefore prolonged. Subsequent testing of oxidation phenotype with oral debrisoquine showed that the subjects with high metoprolol availability were also poor hydroxylators of debrisoquine. The urinary debrisoquine/4-hydroxydebrisoquine ratio was highly correlated with metoprolol AUC, half-life and β-adrenoceptor blockade at 24 h. Thus patients with a genetic defect in drug oxidation, when treated with metoprolol, are likely to have high plasma concentrations and a prolonged effect.

Introduction

The metabolism of some drugs is mainly under genetic control. For example, acetylation of isoniazid and hydralazine exhibits polymorphism (Evans & White, 1964) and this information may be used to determine optimal dosage and the likelihood of toxicity (T.B. Chemotherapy Centre, Madras, 1970; Perry, 1973). More recently, oxidative metabolism of the antihypertensive agent debrisoquine (D) was shown to be controlled by two alleles at a single gene locus (Mahgoub *et al.*, 1977). Over 90% of the white British population are extensive metabolisers (EM) transforming debrisoquine to 4-hydroxydebrisoquine (HD) (Evans *et al.*, 1980; Tucker *et al.*, 1977). In approximately 9% of subjects, however, negligible quantities of this metabolite are formed and these poor metabolisers (PM) have an increased hypotensive response to the drug (Silas *et al.*, 1977). Subsequently it was shown that defective drug oxidation was not confined to debrisoquine but occurred with guanoxan, phenacetin (Sloan *et al.*, 1978) and phenformin (Shah *et al.*, 1980). Furthermore, poor metabolisers of debrisoquine may be more likely to develop plasma concentration related toxicity from impaired metabolism of phenytoin (Idle *et al.*, 1980), nortriptyline (Bertilsson *et al.*, 1980) and perhexiline (Shah *et al.*, 1982).

Our data suggest that the disposition of metoprolol may exhibit polymorphism and believe that oxidation of metoprolol and debrisoquine may be determined at the same gene locus. Since completing this work it has been suggested that a similar defect may also involve the metabolism of alprenolol and timolol (Alvan *et al.*, 1982).

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Methods

Eight healthy volunteers received a 200 mg daily dose of metoprolol (Geigy) for 7 days. On day 7 the tablets were taken at least 1.5 h after a light breakfast and blood was taken at 0, 1, 2, 4, 6, 8, 12 and 24 h. Metoprolol was measured by the h.p.l.c. method of Lefebre *et al.* (1981). The intra-assay coefficient of variation was 4.7% at 100 ng/ml. The area under the plasma concentration-time curve between 0–24 h (AUC) was calculated using the trapezoidal rule.

Prior to metoprolol dosing subjects were exercised on a bicycle ergometer for 4 min in order to determine the work load required to achieve a heart rate above 140 beats/min. The post-exercise heart rate was calculated from the mean of the first four beats on an ECG recording after stopping exercise. On the day of blood sampling β-adrenoceptor blockade (% reduction in exercise tachycardia) was assessed at 0, 2, 12 and 24 h by comparing post-exercise heart rates on metoprolol with those achieved on an identical protocol but before drug dosing using the same predetermined work load.

Oxidation phenotype was determined at least 1 week later by measuring debrisoquine (D) and 4-

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hydroxydebrisoquine (HD) (Lennard *et al.*, 1977) in an 8 h urine collected following a 10 mg single dose of debrisoquine. The D/HD ratio in extensive metabolisers is <12 (mode <1) and >20 in poor metabolisers (Evans *et al.*, 1980). Statistical difference between the phenotypes was determined using the Mann-Whitney test.

Results

There were two poor metabolisers and six extensive metabolisers of debrisoquine (D/HD ratio; PM: 40,41; EM: 1.23, 0.84, 0.57, 0.41, 0.66, 0.19). At a given time plasma metoprolol concentrations were higher in the two poor metabolisers than in any of the extensive metabolisers ($P = 0.036$); mean values (± s.d.) were 2 h: PM, 931 ± 59 ng/ml; EM, 408 ± 200 ng/ml; 12 h: PM, 267 ± 30 ng/ml: EM, 49 ± 42 ng/ml; 24 h: PM, 82 ± 8 ng/ml; EM, 5 ± 8 ng/ml. The AUC and half-life of metoprolol were greater in poor metabolisers ($P = 0.036$) and correlated with $\log_{10}$ D/HD in the group as a whole (Figure 1) and within the group of 6 extensive metabolisers (AUC: $r = 0.80$, $P > 0.05$; half-life: $r = 0.88$, $P < 0.025$).

β-adrenoceptor blockade at 24 h was negligible in most extensive metabolisers but was retained in poor metabolisers (Figure 1). These differences were apparent at 12 h (PM: 25.5 ± 0.7%, EM: 16.0 ± 6.3%, $P = 0.036$) but not at 2 h (PM: 32.2 ± 0.8% EM: 29.2 ± 2.6%). D/HD ratio correlated with % blockade at 24 h in the group as a whole (Figure 1) and within the group of extensive metabolisers ($r = 0.90$, $P < 0.02$).

Discussion

Following oral dosing, metoprolol is completely absorbed and only 10% is excreted unchanged in the urine (Regardh & Johnsson, 1980). Hence differences in AUC will reflect variation in metabolic clearance of the drug. Our data, therefore, indicate impaired metoprolol metabolism in the two poor metabolisers of debrisoquine. Three relatively inactive metabolites of metoprolol are produced by oxidative pathways (Borg *et al.*, 1975). A defect in one of these pathways has been described in a subject in whom bioavailability and half-life were greatly increased (Jordo *et al.*, 1980). This subject has since been shown to be a poor hydroxylator of debrisoquine (Alvan *et al.*, 1982). Interestingly, α-hydroxylation of metoprolol bears a close resemblence to the 4-hydroxylation of debrisoquine in that both routes involve oxidation of an aliphatic carbon atom adjacent to an aromatic ring. Since it only represents about 10% of an oral dose, a deficiency in α-hydroxy-metoprolol production alone cannot explain the observed difference

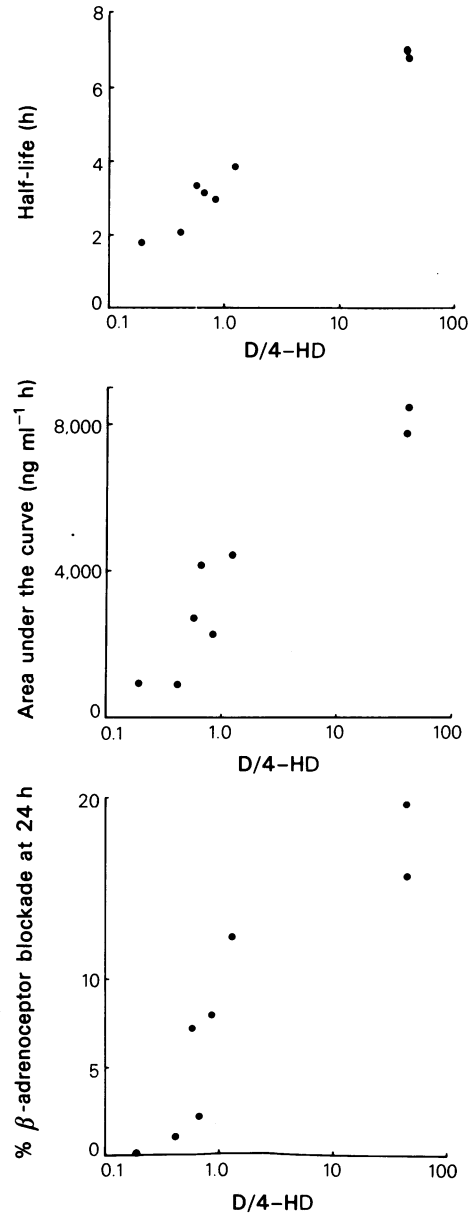

Figure 1 Relationship between D/HD ratio and AUC, half-life of metoprolol and β-adrenoceptor blockade at 24 h; r_s values: AUC = 0.90; half-life = 0.88; β-adrenoceptor blockade = 0.95 ($P < 0.01$).

in AUC between extensive metabolisers and poor metabolisers. A similar discrepancy in the relationship between debrisoquine 4-hydroxylation and bioavailability of the drug was only partially accounted for by impaired transformation via aromatic hydroxy-

lation (Mbanefo *et al.*, 1980) suggesting that the formation of ring-opened carboxylic acids is deficient (Tucker *et al.*, 1977). At least one of the other two pathways of metoprolol metabolism (oxidative deamination and *o*-dealkylation with subsequent rapid oxidation) may, therefore, be impaired. As it normally accounts for 65% of the dose, *o*-dealkylation seems most likely to be defective, a view supported by the fact that the *o*-dealkylation of phenacetin and 4-hydroxylation of debrisoquine are correlated (Sloan *et al.*, 1978).

Metoprolol half-life is said to be 2–4 h (Regardh & Johnsson, 1980). Our data suggest that it may be much greater in some healthy subjects and this may explain the 17-fold variation in plasma concentrations in patients receiving the same dose (von Bahr *et al.*, 1976). The clinical implications are that poor metabolisers need only once daily dosing for the control of angina but that smaller doses may be required to avoid a relative loss of cardioselectivity and side-effects associated with high plasma concentrations (Formgren, 1976). Further studies are in progress in order to define the metabolic defect.

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