Polymorphic metabolism of β -adrenoceptor antagonists

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1 Most β -adrenoceptor blockers undergo extensive oxidative metabolism. The evidence for polymorphism of the debrisoquine type is reviewed.

2 The AUC and half-life of metoprolol were considerably greater in poor metabolisers (PM) of debrisoquine than in extensive metabolisers (EM). Metoprolol α -hydroxylation is impaired and *O*-dealkylation must also be affected. Polymorphism in the former route has been demonstrated in a population of 143 patients to be directly related to debrisoquine phenotype.

3 Bufuralol AUC and half-life are much higher in PM than EM subjects. Hydroxylation at the 1 and 4 positions are affected. Genetic polymorphism for 1-hydroxylation has been shown in family and population studies.

4 Propranolol 4-hydroxylation is defective in PM subjects of debrisoquine but propranolol AUC is not related to phenotype, presumably because other major pathways are unaffected.

5 Oxidation phenotype correlates well with intensity and duration of β -adrenoceptor blockade after metoprolol, PM subjects requiring only once-daily dosing. However, in EM subjects twice-daily dosing is required even if slow release preparations are used, since plasma metoprolol concentrations may remain negligible 24 h after dosing. The β -adrenoceptor blocking effects of propranolol and bufuralol are unlikely to be influenced by oxidation status. Anecdotal reports of toxicity arising in PM subjects taking metoprolol or propranolol need to be substantiated. However, vomiting after the administration of bufuralol often occurs in poor metabolisers.

6 Metabolic interactions with drugs sharing the same enzyme system are discussed. Debrisoquine and bufuralol competitively inhibit each other's metabolism *in vitro*. Furthermore, β -adrenoceptor blockers may be associated with inhibition of metabolism by affecting either hepatic blood flow or intrinsic clearance or both. It remains to be seen whether these potential interactions are of clinical importance.

Keywords bufuralol debrisoquine metoprolol polymorphism propranolol

Introduction

The metabolism of drugs is influenced by both genetic and environmental factors, but in some cases a single gene effect will be predominantly responsible for marked intersubject variation. Thus, genetic polymorphism may account for major differences in the systemic availability of a drug as well as for its therapeutic and toxic

effects. Polymorphic acetylation and ester hydrolysis are the best known examples of this phenomenon. However, some oxidative pathways are now known to be controlled by a single recessive gene. Defective 4-hydroxylation of debrisoquine was the first of these to be described and measurement of the debrisoquine/

4OH-debrisoquine urinary ratio is commonly used to phenotype subjects (Mahgoub *et al.*, 1977; Tucker *et al.*, 1977). Thus, after an oral dose of debrisoquine this ratio is less than 12.6 in extensive metabolisers (EM) and greater than 12.6 in poor metabolisers (PM) (Evans *et al.*, 1980). This classification is useful since other oxidative pathways are also defective in PM of debrisoquine but not in EM (Table 1) (Eichelbaum, 1982). Until recently, population studies demonstrating polymorphic metabolism of these drugs were confined to debrisoquine and sparteine. The incidence of the PM phenotype is 9% amongst whites in the U.K. but varies with the population studied from 1% in Saudis to 30% in Hong Kong Chinese (Kalow, 1982).

Table 1 Pathways known to be impaired in 'poor metabolisers'

Alicyclic hydroxylation	debrisoquine nortriptyline metoprolol bufuralol
Aromatic hydroxylation	phenformin guanoxan despiramine bufuralol propranolol
N-oxidation	sparteine
O-dealkylation	phenacetin encainide 4-methoxyamphetamine

Many β -adrenoceptor blockers undergo extensive first pass oxidative metabolism (Table 2). The possible impact of oxidation phenotype on this process was suggested by a report of four patients with unexpectedly high plasma drug concentrations following therapeutic doses of alprenolol, metoprolol and timolol (Alvan *et al.*,

Table 2 Routes of elimination of β -adrenoceptor blockers in man

	% Metabolised	Major route
Propranolol	> 90	oxidation
Alprenolol	> 90	oxidation
Oxprenolol	> 90	oxidation
Bufuralol	> 90	oxidation
Timolol	> 80	oxidation
Tolamolol	> 90	oxidation
Metoprolol	> 90	oxidation
Labetalol	> 90	conjugation
Acebutolol	60–85	acetylation
Pindolol	65	oxidation
Nadolol	0	renal
Sotalol	0	renal
Atenolol	0	renal

1982). All subjects were poor metabolisers of debrisoquine. This observation was consistent with our own preliminary findings with metoprolol (Lennard *et al.*, 1982a). Other anecdotal reports suggested that PM may be vulnerable to side effects following conventional doses of propranolol, bufuralol and tolamolol (Balant *et al.*, 1978; Shah *et al.*, 1982). In this paper we review the evidence for the polymorphic metabolism of β -adrenoceptor blockers and its clinical implications.

Evidence for polymorphic metabolism

Metoprolol

Plasma drug concentration data The relation between oxidation phenotype and metoprolol kinetics was studied in six poor and six extensive metabolisers of debrisoquine (Lennard *et al.*, 1982b). Each group comprised four hypertensive patients and two volunteers, matched for age and sex. After a single oral dose of metoprolol tartrate 200 mg, plasma drug concentrations were higher in PM than in EM at all time points over 24 h (Figure 1). There was a 20-fold difference in metoprolol availability ($AUC(\infty)$) in the group as a whole and a six-fold difference in metoprolol availability ($AUC(\infty)$) between the phenotypes. In EM the mean elimination half-life was similar to that reported by others (2.8 h) but it was much longer in PM (7.6 h).

Figure 1 Plasma metoprolol concentrations versus time in extensive (●) and poor (○) hydroxylators of debrisoquine. Vertical bars indicate s.d. After Lennard *et al.* (1982b); reproduced with permission from *New Engl. J. Med.*, 307, 1558–1560.

Studies involving chronic once-daily dosing of metoprolol in volunteers (six EM and two PM) confirmed the observation that 24 h after a 200 mg dose, plasma drug concentrations were negligible in EM but well maintained in PM. In the same subjects the administration of so-called 'long-acting' formulations of metoprolol (SA Astra and SR Geigy) was associated with the same bioavailability as that obtained with conventional tablets. However, at the end of a dosing interval, mean plasma metoprolol concentrations were only slightly higher with the newer formulations. Furthermore, in the most extensive metabolisers (debrisoquine metabolic ratio < 1), plasma metoprolol concentrations were undetectable at the end of the dosing interval irrespective of the formulation used, reflecting a greater clearance of the drug in these subjects when compared to PM (Freestone *et al.*, 1982).

Metabolite data Metoprolol is completely absorbed from the gut, poorly bound to plasma proteins and only about 3% of a dose is excreted unchanged in the urine. Therefore, large differences in availability and half-life are explained by differences in metabolism. The major metabolic pathways, *O*-dealkylation, deamination and aliphatic hydroxylation, are responsible for 65%, 10% and 10% of the dose, respectively (Regardh & Johnsson, 1980). Unfortunately, the products of the first two of these pathways are difficult to measure. However, this is not true of α -hydroxymetoprolol and in the single dose study of Lennard *et al.* (1982b) the mean urinary recovery of this metabolite was found to be 11% in EM compared to $< 1\%$ of the dose in PM. In contrast, PM excreted more unchanged meto-

prolol than EM (15% vs 3%). Clearly, defective α -hydroxylation in PM cannot account for all of the observed differences in AUC and half-life in the phenotypes. Precedents for genetic control of *O*-dealkylation exist in the metabolism of phenacetin, encainide and 4-methoxyamphetamine (Kitchen *et al.*, 1979; Sloan *et al.*, 1978; Woosley *et al.*, 1981) and this pathway is presumably also impaired in poor metabolisers of metoprolol.

Population study A wide separation in the ratio of urinary metoprolol/hydroxymetoprolol recovery was observed in the study of Lennard *et al.* (1982b), (EM 0.14–1.19; PM 19–35). This was confirmed subsequently in a larger study (Figure 2) (Lennard *et al.*, 1983). Not only was there complete concordance with respect to debrisoquine phenotype, but the metabolic ratios for debrisoquine and metoprolol were highly correlated in the group as a whole ($r_s = 0.81$, $P < 0.0001$) (unpublished data). These correlations support the view that metoprolol oxidation is genetically determined.

Bufuralol

Plasma drug concentration data Balant *et al.* (1976) studied the pharmacokinetics of bufuralol and tolamolol in 10 healthy subjects. In nine individuals the mean elimination half-life of both compounds was 2.5 h. However, in the remaining subject the half-life of both drugs was 5 h and this was associated with higher plasma drug concentrations and lower metabolite concentrations.

The metabolism of bufuralol was then investi-

Figure 2 Frequency distribution of $\log_{10}$ urinary metoprolol: α -hydroxymetoprolol ratio in 119 unselected hypertensive patients. After Lennard *et al.* (1983); reproduced with permission from *New Engl. J. Med.*, 308, 965–966. ■ poor metabolisers of debrisoquine.

gated in relation to debrisoquine phenotype in the remaining subject's family which comprised 3 PM and 1 EM (Dayer *et al.*, 1982a). Data from the latter was typical of a larger group of control subjects. There was a 3–7-fold increase in bufuralol AUC (∞) in PM and a 2–3-fold increase in half-life. In contrast, plasma 1-hydroxybufuralol concentrations were too low for determination of AUC only in PMs. In addition to aliphatic hydroxylation bufuralol undergoes aromatic 4-hydroxylation, a pathway which is also impaired in PM (Dayer *et al.*, 1983).

Population study Polymorphic control of the 1-hydroxy pathway was confirmed in 154 healthy volunteers using measurements of the ratio of plasma bufuralol/metabolite at 3 h after a single 30 mg dose (Figure 3). There was complete concordance with debrisoquine phenotype (Dayer *et al.*, 1982b).

Propranolol

A large inter-subject variability in plasma propranolol concentrations is well documented. However, the mean plasma propranolol concentration-time profile after a single 80 mg oral dose was similar in EM and PM (Lennard *et al.*, 1984) suggesting that oxidation phenotype is not a major determinant of propranolol availability. Nevertheless, plasma 4-hydroxypropranolol concentrations were significantly lower in PM compared to EM subjects. Propranolol is converted to a large number of oxidative metabolites and 4-hydroxylation usually accounts for only 20% of the dose. Therefore, these data suggest that although 4-hydroxylation of propranolol is impaired in poor hydroxylators of debrisoquine, other major pathways are unaffected.

Clinical implications

The clinical implications of polymorphic drug metabolism depend on the correlation between plasma, drug and metabolite concentrations and therapeutic and adverse effects. While β -adrenoceptor blockade correlates with plasma drug concentrations the antihypertensive effect of β -adrenoceptor antagonists does not.

β -adrenoceptor blockade The intensity of β -adrenoceptor blockade produced by the various agents has been shown to correlate with concentrations of their unchanged forms in plasma. However, in those cases where significant amounts of an active metabolite are formed, its presence will tend to minimise any contribution of variable metabolism to differences in β -adrenoceptor blockade.

The duration of β -adrenoceptor blockade will depend on the half-life of the active compound. Most β -adrenoceptor blockers have an elimination half-life of 2–4 h and this is usually associated with effective β -adrenoceptor blockade for up to 12 h. For this reason the conventional formulations of metoprolol and propranolol are prescribed 8–12 hourly to prevent angina. In contrast, significant β -adrenoceptor blockade is maintained 24 h after dosing with atenolol (half-life 6–9 h) and nadolol (half-life 17 h), both of which are eliminated mainly unchanged by the kidney.

In addition to the correlation between debrisoquine oxidation phenotype and metoprolol kinetics, Lennard *et al.* (1982b) also observed significantly greater β -adrenoceptor blockade in PM than in EM at 24 h after dosage of metoprolol (Figure 4). Data are also available in two PM and two EM who received metoprolol 200 mg, propranolol 80 mg and atenolol 100 mg

Figure 3 Plasma metabolic ratios of bufuralol in 15 healthy Swiss volunteers. ■ poor metabolisers for bufuralol and debrisoquine. After Dayer *et al.* (1982b); reproduced with permission from *Lancet*, i, 509.

Figure 4 Correlation between the debrisoquine/4-hydroxydebrisoquine (D/HD) ratio and: (a) the metoprolol elimination half-life ($r_s = 0.97$, $P < 0.001$); (b) the area under the plasma concentration-time curve (AUC) ($r_s = 0.89$, $P < 0.001$); (c) the 24 h metoprolol/ α -hydroxymetoprolol (M/HM) urinary ratio ($r_s = 0.74$, $P < 0.01$); and (d) the percentage reduction in exercise-induced tachycardia at 24 h (% beta-blockade) ($r_s = 0.92$, $P < 0.001$). (●) extensive hydroxylators and (○) poor hydroxylators. In (c) only five of six data points are available from the extensive hydroxylator group owing to technical difficulties in the urinalysis. After Lennard *et al.* (1982b); reproduced with permission from *New Engl. J. Med.*, 307, 1558–1560.

(Figure 5). Thus, at 24 h extensive metabolisers of metoprolol show little or no reduction in exercise heart rate, while the effect was sustained in poor metabolisers. The metabolites of metoprolol have much less β -adrenoceptor blocking activity than the parent drug. In contrast, the effects of propranolol and atenolol were unrelated to oxidation phenotype. The relationship between oxidation state and β -adrenoceptor blockade with bufuralol has not been studied. However, the activity of the 1-hydroxy metabolite is similar to that of the parent drug (Dayer *et al.*, 1982c) and this should minimise variation in β -adrenoceptor blockade arising from polymorphic metabolism.

The development of a sustained-release formulation of propranolol has illustrated that the duration of effect of rapidly metabolised drugs may be extended significantly (Leahey *et al.*, 1980; Petrie *et al.*, 1980). However, chronic dosing with both of the commercially available

Figure 5 Percentage reduction in exercise heart rate 24 h after a single dose of metoprolol 200 mg (M) and propranolol 80 mg (P) and a once-daily dose of atenolol 100 mg (A) for 7 days, in two poor (PM, 2) and two extensive (EM, 2) metabolisers of debrisoquine.

'long-acting' formulations of metoprolol was associated with marked variability in β -adrenoceptor blockade 24 h after a 200 mg dose, and with insignificant β -adrenoceptor blockade in the most extensive metabolisers (metabolic ratio < 1) (Freestone *et al.*, 1982). Therefore, these formulations may offer no advantage over the conventional tablets since they too must be prescribed twice daily in angina unless the oxidation phenotype is known. The new Oros preparation of metoprolol may prolong the delivery of the drug sufficiently to enable once-daily dosing in some patients (Kendall *et al.*, 1982). However, its performance in relation to oxidation phenotype needs to be assessed should it be marketed.

Adverse effects Although β -adrenoceptor blockers have a high therapeutic ratio, problems related to dose and plasma drug concentrations may arise; these may or may not be a consequence of β -adrenoceptor blockade. Alvan *et al.* (1982) suggested that drop-outs from β -adrenoceptor blocker trials may have been PM of debrisoquine. In the Norwegian Multicentre Study, timolol was withdrawn in 3% of patients because of bradycardia; and this figure is identical to the incidence of the PM phenotype in Sweden, a similar community. However, the hypothesis is unproven and remains doubtful. Bradycardia with β -adrenoceptor blockers is rarely sympto-

matic (Cruickshank, 1983) and important dose-related changes in resting heart rate have not been observed. This is illustrated by the observation that a four-fold increase in propranolol or metoprolol dose was associated with only an additional 5–6 beats/min reduction in resting heart rate (Collste *et al.*, 1980; Leonetti *et al.*, 1975; Serlin *et al.*, 1980). When symptomatic bradycardia follows therapeutic doses of a β -adrenoceptor blocker this must in part be due to high vagal tone (Shand, 1975) or to associated cardiac disease. A report from the Boston Collaborative Drug Surveillance Program found that the majority of life-threatening adverse cardiac reactions to propranolol occurred at doses of 40 mg or less (Greenblatt & Koch-Weser, 1974).

Although β -adrenoceptor blockers are best avoided in known asthmatics, when this is not possible, a cardioselective compound such as metoprolol may be safer than propranolol. However, cardioselectivity is a relative property which may be lost in association with the high plasma drug concentrations expected in poor metabolisers receiving standard doses (Formgren, 1976). This potential disadvantage of metoprolol, over the alternative cardioselective agent atenolol, has yet to be demonstrated, and further studies should be conducted.

Severe vomiting following single doses of bufuralol is common in poor metabolisers (Dayer *et al.*, 1982a), illustrating the importance of dose-related central nervous system toxicity. In clinical practice this particular reaction seems unimportant since the drug is not widely distributed, possibly because nausea was a common occurrence in early tolerability studies. Nevertheless, central nervous system disturbances are amongst the most common complaints in patients taking β -adrenoceptor antagonists (Greenblatt & Koch-Weser, 1974). Furthermore, dose-related sleep disturbance has been demonstrated following therapeutic doses of lipid soluble β -adrenoceptor blockers including metoprolol (Betts & Alford, 1983) suggesting that phenotype may be an important determinant of toxicity.

Drug interactions

There are no clinical data to show that genetic polymorphism influences drug interactions involving β -adrenoceptor blockers. However, these agents are known to inhibit the metabolism of other drugs and, if this inhibition is dose-related, poor metabolisers of β -adrenoceptor

blockers may be at greater risk. In contrast, extensive metabolisers of β -adrenoceptor blockers are more likely to suffer the effects of an interaction resulting from competitive inhibition of metabolism by other drugs. The mechanisms by which β -adrenoceptor blockers inhibit drug metabolism are as follows:

1. Hepatic blood flow may be lowered as a result of β -adrenoceptor blockade. This could affect the clearance of compounds with high hepatic extraction ratios and the effect may be proportional to the intensity of β -adrenoceptor blockade.

2. Intrinsic hepatic metabolism is inhibited by β -adrenoceptor blockers (Greenblatt *et al.*, 1978). The mechanism is uncertain but there is a strong positive correlation with the lipid solubility of the β -adrenoceptor blocker (Deacon *et al.*, 1981). Metoprolol lowered antipyrine clearance by 18% (Bax *et al.*, 1981) whereas atenolol had no effect (Tucker *et al.*, 1982). It is important to know whether this type of interaction is dose-related.

3. Competitive inhibition of the biotransformation of drugs metabolised by the same cytochrome P-450 system as debrisoquine has been shown in studies *in vitro* using human liver microsomes. The same cytochrome P-450 system appears to regulate 4-hydroxylation of debrisoquine, 10-hydroxylation of nortriptyline and 4-hydroxylation of propranolol (Boobis *et al.*, 1982; von Bahr *et al.*, 1982). Furthermore, propranolol inhibits 10-hydroxylation of nortriptyline, although in this case it has not been proven that the mechanism involved is competitive. Mutual competitive inhibition of the metabolism of debrisoquine and bufuralol (4-hydroxylation and 1-hydroxylation respectively) has been demonstrated (Boobis *et al.*, 1983).

Conclusions

β -adrenoceptor blockers eliminated by oxidative metabolism may be subject to polymorphic metabolism. However, this has only been shown conclusively for metoprolol and bufuralol. Propranolol 4-hydroxylation is also affected. Polymorphism explains much of the variation in β -adrenoceptor blockade following metoprolol, whether it is given as conventional tablets or as a slow-release formulation. Although β -adrenoceptor blockers have a high therapeutic ratio, they are frequently used in previously asymptomatic patients. Freedom from adverse reactions is essential. Both respiratory and central nervous system side-effects may be dose-related and it is important to know whether toxicity is correlated with oxidation status.

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Group discussion

E. Mutschler

One problem with our β -adrenoceptor blocker studies was that both enantiomers were measured concomitantly and there was no separate data available for the (+)- and (-)-enantiomers. Are there differences in biotransformation between the two β -adrenoceptor blocker enantiomers in poor and extensive metabolisers?

M. S. Lennard

The kinetics of the enantiomers of metoprolol were investigated in 12 volunteers. We were able to determine the (+)- and (-)-enantiomers concomitantly in the same sample. There were phenotype differences; poor and extensive metabolisers transform the enantiomers differently. With respect to pharmacodynamics there was a shift in the dose response curve for poor when compared to extensive metabolisers.

R. Branch

One wonders what is happening at a molecular level when you have diverse routes of metabolism such as with debrisoquine and metoprolol. We have some early data which suggest that there are three major possibilities. First, a co-factor required for a number of different isoenzymes may be missing; second, an isoenzyme responsible for a rather unique and surprising set of metabolic pathways may be present; third, structural requirements present on more than one isoenzyme may be defective due to genetic determination. We have been successful in following an isoenzyme that appears to have between ten and a hundred-fold greater activity than other isoenzymes. However, this has not yet been tested with other substrates within this correlation. I still have great difficulties in con-

ceiving how one isoenzyme is so important for so many different substrates. This is possibly an interesting entree to an understanding of drug metabolism at a more basic level.

A. J. McLean

It has been shown that with respect to acetylation if you compare urine and plasma, you can make many phenotyping errors using urine data for two reasons. First, the enzyme *N*-acetyltransferase is importantly distributed in the kidney; second, there is non-linear handling of both parent and metabolite when it is transferred into the urine space. Two questions should be considered: what is known about the distribution of these enzymes in the kidney? Until we are certain about enzyme distribution should we not confine ourselves to phenotyping using plasma data?

J. H. Silas

We should not necessarily confine ourselves to plasma phenotyping, partly because of debrisoquine's characteristics. Debrisoquine is an unusual drug in that it undergoes quite extensive first pass metabolism (in those people who can metabolise it) but since it is highly water soluble, is excreted in the urine with little further change. Therefore one can show that the availability of debrisoquine itself is very much reflected by urinary recovery. Debrisoquine differs from metoprolol in this respect, and thus so far as debrisoquine is concerned the use of urinary data is perfectly justified. With sulphadimidine there is an added problem in that one should consider renal clearance of these compounds. As you say, this is a further problem complicating the situation with *N*-acetyltransferase activity. Certainly,