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Prediction of metabolic drug interactions involving β-adrenoceptor blocking drugs

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1 There is evidence, from human and animal studies, that drug-metabolising enzymes exist in multiple forms, the individual enzymes having selective, but not specific, substrate requirements. Consequently drug interactions may arise when two drugs bind to the same enzyme. The degree of enzyme inhibition will be partly dependent on the relative affinities of the drugs for the enzyme and on their rates of turnover. The decrease in drug clearance produced by enzyme inhibition is dependent on the fraction of the drug normally metabolised by the inhibited pathway(s).

2 Cimetidine, a P-450 enzyme inhibitor, increases the systemic bioavailability of propranolol and labetalol, which undergo extensive metabolism, but does not affect the clearance of atenolol, which is excreted largely unchanged. In this situation, both the extent and type of biotransformation are important. Thus, cimetidine has no effect on the clearance of penbutolol, even though the drug is eliminated almost entirely by biotransformation. The major metabolite is penbutolol glucuronide, and it has been shown recently that cimetidine does not inhibit glucuronylation.

3 β-adrenoceptor blockers also act as enzyme inhibitors themselves. For example, antipyrine clearance is decreased by propranolol and to a lesser extent by metoprolol, whereas atenolol has no effect. It has been suggested, therefore, that there is a relationship between the lipid-solubility of β-adrenoceptor blockers and their ability to inhibit drug metabolism.

4 The clearance of lipophilic β-adrenoceptor blockers is dependent on hepatic enzyme activity, and is therefore sensitive to enzyme induction. For drugs with high hepatic clearance and subsequent high presystemic elimination, a moderate increase in the extraction ratio will produce a marked decrease in systemic bioavailability. Thus pentobarbitone enzyme induction increased the hepatic extraction of alprenolol by 29% and decreased the AUC by 78%.

5 The impact of changes in the activity of the drug-metabolising enzymes on drug clearance is dependent upon the extent and type of biotransformation(s) that the interacting drugs undergo. A better understanding of such drug interactions will be obtained by measuring metabolite formation rather than clearance of parent drug.

Keywords antipyrine β-adrenoceptor blockers
biotransformation pharmacodynamics pharmacokinetics

Introduction

β-adrenoceptor blocking drugs are often used in combination with other types of drugs, such as diuretics, vasodilators and antiarrhythmics. Therefore the potential for drug interactions involving β-adrenoceptor blockers is common and often clinically important. Drugs which interact may be classified as altering either the pharmacodynamics or the pharmacokinetics (absorption, metabolism, distribution and excretion) of a β-adrenoceptor blocker. By similar mechanisms, β-adrenoceptor blockers themselves may alter the clinical response to other types of drugs. The purpose of this review is to focus on interactions which involve the drug-metabolising enzymes, with particular reference to the extent and type(s) of biotransformation undergone by the interacting β-adrenoceptor blocker.

The drug-metabolising enzymes

The liver is quantitatively the major site of metabolism for most drugs, although other tissues, such as the gut, kidney, lung and nervous tissue, have important roles in the metabolism of certain drugs. The essential action of the drug-metabolising enzymes is to convert lipophilic drugs into water-soluble metabolites which are excreted more easily into either urine or bile. Drug metabolism reactions consist of phase I biotransformations such as oxidation, reduction and hydrolysis, and phase II biotransformations which involve conjugation of the drug or drug metabolite with a small endogenous macromolecule (Williams, 1974).

Quantitatively, the most important enzymes are the hepatic microsomal mixed-function mono-oxygenases, which by inserting oxygen into a molecule are able to catalyse numerous biotransformations including aliphatic hydroxylation, aromatic hydroxylation and *N*-dealkylation. There is increasing evidence that the terminal enzyme, cytochrome P-450, exists in multiple forms and in certain individuals the ability to perform particular oxidative biotransformations is functionally inadequate or absent (Eichelbaum, 1982). Not only do the enzymes involved in drug oxidation exist in multiple forms. There is evidence from animal experiments for the existence of multiple forms of the enzymes responsible for reduction, hydrolysis and important conjugation reactions such as glucuronylation, sulphation, acetylation, methylation and mercapturate formation (Park, 1982).

Although less information is available for man, it is probable that the corresponding human drug-metabolising enzymes also exist in multiple forms and that the individual enzymes have selective, but not specific, substrate requirements. Consequently, drug interactions may arise when two drugs with unrelated pharmacological properties, and differences in chemical structure, compete for binding to the same enzyme. The degree of enzyme inhibition will be partly dependent on the relative affinities of the two drugs for the enzyme and partly on their rates of turnover. Drug-induced enhancement of the drug-metabolising enzymes, mediated by enzyme induction, may also provide the basis for drug interactions. The phenomenon of enzyme induction involves an adaptive increase in the number of molecules of a specific enzyme in response to an enzyme-inducing agent (Gelehrter, 1976). The molecular mechanism of enzyme induction involves genomal derepression, but the initial step in the process is not known and the molecular characteristics essential for enzyme induction have not been defined. Nevertheless, it is clear that administration of one drug may lead to induction of the enzymes involved in the metabolism of several substrates (Park & Breckenridge, 1981).

Pharmacokinetics of drug interactions

The clearance of a drug from plasma is dependent upon the rate of metabolism and upon the rate of excretion. Thus for a drug that is eliminated by renal excretion and hepatic metabolism, clearance (CL) is given by the following equation:

$$CL = \text{renal clearance} + \text{hepatic clearance}$$

Therefore, the impact on plasma clearance of changes in the activity of the drug-metabolising enzymes will be governed by the amount of the drug normally cleared via either the liver or the kidneys. For example, the plasma clearance of a lipophilic β-adrenoceptor blocker such as propranolol is almost entirely dependent upon hepatic clearance (Foulkes & Siddall, 1975) and is therefore sensitive to changes in hepatic enzyme activity. On the other hand, water-soluble β-adrenoceptor blockers such as atenolol are excreted largely unchanged into urine (Reeves *et al.*, 1978) and consequently the clearance of such a drug is insensitive to changes in enzyme activity. Consistent with this hypothesis, it has been demonstrated that plasma antipyrine clearance and cytochrome P-450 content in liver biopsies were related to the rate of propranolol elimination but not to sotalol, which is excreted unchanged (Sotaniemi *et al.*, 1979).

The extent to which β-adrenoceptor blockers are metabolised in man ranges from minimal to almost complete, and appears to be related to the physicochemical properties of the drug (Bourne, 1981). The more lipophilic β-adrenoceptor blockers are extensively metabolised whereas the more hydrophobic counterparts undergo less extensive metabolism. This was illustrated by Bourne (1981) who plotted the logarithm of the partition between octanol and water (log p) against the proportion of β-adrenoceptor blocking drug excreted unchanged in the urine of man.

The more polar drugs with log $p < 1$ are less extensively metabolised while those of greater lipophilicity (log $p > 2$) are extensively metabolised.

When a drug is eliminated entirely by hepatic metabolism (e.g. propranolol), clearance from plasma is equivalent to hepatic intrinsic clearance (CL_{int}), a measure of hepatocellular activity. For first order elimination, CL_{int} is related to the Michaelis-Menten constants V_{max} and K_m according to the equation (Gillette, 1971; Rane *et al.*, 1977):

$$CL_{int} = V_{max}/K_m$$

in which V_{max} is the maximum rate of reaction and K_m is the substrate affinity constant. In enzyme kinetics, the value of K_{max} is directly proportional to the total concentration of enzyme, and K_m is an inverse function of the affinity of the drug for the enzyme. However, plasma clearance is only equivalent to CL_{int} when hepatic metabolism is independent of liver blood flow, and of binding to plasma proteins.

For a drug that forms more than one metabolite, hepatic intrinsic clearance will be a sum of clearances to the individual metabolites according to the equation (Pang *et al.*, 1978):

$$CL_{int} = \sum_{i}^{n} \frac{V_{max,i}}{K_{m,i}}$$

where $V_{max,i}$ and $K_{m,i}$ denote the Michaelis Menten constants for the i^{th} enzyme. Therefore, an increase in hepatic drug-metabolising enzyme activity mediated by enzyme induction will increase the clearance of the drug. Furthermore, for a drug which undergoes several routes of metabolism, the increase in intrinsic hepatic clearance will be equivalent to the sum of the increases in clearance to the product(s) of the induced enzyme(s).

However, for enzyme inhibition the decrease in clearance of the drug will depend upon the fraction (fm) of the dose normally metabolised by the pathway that is inhibited. Rowland (1975) has developed a pharmacokinetic expression for the effect of enzyme inhibition on the ratio of the new half-life of the drug, in the presence of the inhibitor, to the normal half-life, or to the average concentration of the drug at steady-state (C_{ss}) in the absence and presence of inhibitor.

$$R = \frac{t_{1/2} \text{ inhibited}}{t_{1/2} \text{ normal}} = \frac{C_{ss} \text{ inhibited}}{C_{ss} \text{ normal}} = \frac{1}{fm/(1 + I/K_I) + (1 - fm)}$$

where I is the amount of inhibitor and K_I is the inhibitor constant. Using this model, Rowland (1975) demonstrated that when all the drug has been eliminated by the inhibited route ($fm = 1$), the ratio increases dramatically with increasing inhibitor concentration. When $fm < 0.5$, the maximum increase in the ratio is two-fold and is usually not clinically relevant, unless the therapeutic index of the drug is particularly small.

Metabolism of β-adrenoceptor blockers

The metabolism of β-adrenoceptor blockers has been reviewed by Bourne (1981). The most widely used β-adrenoceptor blocking drugs are all derivatives of oxypropanolamine and contain an aromatic nucleus, a secondary hydroxyl function and an *N*-alkyl group. The principal biotransformations observed for this class of drugs are aromatic hydroxylation, glucuronylation of the hydroxyl function, and *N*-dealkylation (Table 1, Figure 1). However, the relative contribution of these pathways varies from drug to drug.

There may be considerable inter-individual variation in ability to perform a particular biotransformation. For example, individuals vary markedly in their ability to hydroxylate metoprolol, and it has been shown that the metabolism of metoprolol exhibits the debrisoquine type of genetic polymorphism (Lennard *et al.*, 1982). This finding emphasises the need to investigate the metabolism of β-adrenoceptor blockers in panels of phenotyped subjects, in order to assess the importance of a particular metabolic variable.

Propranolol, in common with most β-adrenoceptor blockers, is administered as a mixture of (+)- and (−)-isomers. However, Jackman *et al.* (1981) have shown that differences in the kinetics of (−)-propranolol are small and unlikely to be of clinical significance.

Table 1 Principal drug metabolism reactions for β-adrenoceptor blocking drugs in man

Drug	*Reaction*	*Contribution (%)**	*Reference*
Alprenolol	unchanged	10	Hoffman *et al.* (1978)
	aromatic hydroxylation	>70	
	conjugation	10	
Atenolol	unchanged	90	Reeves *et al.* (1978)
	aliphatic hydroxylation	<10	
Bufuralol	aliphatic hydroxylation		Francis *et al.* (1976)
	aromatic hydroxylation		
	conjugation		
Labetalol	unchanged	5	Martin *et al.* (1978)
	glucuronylation	60	
Metoprolol	unchanged	3	Borg *et al.* (1975)
	O-dealkylation	60–65	
	N-dealkylation	10–13	
	aliphatic hydroxylation	10	
Oxprenolol	unchanged		Reiss *et al.* (1974)
	aromatic hydroxylation		
	N-dealkylation		
	glucuronylation		
Propranolol	unchanged	<1	Foulkes & Siddall (1975)
	aromatic hydroxylation	20–30	
	N-dealkylation	25–65	
	glucuronylation	20–30	
Timolol	unchanged	20	Tocco *et al.* (1975)
	alicyclic hydroxylation	40	
	aliphatic hydroxylation	3	

* Figures denote approximate percentage of total products excreted into urine.

Enzyme induction

The interaction between the enzyme inducer phenobarbitone, and propranolol, has been studied thoroughly in the Rhesus monkey (Branch *et al.*, 1974). The increase in propranolol clearance, observed after 12 days phenobarbitone treatment, was due to enhanced liver blood flow and stimulation of drug metabolism.

The relative contributions to the increase in clearance of a drug made by changes in liver blood flow and enzyme induction may be determined by investigating the disposition of the drug after oral and intravenous administration. For drugs with high hepatic clearance and subsequent high presystemic elimination, a moderate increase in the extraction ratio will give rise to a marked decrease in systemic bioavailability. Thus pentobarbitone enzyme induction increased the hepatic extraction of orally administered alprenolol by 29% and decreased the AUC by 78% (Alvan *et al.*, 1978).

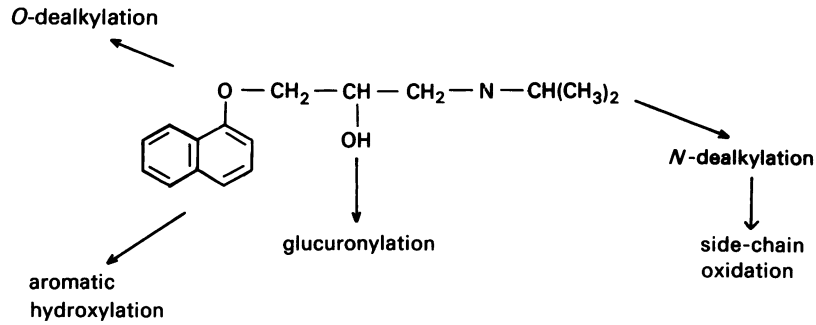

Figure 1 Principal drug metabolism reactions for propranolol in man.

There was, however, no indication of a change in liver blood flow when estimated from the clearance of alprenolol after intravenous administration.

The antibiotic rifampicin, a potent enzyme inducer in man, produces a large reduction in propranolol plasma concentrations due to increased propranolol clearance (Herman *et al.*, 1982). Administration of rifampicin to volunteers for 13 days reduced the AUC for metoprolol and also increased antipyrine clearance (Bennett *et al.*, 1982). It was concluded that the changes in metoprolol kinetics were due to induction of microsomal enzymes.

Barbiturates and rifampicin are potent inducers of the hepatic microsomal mixed-function mono-oxygenase in man (Park & Breckenridge, 1981). It should be anticipated, therefore, that co-administration of such drugs will increase the hepatic clearance of lipophilic β-adrenoceptor blocking drugs. There is no evidence to suggest that β-adrenoceptor blocking drugs may themselves enhance the activity of drug-metabolising enzymes.

Enzyme inhibition

Chlorpromazine reduces the intrinsic (oral) clearance of propranolol by inhibition of propranolol metabolism (Vestal *et al.*, 1979). In an elegant study in which oral unlabelled propranolol and intravenous [^{3}H]-propranolol were measured simultaneously in plasma, it was apparent that chlorpromazine did not affect either liver blood flow or the systemic clearance of propranolol. The reverse interaction, an increase in chlorpromazine levels during propranolol administration, has also been reported (Peet *et al.*, 1980). Chlorpromazine undergoes several oxidative biotransformations mediated by hepatic mono-oxygenases; it is possible, therefore, that chlorpromazine and propranolol compete for the same enzyme.

Cimetidine, an inhibitor of the hepatic mono-oxygenase system, increases the systemic bioavailability of propranolol (Feely *et al.*, 1981; Reinmann *et al.*, 1981), labetalol (Daneshmend & Roberts, 1981) and metoprolol (Kirch *et al.*, 1981), which are all extensively metabolised in man. However, cimetidine has no effect on the plasma concentration of atenolol, which is excreted largely unchanged (Kirch *et al.*, 1981). In this context both the extent and type(s) of β-adrenoceptor blocker biotransformation are important. Thus cimetidine had no effect on the AUC of penbutolol, a drug which is almost totally eliminated by biotransformation. The major metabolite of penbutolol is, however, penbutolol glucuronide (Spahn *et al.*, 1983a). It has been shown that cimetidine reduces the clearance of drugs which undergo oxidative biotransformations (antipyrine, diazepam) but not that of drugs (paracetamol, lorazepam) which are mainly conjugated (Abernethy *et al.*, 1983). Indeed, it was shown that hydroxylation of penbutolol, a minor biotransformation, was blocked by cimetidine (Spahn *et al.*, 1983a). However this argument does not explain why cimetidine reduces the clearance of labetalol, which is metabolised to a mixture of three glucuronides (Martin *et al.*, 1978). Cimetidine also reduces liver blood flow, thereby decreasing the systemic clearance of intravenous propranolol, which is primarily dependent on liver blood flow (Feely *et al.*, 1981).

Ranitidine, another H_2-receptor antagonist, differs chemically from cimetidine in that it contains a furan ring instead of an imidazole group. Ranitidine is not thought to inhibit cytochrome P-450. Nevertheless, it was shown that co-administration with ranitidine increased metoprolol AUC by 50% and increased the mean elimination half-life from 3.9 to 6.0 h (Spahn *et al.*, 1983b). However, ranitidine does not interact with propranolol (Heagerty *et al.*, 1982), indicating either that ranitidine is a selective inhibitor of hepatic mono-oxygenases or that the kinetic interaction with metoprolol involves mechanism(s) other than simple enzyme inhibition.

Enzyme inhibition by β-adrenoceptor blocking drugs

β-adrenoceptor blockers may themselves inhibit drug metabolising enzymes. Greenblatt *et al.* (1978) found that propranolol reduced antipyrine clearance from plasma and the urinary clearance of the metabolite 4-hydroxyantipyrine in volunteers. These results suggest that propranolol acts by inhibiting microsomal enzymes rather than by blocking β-adrenoceptors. Antipyrine clearance is also reduced by metoprolol, whereas atenolol has no effect (Tucker *et al.*, 1982). It has been suggested, therefore, that there is a relationship between the lipid-solubility of β-adrenoceptor blockers and their ability to inhibit drug metabolism (Deacon *et al.*, 1981; Tucker *et al.*, 1982).

Propranolol and metoprolol significantly reduce the elimination of lignocaine, a drug which, in contrast to antipyrine, displays blood flow dependent kinetics (Conrad *et al.*, 1983). The authors suggested that the reduced lignocaine

clearance was due to both a fall in cardiac output and to inhibition of hepatic oxidative metabolism.

At present, it is not possible to predict which types of oxidative biotransformations may be inhibited by β-adrenoceptor blockers or whether inhibition may extend to other types of biotransformation, e.g. conjugation. The use of appropriate model substrates may help answer these questions (Park, 1982). In this context it is interesting to note that propranolol reduces the clearance of theophylline, and the effect is greatest in cigarette smokers whose clearance of theophylline was initially high (Conrad & Nyman, 1980). Theophylline has been suggested as a possible probe for cytochrome P-450 (P-448) mixed-function mono-oxygenases which can be induced by aromatic hydrocarbons (review, Park, 1982).

Conclusions

It is clear that β-adrenoceptor blocking drugs may promote and participate in interactions which involve the drug-metabolising enzymes. The importance of the interaction is dependent upon the extent and type of biotransformation that the interacting drugs undergo. A better understanding of the mechanism(s) involved will be obtained by measuring clearance to metabolites rather than clearance of parent drug. In addition, potential interactions should be investigated in panels of volunteers phenotyped for established pharmacogenetic polymorphisms in metabolism.

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Group discussion

A. M. Breckenridge
How can you reconcile the effects of labetalol in the labetalol/cimetidine interaction with the concepts that you have presented?

B. K. Park
There is a fundamental problem in discussing these interactions, in that concepts are being formed from data researched by different groups of individuals, and for many drugs the information is very scanty. For the metabolism of labetalol I quoted three metabolites; in fact the literature reveals that this was investigated in only three individuals. In order to understand these interactions, we require a better awareness of all of the metabolites and we should also perform controlled studies in the same individuals. Evidence for the existence in these individuals of any genetic polymorphisms or inabilities to perform particular biotransformations is required. More fundamental research is needed to establish the nature of the metabolites, and secondly to investigate inter-individual variation in drug metabolism.

S. Warrington
Regarding the effect of β-adrenoceptor blockers on reducing hepatic blood flow, since you have concentrated on metabolism, do you feel that liver blood flow is unlikely to be of great importance with respect to interactions of β-adrenoceptor blockers with other drugs?

B. K. Park
No, quite the reverse, blood flow is important both in terms of the effect of β-adrenoceptor blockers themselves on reducing cardiac output and reducing liver blood flow, as well as for interactions involving barbiturates. My brief today was to concentrate on metabolism. Dr Branch has shown how one can separate the effects of blood flow and enzyme induction. Certainly, from haemodynamic and pharmaco-