Eur J Clin Pharmacol (1985) 28 [Suppl]: 77-84

**European Journal of Clinical Pharmacology**


*β-Blockers and Genetic Polymorphism*

# Polymorphic Metabolism of the β-Adrenoreceptor Blocking Drugs and its Clinical Relevance

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**Summary.** Although β-blockers are structurally closely related, there are marked differences in the extent of metabolism, related mainly to relative lipophilicity. Lipophilic β-blockers are metabolized by C-oxidative pathways and glucuronidation. Metabolism of lipophilic β-blockers is important in determining pharmacokinetics, formation of active metabolites, stereoselectivity and isomer preference, and interphenotypic variation. The oxidative clearance of metoprolol, timolol and bufuralol is regulated/influenced by the debrisoquine hydroxylation gene locus. The metabolism of these lipophilic β-blockers thus exhibits polymorphic characteristics, there being significant interphenotype differences in pharmacokinetics (bioavailability, peak plasma level, plasma terminal t½) between the poor and extensive metabolizers of debrisoquine. There are similar interphenotype differences in β-blocker pharmacodynamics in terms of β-blockade. A number of adverse effects of lipophilic β-blockers have been hypothesized to predominate in the poor metabolizer phenotype including unacceptable bradycardia, loss of cardioselectivity, greater CNS side-effects, and interactions with drugs metabolized by the same polymorphic systems. However, objective evidence for this is lacking.

**Key words**: β-blockers, debrisoquine metabolism, extensive metabolizers, genetic polymorphism, poor metabolizers; glucuronidation, lipophilicity, pharmacodynamics, pharmacokinetics

Currently used β-adrenoreceptor blocking drugs (β-blockers) are of two structural types: derivatives of oxypropanolamine or of phenylethylamine. The majority are derivatives of the former and have the general structure:

$$R^1-O-CH_2-CH(OH)CH_2NH-R^2$$

where $R^1$ is usually a substituted aromatic ring, and $R^2$ an alkyl group and almost invariably isopropyl. Examples of β-blockers based upon this structure are alprenolol, atenolol, metoprolol, pindolol and propranolol. Less commonly, β-blockers are based upon the phenylethylamine structure and examples include pronethalol, sotalol and bufuralol. For a review of the relationship between chemical structure and pharmacological activity, the reader is referred to Wong and Schreiber (1972). From the point of view of the metabolism of the β-blockers there are three important structural points to note. Firstly, they are relatively strong bases due to the isopropylamine group. Secondly, they vary in their polarity quite markedly according to their detailed chemical structure. Thirdly, they all possess within their structures a single chiral centre so that each β-blocker occurs as a pair of enantiomers. All currently used β-blockers are marketed as the racemic form (i.e. equal parts of each enantiomer) and this has some interesting pharmacokinetic, and possibly pharmacodynamic, consequences.

## Pathways of Metabolism of β-Blockers

It is important to note that the extent of metabolism of the β-blockers is highly variable and ranges from minimal to virtually complete biotransformation. It is well-established that the extent of β-blocker metabolism is mainly related to their lipophilicity. Hydrophilic drugs such as atenolol, nadolol and practolol are minimally metabolized whereas the more lipophilic drugs such as alprenolol and propranolol are virtually completely metabolized. Bourne (1981) has pointed out the excellent relationship that exists between log P (log of the partition between octanol and water, a measure of lipophilicity) and the extent of metabolism of several β-blockers in man. A distinction is therefore commonly made between the hydrophilic β-blockers such as atenolol and nadolol and

**Table 1.** Pathways of metabolism of β-blockers

| Structure: $R-O-CH_2CH(OH)CH_2NHCH(CH_3)_2$ | |
|---|---|
| Metabolic pathway | Examples |
| Aromatic hydroxylation | alprenolol, bufuralol, oxprenolol, propranolol |
| *O*-Dealkylation | metoprolol, oxprenolol |
| *N*-Dealkylation | propranolol, alprenolol |
| Oxypropanolamine side-chain dealkylation and further oxidation | propranolol, metoprolol, alprenolol |
| Glucuronic acid conjugation | labetalol, propranolol, oxprenolol |

the lipophilic ones such as propranolol and oxprenolol, although it should be pointed out that some, such as acebutolol, timolol and pindolol occupy an intermediate position. This paper, by definition, will be concerned with those lipophilic β-blockers that undergo extensive biotransformation.

The routes of metabolism of the β-blockers are, as for all metabolic reactions, structure-dependent, and are therefore, largely determined by the particular functional groups and the metabolic options that these confer. Since structurally, the β-blockers form a fairly close family of related substances we find that they are metabolized by a fairly narrow and common spectrum of metabolic pathways (Table 1).

The structures of these drugs afford opportunities for C-oxidative reactions and several β-blockers undergo the metabolic reactions of aromatic hydroxylation and *O*- and *N*-dealkylation. Following *N*-dealkylation the oxypropanolamine side-chain may be subject to further oxidative metabolism leading to a glycol and subsequently lactic and acetic acid derivatives. Oxidative *O*-dealkylation also occurs with drugs such as metoprolol and oxprenolol. It is conceivable that the complete oxypropanolamine side-chain could be removed by oxidative *O*-dealkylation but when this occurs (propranolol and bunolol) it appears to be a relatively minor pathway. The formation of 4-hydroxypropranolol from propranolol probably involves epoxide formation (Nelson and Powell 1979). Epoxidation also occurs in the rat with alprenolol and involves the allylic side-chain (Hoffman et al. 1979).

A further metabolic pathway of major significance for the disposition of β-blockers is that of glucuronic acid conjugation. This frequently occurs at the secondary alcohol function on the side-chain and in this way the β-blocker may be eliminated by direct conjugation with glucuronic acid. A second option is that this reaction occurs following the introduction of a suitable centre, by C-hydroxylation, into the parent drug molecule, which can then participate in glucuronidation. Thus, both propranolol and oxprenolol (Riess et al. 1974) are metabolized in man to phenolic metabolites which are subsequently excreted as glucuronic acid conjugates. A further point to consider is that the metabolism of racemic β-blockers may be stereoselective. Thus, one isomer may be preferentially metabolized. As Trager and Testa (1984) have pointed out, the structural and enzyme components of all living cells are themselves asymmetric and it is to be expected that they will differentially interact with the two enantiomers of an asymmetric molecule. Therefore, in the case of a racemic mixture, what the body 'sees' are two distinct and discrete chemical entities which may be metabolized in different ways. Although stereoselective metabolism of β-blockers has only been established for a few of these drugs, propranolol (Walle et al. 1984) and metoprolol (Hermansson and von Bahr 1982; Lennard et al. 1983), it probably occurs with all of them to a greater or lesser extent. Stereoselective metabolism becomes particularly significant in view of the known differences in pharmacological activities and potencies of the enantiomers. Thus, (−)-propranolol has 20–50 times (depending on the tissue and species) the β-blocking activity of (+)-propranolol; but both isomers are approximately equipotent with respect to negative inotropic activity (Barrett and Cullum 1968).

Similarly, according to Lennard et al. (1983) most of the β-blocking action of racemic metoprolol resides in the (S)-enantiomer. The situation is more complex with labetalol, which has two chiral centres and, therefore, exists as four stereoisomers. Labetalol used in animal and human investigations is a mixture of equal proportions of the four enantiomers. A study of the pharmacological properties of each individual stereoisomer aided the understanding of the $\alpha_1$- and β-adrenoreceptor blocking properties of labetalol (Brittain et al. 1982). It was concluded that while all four stereoisomers contribute to the overall pharmacological profile of labetalol, nevertheless, most of the $\alpha_1$-adrenoreceptor blocking activity is attributable to the SR-isomer while nearly all the β-blocking action is associated with the RR stereoisomer.

Past attempts to investigate possible relationships between plasma pharmacokinetics and β-blockade for various β-blockers have probably been limited by failure to take into account stereoselective metabolism of the racemic forms of drugs. In recent years a variety of stereospecific assay methods involving the formation of diastereoisomers have been introduced, which now renders this type of study readily feasible.

## Relevance of Metabolic Disposition to the Clinical Pharmacology of the β-Blockers

Metabolic disposition may be relevant for one general and three specific reasons: (1) for those lipophilic β-blockers that undergo extensive metabolism, biotransformation is a key determinant of their pharmacokinetics; (2) formation of active metabolites; (3) stereospecific metabolism (see above); and (4) interindividual variation and sources of variable metabolism.

The formation of active metabolites occurs with a number of β-blockers and this is probably not too surprising in view of the relatively minor changes in chemical structure that result as a consequence of for example, C-oxidative metabolism. What has been somewhat difficult and controversial has been the assessment of the relative importance of these active metabolites in relation to the total pharmacology of the parent drug. The formation of active metabolites through biotransformation occurs with acebutolol, alprenolol, bufuralol, bunolol and propranolol and quite probably occurs with several other β-blockers. Acebutolol for example is metabolized in part to an *N*-acetyl derivative which is supposed to be as active as the parent drug with respect to β-blocking properties (Kaye et al. 1976). The aromatic hydroxylation of both alprenolol and propranolol generates metabolites with β-blocking properties. It is believed that 4-hydroxyalprenolol contributes to the β-blocking action produced by the parent drug probably during the first few hours after dosing but not subsequently (Ablad et al. 1974; Collste et al. 1979a). Propranolol has long been known to undergo metabolic conversion at least in part to 4-hydroxypropranolol, an active β-blocker. The importance of this metabolite in terms of its contribution to the overall β-blocking effects of the drug has long been unclear despite the fact that it is a major metabolite. Recent evidence suggests that its importance in this respect has been overestimated. Thus, Walle et al. (1984) have shown that the aromatic hydroxylation of racemic propranolol is in favour of the less pharmacologically active (+)-propranolol. They observed that the overall ring hydroxylation reaction strongly favoured (+)-propranolol with a (−)/(+)-enantiomer ratio of 0.59. The second line of evidence derives from comparative studies between extensive metabolizer (EM) and poor metabolizer (PM) phenotypes with respect to the β-blocking action of racemic propranolol and the extent of 4-hydroxypropranolol formation. The findings of two studies indicate little interphenotype difference in β-blocking action despite significant differences in the extent of 4-hydroxypropranolol formation suggesting that the latter contributes little to the overall pharmacological effects of propranolol (Raghuram et al. 1984; Lennard et al. 1984). Bufuralol is metabolized along several pathways, one of these involving oxidation of the aliphatic ethyl sidechain generating a secondary alcohol and the corresponding ketone both of which have pharmacological activity similar to the parent compound (Francis et al. 1976). In man bunolol gives rise to dihydrobunol, a major reductive metabolite whose β-blocking activity is equipotent with the parent drug (DiCarlo et al. 1977).

## Interindividual Variation in the Metabolic Disposition of β-Blockers

Extensive interindividual variation in the metabolism of lipophilic β-blockers is clinically relevant as are the major differences in linked events such as bioavailability, pharmacokinetics and response in clinical trials of new drugs using fixed dose regimes. The extensive intersubject variation in the disposition of a number of β-blockers is indicated by the marked variation in peak plasma levels as summarized in the review of Frishman (1979). Variation is about four-fold for pindolol and sotalol, five-fold (oxprenolol), seven-fold (metoprolol) and 10–20 fold for alprenolol and propranolol. By contrast, variation in the peak plasma level of atenolol, which is essentially non-metabolized is stated to be of a low order. Many studies over the years have been directed towards identifying those factors responsible for metabolic variation. In the case of propranolol where intersubject variability in drug concentration may vary up to 20-fold, a number of contributing factors have been identified including age (Vestal et al. 1979), hepatic dysfunction (Wood et al. 1978), thyroid disease (Feely et al. 1981a; Wells et al. 1983), cigarette smoking (Vestal et al. 1979) and concomitant drug use (Feely et al. 1981b; Sotaniemi et al. 1979; Herman et al. 1982). However, even when these differences are taken into account, considerable differences remain. It is now believed that the major cause of intersubject variation in the plasma levels of propranolol, as for many other lipophilic drugs, is a difference in hepatic metabolism, particularly oxidative biotransformation. Intensive studies over the past two decades have now firmly established that interindividual differences in the oxidative metabolism of many lipophilic drugs have their origins in variations in the functional expression of the cytochrome P-450 isozyme system as regulated and influenced by a variety of genetic, environmental, physiological and pathological factors. From the genetic point of view, it has been widely surmised

**Table 2.** Some features of the debrisoquine hydroxylation polymorphism

| | |
|---|---|
| Phenotypes | Extensive (EM) and poor (PM) metabolizers |
| Substrate for the gene product | Typically drugs with strongly basic N-centres |
| Metabolic reactions regulated | Wide variety of C-oxidative reactions including aromatic, alicyclic and aliphatic hydroxylation and *O*-dealkylations |
| Global heterogeneity | Marked, frequency of PM phenotype varies 1-12% |
| Determinant of variability | Major source of interindividual variation in drug oxidation/oral bioavailability/systemic pharmacokinetics and drug response |

**Table 3.** Pharmacokinetic and clinical consequences of impaired drug oxidation in the PM phenotype

| Pharmacokinetic effect | Clinical consequence |
|---|---|
| (1) Reduced first-pass metabolic loss; increased peak plasma levels and bioavailability | Exaggerated pharmacological responses; concentration-dependent side-effects |
| (2) Reduced metabolic elimination | Drug accumulation |
| (3) Alternative metabolic pathway ('metabolic switching') | Possible formation of toxic metabolites |
| (4) Failure to generate the pharmacologically active metabolite | Therapeutic failure |
| (5) Competing substrates | Altered pharmacokinetics; drug interactions |

that the regulation of drug oxidation was, in the main, polygenic and multifactorial in nature. However, in recent years a number of genetic polymorphisms of drug oxidation have been uncovered and, indeed, polymorphism may be a general feature of the cytochrome P-450 system (Smith 1985). It is now clear that the oxidative biotransformation of a number of drugs is under single gene control and that variable oxidation patterns arise from the occurrence of allelomorphic variants of the gene in the population. One of these polymorphisms, the so-called debrisoquine hydroxylation polymorphism is particularly relevant to the biotransformation of several β-blockers since the regulation of their oxidation appears to be regulated from the same locus as that governing the alicyclic hydroxylation of debrisoquine. Therefore, the debrisoquine hydroxylation polymorphism has considerable bearing on interindividual differences in metabolism of lipophilic β-blockers such as metoprolol, bufuralol and timolol.

## The Debrisoquine Hydroxylation Polymorphism

The discovery of this polymorphism of drug oxidation arose from observations on an affected individual who was unable to effect the more normally encountered metabolic reaction of this drug, namely benzylic oxidation to give 4-hydroxydebrisoquine. Subsequent population and family studies showed that the trait of impaired drug oxidation was a genetically determined recessive phenomenon transmitted in an apparently simple Mendelian fashion (Mahgoub et al. 1977). Two phenotypes were recognized: extensive metabolizers (EMs) who phenotypically effectively hydroxylated the probe drug debrisoquine and poor metabolizers (PMs) who displayed the trait of impaired oxidative metabolism. This polymorphism has been extensively studied over the past few years and some of its major characteristics are shown in Table 2. For further information on these aspects, the reader is referred to the review by Idle and Smith (1984).

## Metabolism of β-Blockers and the Debrisoquine Oxidation Polymorphism

The lipophilic β-blockers are characterized structurally by the presence of the basic oxypropanolamine side-chain and metabolically they undergo extensive oxidation. It is perhaps not too surprising therefore that their oxidative metabolism appears in the main to be regulated from the debrisoquine hydroxylation gene locus and that it is highly variable in the population. Silas et al. (1984) have reviewed the evidence for the polymorphic metabolism of three β-adrenoreceptor antagonists (metoprolol, bufuralol and propranolol) and the relationship with the debrisoquine oxidation polymorphism. Such evidence consisted of population, and in the case of bufuralol, family studies, as well as interphenotype comparisons using individuals previously phenotyped with debrisoquine for oxidation status.

## Pharmacokinetic and Clinical Consequences of Genetically Determined Impaired Drug Oxidation

The characterization of the debrisoquine hydroxylation polymorphism has allowed us to rationalize many diverse observations related to exaggerated drug effects and apparently idiosyncratic adverse drug responses. The fact that metabolic oxidation of some drugs, a major component of the elimination process, is discontinuous in terms of its distribution in the population, means that the overall disposition

**Table 4.** Interphenotype comparisons of the pharmacokinetic properties of four lipophilic β-blockers

| Drug | Oral bioavailability[a] ratio PM/EM | Peak plasma concentration (ng/ml) ratio PM/EM | Plasma t½ (h) | | Reference |
|---|---|---|---|---|---|
| | | | EM | PM | |
| Propranolol | 1 | 0.9 | 4.0 | 4.3 | Raghuram et al. 1984 |
| Bufuralol | 2.0 | 2.4 | 2.5 | 6 | Dayer et al. 1982; 1983 |
| Timolol | 2.1 | - | 2.8 | 3.5 | Lewis et al. 1984 |
| Metoprolol | 5.8 | 2.9 | 2.8 | 7.6 | Lennard et al. 1982 |

[a] Based upon comparisons of AUC values after oral dosing

**Table 5.** Oxidation phenotype and clinical responses to β-blockers

| Drug | Effect on PM phenotype | Reference |
|---|---|---|
| Propranolol | No significant differences from EM phenotype with respect to cardiovascular response | Lennard et al. 1984<br>Raghuram et al. 1984 |
| Timolol | Prolonged β-blockade | Lewis et al. 1984 |
| Metoprolol | More intense and prolonged β-blockade | Lennard et al. 1982 |
| Bufuralol | Moderate hypotension; nausea and vomiting; cholinergic effects | Dayer et al. 1982 |

and linked associated events for these drugs, such as response and susceptibility to exaggerated and adverse effects, may show a similar discontinuity. It is now clear that the poor metabolizer (PM) phenotype constitutes a subgroup with a propensity to develop exaggerated responses and untoward drug effects (Idle and Smith 1984). This increased susceptibility is a direct consequence of the impaired ability of PMs to effect the metabolic oxidation of a range of drugs. The major pharmacokinetic and clinical consequences of this genetically determined deficiency of drug oxidation are summarized in Table 3. While this summarizes the range of possible consequences, it is clear that not all these situations apply to the β-blockers. Indeed, it is probable that only point (1) is of proven relevance, whereas point (5) may have some significance, at least in theory, but objective evidence is lacking.

An interphenotype comparison of the pharmacokinetic properties of four lipophilic β-blockers whose oxidative metabolism is regulated/influenced by the debrisoquine hydroxylation locus is given in Table 4. It is clear that these drugs show some interphenotype differences with respect to oral bioavailability, peak plasma concentrations and terminal plasma t½ values. These are most marked in the case of metoprolol and least evident for propranolol. The overall plasma pharmacokinetics of propranolol, as parent drug, are similar for the two phenotypes. However, substantial differences occur with respect to the plasma levels of 4-hydroxypropranolol; AUC values for this metabolite are some five times greater in the EM than in the PM phenotype. Despite the substantial difference in production of the pharmacologically active 4-hydroxypropranolol the extent of β-blockade induced by oral doses of propranolol are similar for the two phenotypes suggesting that this metabolite does not contribute substantially to the overall β-blocking effects of the drug (Raghuram et al. 1984; Lennard et al. 1984). Overall, the data suggests that although the aromatic 4-hydroxylation pathway of propranolol metabolism is regulated by the debrisoquine gene locus, other independent pathways of metabolism are quantitatively more important. The major metabolic source of variable propranolol metabolism therefore remains unidentified.

The most marked interphenotype differences in disposition pharmacokinetics have been observed for bufuralol and metoprolol, although for both drugs a full qualitative and quantitative account of their metabolism is still, apparently, unavailable. For metoprolol, interphenotype differences in oral bioavailability can vary up to six-fold with an approximately three-fold longer plasma elimination half-life in PMs. Probably this difference is largely a function of defective *O*-dealkylation in PMs. Significant interphenotype differences also occur with respect to the stereoselective metabolism of racemic metoprolol (Lennard et al. 1983). Thus, EMs preferentially eliminate the (R)-enantiomer resulting in the accumulation of the more active (S)-isomer. By contrast, in PMs clearance of the (S)-isomer is slightly preferred. The authors also pointed out the importance of taking into account interphenotype differences in stereoselective elimination of metoprolol when considering plasma concentration/effects relationships. Substantial interphenotype differences in clinical response to several β-blockers have been observed (Table 5). These differences are largely concentration-dependent and almost certainly reflect differences in first-pass metabolic loss.

Four lipophilic β-blockers have been examined with respect to interphenotype differences in re-

sponse (Table 5). Differences have been observed for three of these, namely, timolol, metoprolol and bufuralol but their clinical significance is not fully clear. In the case of propranolol, two independent studies have revealed no significant interphenotype differences with respect to the β-blockade induced by oral doses of the drug (Lennard et al. 1984; Raghuram et al. 1984). This is consistent with the observation that although the drug is metabolized in part along a pathway regulated by the debrisoquine hydroxylation gene, the greatest proportion of the drug is transformed by other independent pathways. Both timolol and metoprolol have been reported to produce a more prolonged β-blockade in EM subjects. Thus, following oral doses of timolol (Lewis et al. 1984) and metoprolol (Lennard et al. 1982) PMs showed significant residual β-blockade 24 hours later, but this was not evident in EMs. The clinical relevance of these interphenotype differences in β-blockade are probably minimal since clinical response is readily ascertained and dosage adjustments easily made.

In terms of adverse effects, β-blockers are characterized by a relatively high therapeutic ratio. A number of adverse effects have been hypothesized to be a particular feature of PMs but objective evidence is lacking. Alvan et al. (1982) have suggested that PMs are likely to develop unusually high levels of certain β-blockers and, therefore, be at risk of concentration dependent side-effects such as bradycardia. In the Norwegian study, on the use of β-blockers to prevent recurrences of myocardial infarction, 3% of the patients receiving timolol dropped out due to unacceptable bradycardia (Norwegian Multicentre Study Group 1982). Whether or not these affected individuals were PMs is unknown but would be interesting to ascertain. The incidence of drop-outs in this trial was of the same order as the incidence of the PM phenotype in Sweden (Alvan et al. 1982). It has also been hypothesized that the cardioselective properties of some β-blockers might be lost in PMs. Cardioselectivity is a relative property which might be lost if high plasma concentrations are achieved in PMs as opposed to EMs as is possible with metoprolol. Once again objective evidence for this has not been published.

Disturbance of the central nervous system including hallucinations, nightmares, lassitude and depression have been reported by patients receiving β-blockers (Greenblatt and Koch Weser 1973; Greenblatt and Shader 1972). Recent studies suggest that CNS related side-effects are more commonly seen with the lipophilic β-blockers than with their hydrophilic counterparts (Betts and Alford 1983; Westerlund 1982, 1983; Cove-Smith 1983).

Whether or not the development of CNS disturbances with lipophilic β-blockers is concentration dependent is unknown but if this is the case then PMs may be at greater risk than EMs.

Another hypothetical situation that should be mentioned is that of drug interactions arising from the polymorphic drug oxidation system. It is now clear that a number of drugs that are substrates for the polymorphic debrisoquine hydroxylation cytochrome P-450 pathway compete with one another for metabolism by this enzyme system (Idle and Smith 1984). In the case of β-blockers, propranolol has been shown to inhibit the 10-hydroxylation of nortiptyline, a substrate for polymorphic metabolism (Boobis et al. 1982; von Bahr et al. 1982). Debrisoquine itself is a competitive inhibitor of the metabolic hydroxylation of bufuralol (Boobis et al. 1983). Unpublished volunteer studies from our own laboratory indicate that oral doses of propranolol, but not atenolol, can interact with debrisoquine oxidative metabolism. It remains an interesting question, therefore, as to whether or not the use of certain lipophilic β-blockers concomitantly with other polymorphically handled drugs may shift the pattern of metabolism towards the saturable type.

## Conclusions

Although β-blockers are structurally closely related, there are marked differences in the extent to which they are metabolized. This appears to be influenced by their relative lipophilicity. Hydrophilic β-blockers such as atenolol, nadolol and practolol are minimally metabolized whereas their lipophilic counterparts, such as propranolol and metoprolol undergo extensive biotransformation. Lipophilic β-blockers are metabolized by a common cluster of metabolic reactions, which, in the main, involve C-oxidative pathways such as aromatic hydroxylation, *O*- and *N*-dealkylation, as well as metabolic conjugation with glucuronic acid. Metabolic transformation of the lipophilic β-blockers is important since it: (1) is a major determinant of their pharmacokinetic disposition; (2) can result in the formation of active metabolites; (3) may be stereoselective and therefore show isomer preference; and (4) exhibits considerable interindividual variation.

The source of metabolic variation of the lipophilic β-blockers has not been fully defined. However, for some lipophilic β-blockers, namely, propranolol, metoprolol, timolol and bufuralol, their oxidative clearance is regulated/influenced by the debrisoquine hydroxylation gene locus. Their metabolism in the population, therefore, at least in part, exhibits

polymorphic characteristics. Significant interphenotype differences (extensive metabolizers, EMs versus poor metabolizers, PMs) with respect to the pharmacokinetic disposition (relative bioavailability, peak plasma levels, plasma terminal t½ values) have been demonstrated for metoprolol, timolol and bufuralol. Similarly, interphenotype differences with respect to β-blockade have been shown to occur with metoprolol and timolol and for toxicity with bufuralol. The interphenotype difference in cardiovascular response to β-blockers is probably of little clinical consequence since clinical response can be readily determined and appropriate change in dosage made.

A number of adverse effects of lipophilic β-blockers have been hypothesized to be a particular feature of the PM phenotype. While these theories are plausible, objective evidence is on the whole lacking. Examples of such suggested phenotype (PM) related toxicity include: the occurrence of unacceptable bradycardia; loss of cardioselectivity; greater risk of CNS related side-effects; and drug interactions arising from the concomitant use of other drugs that are also metabolized by the same polymorphic system.

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# Group Discussion

*C. T. Dollery*

Regarding the penetration of these drugs into the brain, I have always believed that lipid solubility was probably a determinant of the rate of transit into the brain and of the ultimate equilibrium concentration. Presumably by maintaining a concentration gradient for a long time a drug will eventually penetrate into the brain. However, Dr. Cruickshank's data showed that atenolol, even when dosed chronically, appeared in the CSF but at a much lower concentration than was measured simultaneously in plasma, apparently without protein binding being a factor. Do you think my concept, that things will penetrate in the end if you maintain the concentration, is right or wrong?

*R. L. Smith*

With lipophilic β-blockers, you are dealing with drugs with very large volumes of distribution. There are differences between tissues. For instance, the lung is a tissue that will take up these materials to a large degree. The brain shares in that property to some extent. However, with the very polar β-blockers, such as atenolol, even though you put intense pressure upon them in terms of concentration gradients it is extremely difficult to push them into certain tissues. I would make one point. Dose is not equivalent to exposure, and I would be happier to see evidence that trialists are attempting to measure actual exposure by assessing for example plasma levels in their comparative trials.

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Can drugs be used to change the pattern of slow metabolizer status to extensive metabolizer status?

*R. L. Smith*

In phenotypically extensive metabolizers certain drugs (e.g. metoprolol, dextropropoxyphene) when given concurrently with debrisoquine or phentormin will compete metabolically and the metabolic ratio can be pushed towards that of a poor metabolizer. The reverse process, that of producing a phenocopy by pushing poor metabolizers into extensive metabolizers, has not been achieved. Various attempts have been made to use selective enzyme inducers, such as rifampicin and phenobarbitone, but as yet it has not proved possible to induce a poor metabolizer.