The oral clearance and β -adrenoceptor antagonist activity of propranolol after single dose are not related to debrisoquine oxidation phenotype

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Introduction

Using debrisoquine as a model substrate for investigating polymorphic drug oxidation, we have demonstrated a large genetic influence on the metabolism and β -adrenoceptor antagonist activity of metoprolol (Lennard *et al.*, 1982). Anecdotal evidence has suggested that the metabolism of a number of other β -adrenoceptor antagonists, which are extensively metabolised by oxidative routes, may also be under this type of genetic control (Alvan *et al.*, 1982; Shah *et al.*, 1982). In the present study the relationship between debrisoquine oxidation phenotype and the pharmacokinetics and pharmacodynamics of propranolol were investigated.

Methods

Eleven healthy males with a broad-ranging ability to 4-hydroxylate debrisoquine (debrisoquine/4-hydroxydebrisoquine (D/HD) metabolic ratio 0.19–208) were studied. The group comprised seven extensive (EM) and four poor (PM) metabolisers of debrisoquine. Each subject was given oral propranolol hydrochloride 80 mg and serial samples of blood were taken up to 24 h after dosing for the h.p.l.c. measurement (Lo *et al.*, 1982) of plasma concentrations of propranolol and 4-hydroxypropranolol (after enzymatic hydrolysis of its conjugate(s)).

β -adrenoceptor blockade was assessed at 2, 12 and 24 h using bicycle ergometry.

Results

Plasma 4-hydroxypropranolol concentrations at 2 h were, on average, five times higher in EM than in PM subjects (EM = 719 ± 313 ng/ml; PM = 152 ± 23 ng/ml, $P < 0.001$). The ratio, 4-hydroxypropranolol AUC/propranolol AUC was inversely correlated with the D/HD ratio ($r_s = -0.93$, $P < 0.001$). Mean plasma propranolol concentrations were almost identical in EM compared with PM subjects (EM < PM, $P > 0.05$) and at 24 h both phenotypes had measurable plasma concentrations of the drug (EM = 2.1 ± 1.4 ng/ml; PM = 2.1 ± 1.9 ng/ml). There was no relationship between AUC for propranolol and D/HD ratio ($r_s = 0.56$, $P > 0.05$). The elimination half-life of propranolol was similar in both phenotypes (EM = 4.0 ± 0.9 h; PM = 4.3 ± 1.2 h, $P > 0.05$). β -adrenoceptor blockade (expressed as the percentage reduction in exercise heart rate) was not related to D/HD ratio at either 2 h ($r_s = 0.06$, $P > 0.05$) or 12 h ($r_s = -0.28$, $P > 0.05$). At 24 h, β -adrenoceptor blockade was less than 10% in all subjects.

Discussion

These results indicate that the 4-hydroxylation of propranolol is impaired in poor metabolisers of debrisoquine. However, in contrast to our findings with metoprolol, debrisoquine oxidation phenotype does not appear to be a major determinant of the pharmacokinetics and pharmacodynamics of propranolol.

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