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INHIBITION OF OXIDATIVE DRUG METABOLISM BY β-ADRENOCEPTOR ANTAGONISTS IS RELATED TO THEIR LIPID SOLUBILITY

Significant correlations between the lipid solubility of β-adrenoceptor antagonists and their pharmacokinetic characteristics have been reported. Relationships have been described between octanol/pH 7.4 buffer partition coefficients of these drugs and the extent of their binding to human plasma protein (Jack, 1981), penetration into human brain tissue (Neil-Dwyer *et al.*, 1981) and rat lung (Street *et al.*, 1978) and extent of metabolism in man (Johnsson & Regardh, 1976; Smith & Tucker, 1981; Woods & Robinson, 1981). Facino & Lanzani (1979) observed a strong correlation between partition coefficients in a series of β-adrenoceptor antagonists and their affinity constants for binding to the rat liver microsomal cytochrome P-450 system. There are also reports that propranolol and metoprolol can inhibit drug metabolism in both animals and man and that the effect of propranolol, the more lipid-soluble agent, is greater than that of metoprolol (Topham, 1970; Greenblatt, Franke & Huffman, 1978; Bax, Crewe & Tucker, 1980; Peet, Middlemass & Yates, 1980; Conrad & Nyman, 1980; Bax, Lennard & Tucker, 1981). We describe here results of preliminary studies relating the lipid-solubility of a series of β-adrenoceptor antagonists to their ability to inhibit the metabolism of lignocaine by rat liver microsomes.

Rat liver microsomes together with co-factors (Mazel, 1971) were incubated at pH 7.4 and 37°C for 7 min after the addition of lignocaine HCl (3.46 μM base) with and without a β-adrenoceptor antagonist (50 μM base). The reaction was terminated by addition of 4M NaOH and the unchanged lignocaine was measured by g.l.c. (Bax, Tucker & Woods, 1980). Microsomal protein was determined by the method of Lowry *et al.* (1951). The microsomes were obtained from male Sprague-Dawley rats (200–250 g, Tucks Ltd). β-adrenoceptor antagonists were gifts from Astra Chemicals Ltd, (alprenolol HCl, metoprolol tartrate); Ciba Labs., (oxprenolol HCl); Duncan Flockhart Ltd, (sotalol HCl); Glaxo Ltd, (labetalol HCl — a combined α- and β-adrenoceptor antagonist); ICI Ltd, (atenolol HCl, propranolol HCl); May & Baker Ltd, (acebutolol HCl); Merck, Sharp & Dohme Ltd, (timolol maleate) and Squibb & Sons Ltd, (nadolol).

The mean ± s.d. control rate of lignocaine metabolism was 2.85 ± 0.44 m μmol mg $^{-1}$ protein 7 min^{-1} (n = 6). Percentage inhibition of the rate of metabolism of lignocaine was calculated for each β-adrenoceptor antagonist and plotted against the logarithm of the octanol/pH 7.4 buffer partition coefficient measured at 37°C (Woods & Robinson, 1981).

A strong linear correlation was observed between inhibition of lignocaine metabolism and log partition coefficient of the β-adrenoceptor antagonists (r^2 = 0.897; $P < 0.0001$; Figure 1).

The metabolism of lignocaine in the rat mainly involves oxidative reactions, namely aromatic hydroxylation and *N*-dealkylation (Keenaghan & Boyes, 1972). Therefore, it might be expected that drugs which are metabolised in similar ways would be more likely to inhibit the metabolism of lignocaine. Thus the results obtained could simply be a reflection of the proportion of each β-adrenoceptor antagonist metabolised by enzymes common to those which transform lignocaine. The metabolism of alprenolol, labetalol, metoprolol, oxprenolol, propranolol and timolol is largely oxidative whereas acebutolol under-

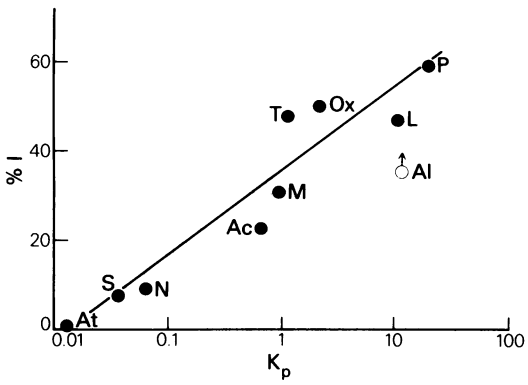

Figure 1 Relationship between percentage inhibition of lignocaine metabolism by rat liver microsomes, (%I) and octanol/pH 7.4 buffer partition coefficient, (Kp), for a series of β-adrenoceptor antagonists. (Initial lignocaine concentration = 3.46 μM; a similar relationship was obtained using 34.6 μM. Each point represents the mean result of four replicate experiments. Key: At = atenolol; S = sotalol; N = nadolol; Ac = acebutolol; M = metoprolol; T = timolol; Ox = oxprenolol; L = labetalol; Al = alprenolol; P = propranolol.)

Note: Owing to interference with the chromatography of lignocaine by alprenolol at low lignocaine concentrations the datum point for alprenolol refers to the result obtained using an initial lignocaine concentration of 34.6 μM. The arrow on this point indicates that greater inhibition of lignocaine metabolism is anticipated at an initial lignocaine concentration of 3.46 μM. The regression line excludes this point.

goes mainly non-oxidative reactions and atenolol, sotalol and nadolol appear to be unmetabolised (Smith & Tucker, 1981). However, lipid-solubility and extent of metabolism are correlated anyway. Moreover, the fact that sotalol and nadolol did inhibit lignocaine to a small extent, despite not being metabolised themselves, suggests that the relationship between inhibition and lipid-solubility is more fundamental than that between inhibition and extent or route of metabolism of the inhibitor. Another issue is whether β-adrenergic receptor antagonists may also inhibit non-oxidative routes of drug metabolism, including phase II conjugative reactions. The only information available on this point is that alprenolol and salicylate do not compete for glucuronide formation (Johnsson & Regardh, 1973).

Further studies are required to establish the mechanism of the inhibition of oxidative drug metabolism produced by β-adrenoceptor antagonists and to determine the values of inhibition constants. Nevertheless, the present findings, together with those cited previously (Topham, 1970; Greenblatt *et al.*, 1978; Bax *et al.*, 1980; Peet *et al.*, 1980); Conrad & Nyman, 1980; Bax *et al.*, 1981), suggest that in view of the widespread clinical use of β-adrenoceptor antagonists a propensity to inhibit the metabolism of other drugs may be an important consideration in predicting response to therapy, particularly when the more lipid-soluble antagonists are prescribed. There may also be implications for the choice of β-adrenoceptor blocker under certain clinical conditions and further studies of the effects of these agents on the metabolism of drugs with low therapeutic indices are indicated.

Reprint requests should be addressed to G.T.T.

CAROLINE S. DEACON, M.S. LENNARD, N.D.S. BAX, H.F. WOODS & G.T. TUCKER

University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF

Received May 8, 1981

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DOES RIFAMPICIN INCREASE SERUM LEVELS OF TESTOSTERONE AND OESTRADIOL BY INDUCING SEX HORMONE BINDING GLOBULIN CAPACITY?

In a recent study we found that a 2 week course of the antibiotic rifampicin in eight male volunteers reduced by 70% serum levels of 25-hydroxyvitamin D (25-OHD), the major circulating metabolite of the vitamin (Brodie *et al.*, 1980). As there was concomitant induction of hepatic monooxygenase activity, as evidenced by significant increases in the hydroxylation of antipyrine and cortisol, it seems possible that induction of vitamin D wastage pathways explained the fall in 25-OHD. As testosterone and oestradiol are also endogenous substrates for the hepatic monooxygenase system (Gustafsson & Ingelman-Sundberg, 1975), we have investigated the possibility that the levels of these hormones are altered by rifampicin treatment, using sera stored from our previous study. As both are bound in plasma to sex hormone binding globulin (SHBG) (Iqbal & Johnson, 1977) the binding capacity of this carrier protein was also measured.

Eight healthy male subjects, aged 29–35 years, took rifampicin 600 mg daily for 2 weeks. Serum samples were obtained at the beginning of the study (week 0), on the day following cessation of rifampicin treatment (week +2) and 2 weeks after the last rifampicin dose (week +4). All blood samples were centrifuged immediately and the sera stored at −20°C until analysis. Serum testosterone and oestradiol were measured by radioimmunoassay (Kjeld, Puah & Joplin, 1976) and SHBG binding capacity by affinity chromatography (Iqbal & Johnson, 1977). All samples were run in a single assay. Statistical analysis was by Student's *t*-test for paired values. The results are shown in Table 1. All subjects showed a rise in serum testosterone after 2 weeks treatment with

Table 1 Effect of treatment with rifampicin on serum testosterone, oestradiol and sex hormone binding globulin (SHBG) levels in eight male subjects (mean ± s.d.). Rifampicin was taken from week 0 to +2.

Assay	*Normal range in males*	*Week 0*	*Week +2*	*Week +4*
Testosterone (nmol l^{-1})	10–28	24.5 ± 5.7	35.9*** ± 7.4	27.8 ± 6.8
Oestradiol (pmol l^{-1})	<150	128 ± 9	127 ± 5	268** ± 140
SHBG (nmol DHT bound l^{-1})	20–40	27.5 ± 4.5	40.5** ± 6.1	32.6* ± 4.1

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$
DHT = 5α-dihydroxytestosterone