Comparison of β -adrenoceptor antagonists as modulators of drug metabolism: effect of lipophilicity on microsomal phase I and II reactions

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The effect of β -adrenoceptor antagonists with varying lipophilicity on microsomal phase I and II reactions was investigated using rat hepatic microsomes. The degree of inhibition of ethoxyresorufin deethylase paralleled octanol/water partition coefficients: propranolol > alprenolol > timolol > metoprolol > atenolol. Propranolol (highly lipophilic) and atenolol (hydrophilic) also had widely different effects on 7-ethoxycoumarin deethylase inhibition and on disopyramide *N*-dealkylation. However the inhibition of harmol conjugation was not related in the same way to octanol/water partition coefficient as was the phase I reactions.

Keywords atenolol ethoxyresorufin deethylation microsomes propranolol

Introduction

Lipophilic β -adrenoceptor antagonists may interfere with the metabolism of other drugs, thereby complicating their therapeutic use. Atenolol is the least lipophilic of the β -adrenoceptor antagonists, requiring minimal hepatic metabolism and being eliminated almost entirely unchanged in the urine (Cruickshank, 1980). Such a drug might have advantage over the lipophilic β -adrenoceptor antagonists, particularly if drug metabolism is impaired by hepatic disease. *In vitro* techniques were used to compare the effect of a number of β -adrenoceptor antagonists, including atenolol and propranolol, upon microsomal phase I and II reactions.

Methods

Utilising hepatic microsomes from untreated rats, the ethoxyresorufin deethylation and harmol glucuronidation were measured by standard methods (Prough *et al.*, 1978; Ullrich & Weber, 1972) to determine the effect of alprenolol, atenolol, metoprolol, propranolol

and timolol on microsomal phase I and II reactions. The effects on 7-ethoxycoumarin and disopyramide dealkylation activity of the most and the least lipid soluble β -adrenoceptor antagonists, propranolol and atenolol, respectively, were also determined.

Results

The rank order of potency of the β -adrenoceptor antagonists in inhibiting ethoxyresorufin deethylase paralleled their octanol/water partition coefficients (o/w). Thus, the order of potency was: propranolol (o/w = 13.4) > alprenolol (8.8) > timolol (0.6) > metoprolol (0.4) > atenolol (0.01).

Propranolol was the most potent inhibitor of ethoxyresorufin deethylase and 7-ethoxycoumarin deethylase (Figures 1a and 1b), whereas atenolol had almost no effect on these cytochrome P-450 catalysed reactions.

Inhibition of ethoxycoumarin deethylase by propranolol was non-competitive with a K_i value

Figure 1 (a) The effect of various concentrations of inhibitor (atenolol (▲) or propranolol (●)) on ethoxyresorufin deethylase. (b) The effect of various concentrations of inhibitor (atenolol (▲) or propranolol (●)) on 7-ethoxycoumarin deethylase.

Figure 2 The effect of various concentrations of atenolol (▲) and propranolol (●) on disopyramide mono-*N*-dealkylation.

of 300 μM. The K_i value for atenolol could not be established. These two β -adrenoceptor antagonists also had vastly differing effects on disopyramide *N*-dealkylation (Figure 2).

The inhibition of harmol conjugation was not related in the same way to o/w as the phase I reactions.

Discussion

These data indicate that propranolol has a potential for inhibiting drug metabolism catalysed by cytochrome P-450. This is in agreement with the report that both propranolol and metoprolol inhibit antipyrine clearance in man (Bax *et al.*, 1981; Deacon *et al.*, 1981). Marked inhibition of a dealkylation reaction of drugs such as disopyramide may occur. These findings also suggest that inhibition of microsomal drug metabolism by propranolol may have a greater significance than previously thought. Atenolol seems to be almost completely devoid of any effect on the liver microsomal metabolism. This marked contrast between a highly lipid soluble and a non-lipophilic β -adrenoceptor antagonist may be clinically significant.

References

- Bax, N. D. S., Lennard, M. S. & Tucker, G. T. (1981). Inhibition of antipyrine metabolism by beta-adrenoceptor antagonists. *Br. J. clin. Pharmacol.*, **12**, 779–784.
- Cruickshank, J. M. (1980). The clinical importance of cardioselectivity and lipophilicity in beta-blockers. *Am. Heart J.*, **100**, 160–178.
- Deacon, C. S., Lennard, M. S., Bax, N. D. S., Woods,

- H. F. & Tucker, G. T. (1981). Inhibition of oxidative drug metabolism by β -adrenoceptor antagonists is related to their lipid solubility. *Br. J. clin. Pharmac.*, **12**, 429–430.
- Prough, R. A., Burke, M. D. & Mayer, R. T. (1978). Direct fluorimetric method for measuring mixed function oxidase activity. *Methods Enzymol.*, **52**, 372–377.
- Ullrich, V. & Weber, P. (1972). The o-dealkylation of 7-ethoxycoumarin by liver microsomes. *Hopps-Seyler's Z. Physiol. Chem.*, **353**, 1171–1177.