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Clinical significance of the sparteine/debrisoquine oxidation polymorphism

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Summary. The sparteine/debrisoquine oxidation polymorphism results from differences in the activity of one isozyme of cytochrome P450, the P450db1 (P450 IID1). The oxidation of more than 20 clinically useful drugs has now been shown to be under similar genetic control to that of sparteine/debrisoquine. The clinical significance of this polymorphism may be defined by the value of phenotyping patients before treatment. The clinical significance of such polymorphic elimination of a particular drug can be analyzed in three steps: first, does the kinetics of active principle of a drug depend significantly on P450db1?; second, is the resulting pharmacokinetic variability of any clinical importance?; and third, can the variation in response be assessed by direct clinical or paraclinical measurements? It is concluded from such an analysis that, in general, the sparteine/debrisoquine oxidation polymorphism is of significance in patient management only for those drugs for which plasma concentration measurements are considered useful and for which the elimination of the drug and/or its active metabolite is mainly determined by P450db1. At present, this applies to tricyclic antidepressants and to certain neuroleptics (e.g. perphenazine and thioridazine) and antiarrhythmics (e.g. propafenone and flecainide). Phenotyping should be introduced in to clinical routine under strictly controlled conditions to afford a better understanding of its potentials and limitations. The increasing knowledge of specific substrates and inhibitors of P450db1 allows precise predictions of drug-drug interactions. At present, the strong inhibitory effect of neuroleptics on the metabolism of tricyclic antidepressants represents the best clinically documented and most relevant example of such an interaction.

Key words: sparteine, debrisoquine, pharmacogenetics; oxidation polymorphism, clinical significance, oxidative drug metabolism, genetic control

Pharmacogenetics is concerned with the contribution of genetic factors to the variability of response to drugs. The impact of specific genetic factors is determined by the relative contribution of non-genetic constitutional factors, such as age, disease and environment.

To date, genetic factors affecting pharmacokinetics, in particular drug metabolism, have been the most extensively studied and best documented area of interest. The cDNAs for a number of important human drug receptors have recently been cloned (Frielle et al. 1987; Webb et al. 1987), and it should now be possible to study in a broader context the importance of genetic factors in pharmacodynamic variability.

Hepatic oxidation is by far the most important route of drug metabolism modifying the biological activity of drugs. The discovery of a common genetic polymorphism in the oxidation of debrisoquine and sparteine (Mahgoub et al. 1977; Eichelbaum et al. 1979a) created new interest in the role of pharmacogenetics in clinical pharmacotherapy. The population segregates into two phenotypes with respect to the oxidation of sparteine and debrisoquine. In Caucasians about 7% are classified as phenotypically poor metabolizers (PM) and the remainder as extensive metabolizers (EM) (Steiner et al. 1988b). The frequency of the PM phenotype appears to be markedly lower in non-Caucasian

Table 1. Pharmacokinetic consequences of polymorphism for drugs eliminated via the sparteine/debrisoquine oxygenase, P450db1

Biotransformation	Consequence for poor metabolizers	Drug	Reference
$D \overset{*}{\Rightarrow} M_a$	*1. Accumulation of drug, D*	Beta-blockers	
$\downarrow$		Metoprolol	Lennard et al. 1983
M_b		Timolol	Lewis et al. 1985
		Bufuralol	Dayer et al. 1985
		Antiarrhythmics	
		Sparteine	Eichelbaum et al. 1979b
		N-propylajmaline	Zekorn et al. 1985
		Propafenone	Siddoway et al. 1987
		Flecainide	Beckmann et al. 1988
		Tricyclic antidepressants	
		Nortriptyline	Bertilsson et al. 1980
		Desipramine	Bertilsson and Åberg-Wistedt 1983
		Clomipramine	Balant-Gorgia et al. 1986**
		Neuroleptics	
		Perphenazine	Dahl-Puustinen et al. (in press)
		Thioridazine	von Bahr et al. (in press)
		Miscellaneous	
		Debrisoquine	Sloan et al. 1983
		4-Hydroxyamphetamine	Kitchen et al. 1979**
		Phenformin	Oates et al. 1983
		Amiflamine	Alvan et al. 1984
		Perhexiline	Cooper et al. 1987
		Dextromethorphan	Schmid et al. 1985**
		Guanoxan	Sloan et al. 1978**
		Indoramin	Pierce et al. 1987
		Methoxyphenamine	Roy et al. 1985
		CGP 1S 21OG	Gleiter et al. 1985
	2. Reduced formation of active metabolite, M_a	Encainide (active metabolite O-desmethylencainide)	Wang et al. 1984
	3. Increased formation of toxic metabolite, M_b	No known examples	
$D \Rightarrow M_a$	*4. Reduced formation of*	Codeine	Dayer et al. 1988
$\overset{*}{\downarrow}$	*active metabolite M_b*	(active metabolite: morphine)	
M_b			
$D \Rightarrow M_a$	*5. Accumulation of*	Imipramine	Brøsen et al. 1986a+b
$\overset{*}{\downarrow}$ $\Downarrow^*$	*active metabolite, M_a*	(active metabolite: desipramine)	
M_b M_c			
$D \overset{*}{\Rightarrow} M_a$	*6. Accumulation of drug, D,*	Amitriptyline	Mellström et al. 1983
$\overset{*}{\downarrow}$ $\Downarrow^*$	*and active metabolite, M_a*	(active metabolite: nortriptyline)	Baumann et al. 1986
M_b M_c			

$\Rightarrow$: important pathway; $\rightarrow$: less important pathway; *: pathway catalyzed by the P450 which oxidizes sparteine and debrisoquine; **: only urine data available

populations (Nakamura et al. 1985; Lou et al. 1987; Iyun et al. 1986). PM are homozygous for an autosomal recessive allele, and EM comprise heterozygotes and homozygous dominants (Evans et al. 1980; Steiner et al. 1985). It has recently been shown that the so-called recessive allele exists in several forms (Gonzalez et al. 1988). It is not yet clear if the existence of multiple mutated alleles can explain some of the pronounced variability in drug clearance seen within the EM phenotype (Brøsen et al. 1986a).

The sparteine/debrisoquine oxidation polymorphism is a reflection of differences in the activity of a specific isozyme of cytochrome P-450, P450db1 (or P450IID1, Nebert et al. 1987; or P450bufI, Zanger et al. 1988). Recent studies strongly suggest that P450db1 is absent altogether in PM, but other P450s may contribute to a minor extent to the oxidation of at least some compounds that are mainly dependent on P450db1 for elimination (Boobis et al. 1983; Zanger et al. 1988; Gonzalez et al. 1988).

The sparteine/debrisoquine oxidation polymorphism has a strong impact on the metabolism of several drugs in patients, notably the tricyclic antidepressants (Bertilsson et al. 1980, Mellström et al. 1983; Bertilsson and Åberg-Wistedt 1983; Brøsen et al. 1986a, b), metoprolol (Lennard et al. 1983), propafenone (Siddoway et al. 1987), flecainide (Beckmann et al. 1988), and certain neuroleptics (Dahl-Puustinen et al., in press; von Bahr et al., in press).

Another drug oxidation polymorphism that has been revealed in studies of the 4-hydroxylation of S-mephenytoin (Küpfer and Preisig 1984) is related to the activity of a different isozyme of P450 (P450meph, Meyer et al. 1986). P450meph also oxidizes mephobarbital (Küpfer and Branch 1985), hexobarbital (Knodell et al. 1988) and is partially responsible for the elimination of diazepam and N-desmethyldiazepam (Bertilsson et al., in press). The broader clinical significance of the mephenytoin polymorphism has yet to be established.

The discovery of genetic polymorphism of drug oxidation has had a considerable impact on experimental and biochemical research on drug metabolism. In contrast, its impact on the clinical use of therapeutics is still limited. The clinical perspective of the sparteine/debrisoquine oxidation polymorphism is reviewed here.

Clinical significance of the sparteine/debrisoquine oxidation polymorphism

Interindividual variation in drug metabolism is inevitable, but is often inconvenient from a clinical point of view. Genetic polymorphism is a special case, in which most variability is due to genetic inheritance (Steiner et al. 1985). This should not be regarded as a particular disadvantage, since it should be possible to predict the optimal treatment or dosage from the patient's phenotype. The significance of the sparteine/debrisoquine oxidation polymorphism in clinical use of a particular drug would be demonstrated if the value were accepted of routinely phenotyping patients prior to treatment. The clinical significance of polymorphic drug oxidation in relation to a particular drug would require, first, that the kinetics of the drug was significantly dependent on P450db1, second, that the resulting pharmacokinetic variability was of clinical importance and, third, that the interindividual variability in response could not be determined by direct clinical or paraclinical measurements. The latter two points are in fact characteristics of drugs for which plasma level monitoring is also considered useful.

Table 2. Drugs which have been shown not to be eliminated via the sparteine/debrisoquine oxygenase (P450db1)

Drug	Reference
Amobarbital	Inaba et al. 1980
Antipyrine	Danhof et al. 1981
Metaqualone	Oram et al 1982
Ethinyloestradiol	Back et al. 1984
Theophylline	Dahlqvist et al. 1984
Propranolol[a]	Lennard et al. 1984
Mephenytoin	Küpfer and Preisig 1984
Maprotiline	Gabris et al. 1985
Carbamazepine	Eichelbaum et al. 1985
Tolbutamide	Miners et al. 1985
Pinacidil	Shaheen et al. 1986
Quinidine	Mikus et al. 1986
Nifedipine	Beerahee et al. 1987
Phenytoin	Steiner et al. 1987
Prazosin	Lennard et al. 1988
Haloperidol	Gram et al. 1988
Codeine[b]	Dayer et al. 1988
Cyclosporine	Kronbach et al. 1988[c]
Diazepam N-desmethyldiazepam	Bertilsson et al. (in press)
Midazolam	Kronbach et al. (personal communication)[c]

[a] 4'-hydroxylation of propranolol, a minor pathway, is impaired in poor metabolizers

[b] O-demethylation, a minor but important pathway is impaired in poor metabolizers (see text)

[c] Demonstrated in human liver microsome preparations in vitro

Drug elimination and P450db1

Sparteine, debrisoquine or dextromethorphan (Schmid et al. 1985) may be used for the phenotyping procedure. A PM subject is defined as one in whom the metabolic ratio (MR = amount of parent compound/amount of metabolite) in an 8–12 h urine sample is >20 for sparteine (Eichelbaum et al. 1982), >12.6 for debrisoquine (Evans et al. 1980) or >0.3 for dextromethorphan (Schmid et al. 1985).

The pharmacokinetic significance of P450db1 depends on its relative contribution to the overall elimination (clearance) of the drug (Jackson et al. 1986). The phenotype can predict the overall elimination of a drug or active metabolite when they are substrates for P450db1, and elimination via alternative isozymes of P450, non-oxidative metabolism or excretion unchanged does not occur to any significant extent in the EM. These criteria are largely met for the drugs listed in Table 1. For the drugs listed in Table 2 no such difference in total clearance between EM and PM has been shown. It may be inferred, therefore, that these drugs are oxidized by dif-

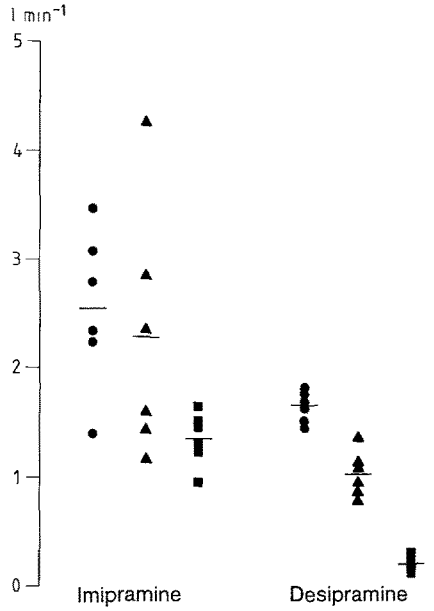

Fig. 1. Apparent clearance of imipramine and desipramine after a single oral dose of 100 mg of both drugs on separate occasions. 100 mg in 6 rapid extensive metabolizers (●), 6 slow extensive metabolizers (▲) and 6 poor metabolizers (■). (Data from Brøsen et al. 1986a)

ferent isozymes of P450, and, in consequence, the sparteine/debrisoquine oxidation polymorphism should not be expected to be of any significance for their clinical use. Codeine, however, is an exception to this statement; in EM a maximum of 10% of codeine is O-demethylated to morphine, which is believed to be the active analgesic component. O-Demethylation is catalyzed by P450db1 (Dayer et al. 1988), and this explains why codeine has no analgesic effect in PM (P. Dayer, personal communication).

Biotransformation of the drugs listed in Table 1 is markedly reduced in PM, and total clearance typically is about five times lower in PM than in EM (e.g. desipramine; Fig. 1). the difference is less pronounced when the drug is only partly oxidized by P450db1 (e.g. imipramine; Fig. 1).

Steiner (1985) showed that genetic inheritance accounted for as much as 80% of the total variability in debrisoquine MR. This is an unusually high degree of genetic contribution, but it is important to realize that a number of confounding factors in the individual patient may alter the relative importance of P450db1 in the overall elimination of a given drug (Table 3).

Selective induction of P450db1 in EM (1.1, Table 3) will exaggerate the difference in metabolic clearance between phenotypes. However, enzyme inducers have only a limited effect on the elimination of drugs that are largely dependent on P450db1 for their clearance (Eichelbaum et al. 1986).

Conversely, induction of alternative drug metabolising enzymes will reduce the relative contribution of P450db1, and so may obscure the effect of the genetic polymorphism (2.1, Table 3). This has been suggested as an explanation for the effect of cigarette smoking on amitriptyline demethylation (Mellström et al. 1983).

The phenotypic difference may also be reduced or abolished by functional impairment of P450db1 in EM (Table 3); for example, quinidine is a very potent competitive inhibitor of sparteine oxidation in human liver microsomes in vitro (Otton et al. 1984) and the in vivo metabolism of sparteine and debrisoquine is almost completely abolished in patients treated with quinidine (Brinn et al. 1986; Speirs et al. 1986; Brøsen et al. 1987). Hence, an EM would appear to change to phenotypical PM, and the underlying genetic variation in metabolism would be completely lost (2.2, Table 3). Similar findings have been reported during treatment with thioridazine, levomepromazine, and propafenone (Syvählahti et al. 1986; Siddoway et al. 1987). Phenotyping during treatment with a potent inhibitor is uninformative.

The activity of P450db1 is also impaired by tricyclic antidepressants and some neuroleptics, but not to such an extent that the EM phenotype appears to change to PM (Nordin et al. 1985; Brøsen et al. 1986b; Gram et al., 1989). Such weak inhibitors may still contribute to the pharmacokinetic variability found in EM subjects.

Another functional characteristic of P450db1 appears to be non-linear kinetics for some drugs in EM but linear kinetics in PM (2.3, Table 3). With oral dosing this probably reflects saturation of P450db1 during the first pass through the liver (Brøsen and Gram 1988). The apparently much higher Michaelis-constant, K_m, for bufuralol-oxidation found in PM than EM (Dayer et al. 1984) probably reflects the activity of a different isozyme of P450, for which saturation would not be a problem at the drug concentrations or doses yielding saturation in EM. As a consequence, the difference in clearance between phenotypes is reduced but not extinguished when

Table 3. Pharmacokinetic factors that theoretically can alter the relative significance of the sparteine/debrisoquine oxygenase (P450db1) for the elimination of a particular drug

1. Increased significance of P450db1
1.1. Selective induction of P450db1 in extensive metabolizers (not important)
2. Decreased significance of P450db1
2.1. Induction of alternative P450's
2.2. Inhibition of P450db1
2.3. Saturation of P450db1

the dose is increased, as has been shown for propafenone (Fig. 2; Siddoway et al. 1987).

Stereoselective metabolism is another important characteristic of P450db1. Metoprolol is administered as the racemate, and in EM the inactive R-enantiomer is metabolized faster than the active S-enantiomer, whereas metabolism is not stereoselective in PM (Lennard et al. 1983). Accordingly, the difference in plasma concentrations between phenotypes is smaller for the active S-enantiomer than for the inactive R-enantiomer (Fig. 3).

For most of the drugs listed in Table 1 it is well documented that their oxidation co-segregates with that of sparteine and debrisoquine. However, the demonstration of a genetic polymorphism in drug oxidation requires both family and population studies, which so far have been carried out only with a limited number of these compounds.

Role of the sparteine/debrisoquine oxidation polymorphism in drug therapy

Most studies in this field have established an association between a polymorphic drug oxidation phenotype and some pharmacokinetic measurements for a given drug. Before the sparteine/debrisoquine oxidation polymorphism can be considered to be of clinical significance in drug therapy, however, several additional characteristics of the drug should be considered.

Several of the drugs in Table 1 with established polymorphic metabolism are either obsolete or unimportant. As a general rule, a genetic polymorphism will have clinical relevance only for drugs that are widely available.

Second, the pharmacodynamic properties of the drug must be considered. Some drugs have a wide therapeutic plasma concentration range (i.e. a large therapeutic index), and may therefore be prescribed in standard doses without problems, evens if genetic polymorphism in their metabolism results in significant pharmacokinetic variability. Some drugs may have a small therapeutic index, but their dose is easily titrated on the basis of clinical or paraclinical effects. In both cases neither phenotyping nor direct assessment of the pharmacokinetic variability is necessary. The beta-adrenoceptor antagonists, metoprolol and timolol may be considered to fulfil both these requirements (Table 4), although it is not yet known whether a chronically elevated plasma level of a beta-adrenoceptor antagonist during long-term treatment may harm the PM patient.

The potential clinical importance of the sparteine/debrisoquine oxidation polymorphism is associated with those drugs for which assessment of pharmacokinetic variability (by drug level monitoring) is important. Such drugs are characterized by a low therapeutic index and the lack of means to titrate the dose on the basis of immediate measures of effect. For drugs with a metabolism that cosegrate with the sparteine/debrisoquine oxidation polymorphism, this applies to tricyclic antidepressants (Gram et al. 1984), neuroleptics (Dahl 1986), and possibly to flecainide and propafenone (Table 4).

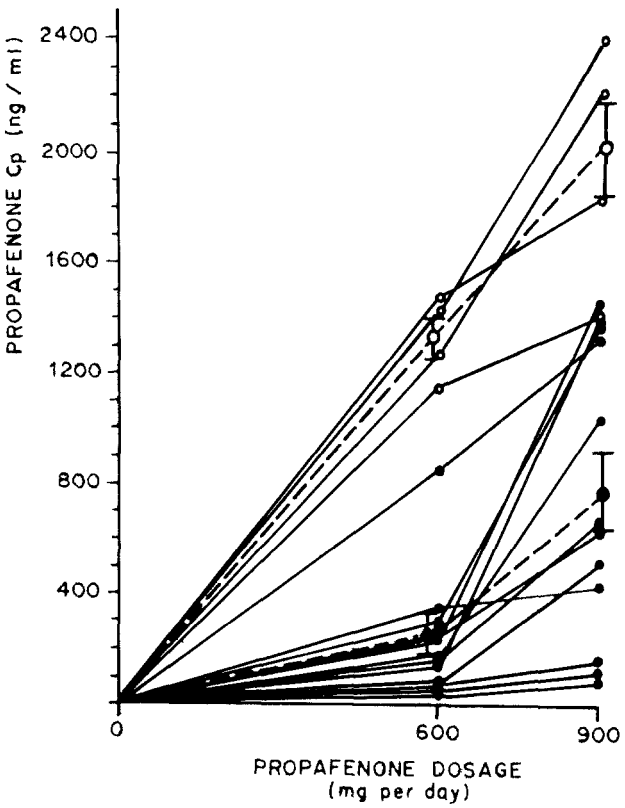

Fig. 2. Relationship between daily propafenone dose and trough plasma concentration during steady-state in 13 extensive metabolizers (●) and 4 poor metabolizers (○). After Siddoway et al. 1987 (with permission from author and publisher) $\tilde{\bar{x}} \pm$ SEM

For tricyclic antidepressants there are two patient groups at risk (Fig. 4). One group comprises PM and slow EM subjects. If given the standard recommended doses these patients will develop toxic plasma concentrations (Fig. 4). The other group comprises rapid EM, who suffer therapeutic failure because the attained plasma concentrations are far too low (Fig. 4). At least 20–30% of patients belong to these risk groups (Brøsen et al. 1986b). Side effects during the therapeutic use of tricyclic antidepressants are rarely, if ever, life-threatening, but they are often so unpleasant (dry mouth, sedation and tremor) that the treatment is stopped. Toxic reactions may be misinterpreted as symptoms of depression or

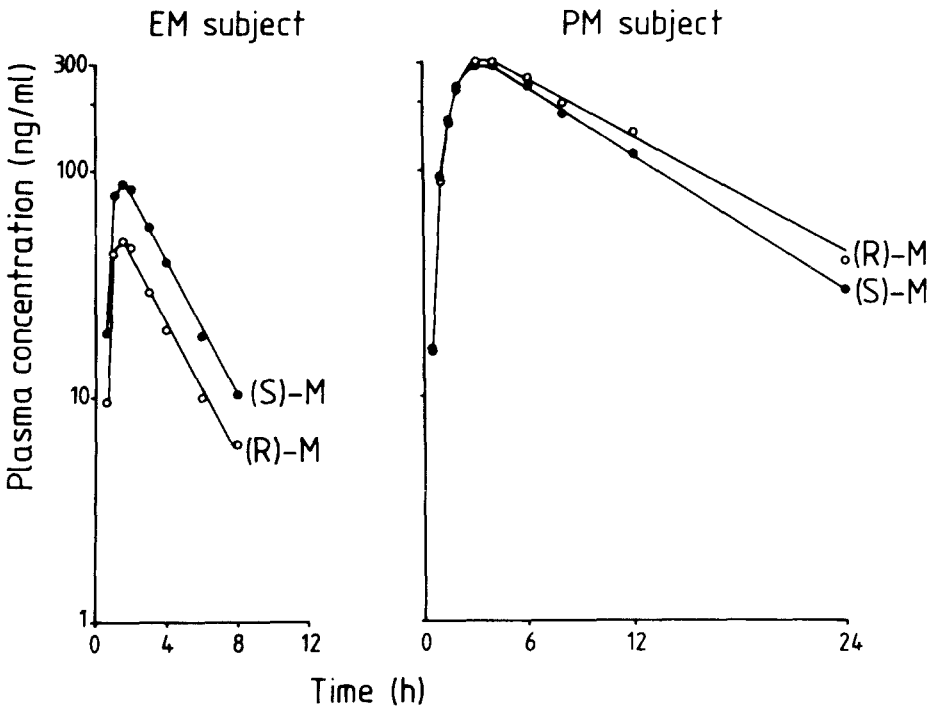

Fig. 3. Log plasma concentration-time curve for S-metoprolol (S)-M and R-metoprolol (R)-M after 200 mg metoprolol by mouth in 1 extensive metabolizer and one poor metabolizer of debrisoquine. After Lennard et al. 1983. (With permission from author and publisher)

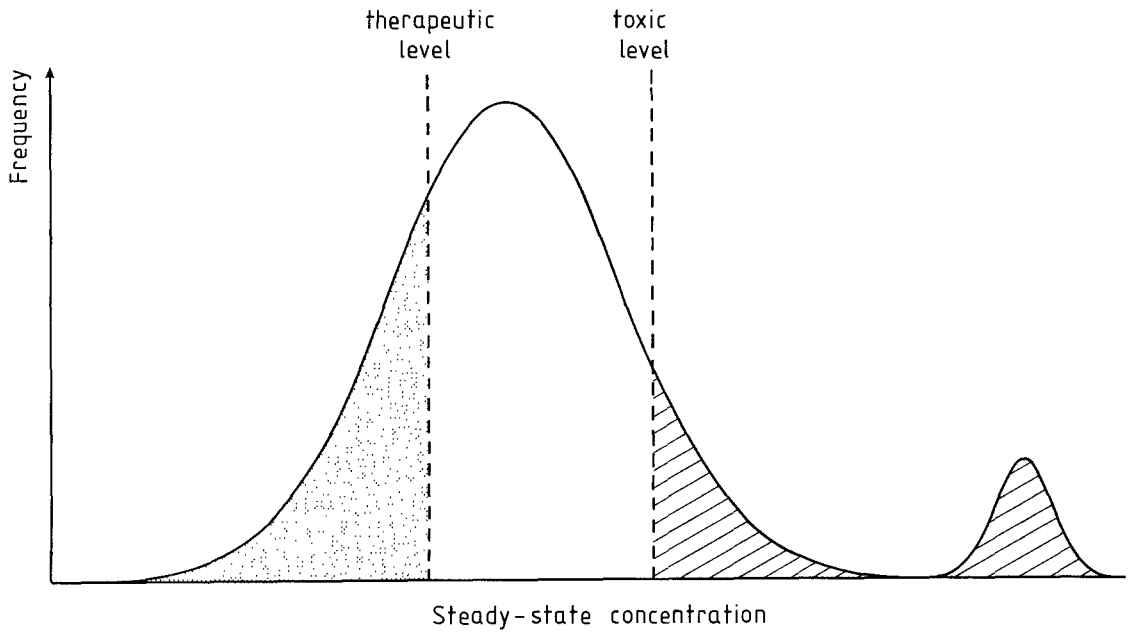

Fig. 4. Theoretical distribution of steady-state concentration during treatment with a fixed dose of a drug of which the metabolism is exclusively dependent on sparteine/debrisoquine oxygenase (P450db1). Higher mode poor metabolizers; lower mode extensive metabolizers. ▨, therapeutic failure; □, improvement; ▨, toxicity

may occur as clear CNS-toxicity at drug levels only 50–100% above the therapeutic plasma concentration (Preskorn, in press). The clinical picture both in the rapidly and slowly metabolizing patients is therefore much the same: recurrent depressive episodes not responding to treatment due to lack of dose individualization (Bertilsson et al. 1985; Sjöqvist and Bertilsson 1986).

In a recent study, the dose of imipramine required to produce a therapeutic plasma concentration (imipramine plus desipramine: 700–900 nM) ranged from 50 to 400 mg per day in 32 EM patients, and in two PM it was 50 mg per day (Brøsen et al. 1986b). The therapeutic dose did not exhibit distinct bimodality but the PM subjects represented the

lower extreme. The correlation between the dose and the sparteine or debrisoquine MR was relatively weak, although statistically significant. Phenotyping was useful mainly in separating EM and PM, but it coult not replace drug plasma concentration monitoring to achieve the target concentration. However, dosing according to phenotype or metabolic ratio would have yielded less variability in steady state level than use of a standard dosing scheme. The weak correlation was due to the activity of alternative isozymes of P450 for demethylation, and possibly for hydroxylation, and confounding factors such as dose-dependent kinetics (Table 4) and non-metabolic variation in MR.

Drug-drug interactions related to selective inhibition of the P450db1 isozyme

The testing of different drugs for their ability competitively to inhibit the oxidation of sparteine, debrisoquine, desipramine or bufuralol in vitro has proven to be a useful primary screening procedure (Boobis et al. 1983; Otton et al. 1984; Inaba et al. 1985; von Bahr et al. 1985; Fonne-Pfister and Meyer 1988). A compound not inhibiting oxidation of the model drug can be excluded as a substrate for P450db1, whereas a compound that does competitively inhibit it may be a substrate of P450db1. Some of these inhibitors, e.g. quinidine, propafenone and certain neuroleptics (Table 5) are very potent, with inhibitor constant values (K_i) in the nanomolar or low micromolar range.

Thus, the P450db1 may be the site for important and predictable drug-drug interactions. This aspect may turn out to be as important clinically as the genetic polymorphism. Several studies in vitro and in vivo have shown that quinidine is a selective inhibitor of the P450db1 (Table 5). Since P450db1 is absent from the livers of PM (Zanger et al. 1988), it is understandable that the relative impairment of oxidation is more pronounced in EM than in PM (Brinn et al. 1986; Steiner et al. 1988a). The picture may become even more complicated if a potent inhibitor like propafenone (Tables 1 and 5; Fig. 2) is also eliminated by P450db1, because PM then develop much higher inhibitor concentrations than EM when the same dose is given. At higher inhibitor concentrations there may be significant inhibition of other P450 isozymes as well. It is likely that this could explain the drug concentration-related adverse reactions in a PM during combined treatment with metoprolol and propafenone (Wagner et al. 1987b).

When potent inhibitors like quinidine or propafenone are added to treatment with a polymorphically oxidized drug (Table 1), the pharmacokinetics are indistinguishable from those observed in PM, which means in practice that the plasma concentration may increase about five-fold (Wagner et al. 1987a; Brøsen and Gram, accepted).

The clinical significance of such interactions depends on the frequency of the drug combination, the role of P450db1 in overall elimination of the drug, the potency of the inhibition, the clinical consequences of a raised plasma drug level (therapeutic index), and the feasibility of clinical dose titration.

It was reported several years ago that neuroleptics strongly inhibited, the metabolism of tricyclic antidepressants (Gram and Overø 1972; Gram 1975) and this has subsequently been confirmed by several

Table 4. Non-pharmacokinetic factors determining the clinical significance of the sparteine/debrisoquine oxidation polymorphism for drug known to be eliminated via P450db1

Drug	Important and widely available	Plasma concentration monitoring recommended?	Conclusion: possible clinical significance
Metoprolol	Yes	No	No[a]
Timolol	Yes	No	No
Bufuralol	No	No	No
Sparteine	No	No	No
N-Propylajmaline	No	Yes[b]	No
Propafenone	Yes	Yes[c]	Yes
Flecainide	Yes	Yes	Yes
Nortriptyline	Yes	Yes[d]	Yes
Desipramine	Yes	Yes[d]	Yes
Clomipramine	Yes	Yes[d]	Yes
Imipramine	Yes	Yes[d]	Yes
Amitriptyline	Yes	Yes[d]	Yes
Debrisoquine	No	No	No
4-Hydroxyamphetamine	No	No	No
Phenformin	No	No	No
Amiflamine	No	No	No
Perhexilline	No	No	No
Dextromethorphan	Yes	No	No
Guanoxan	No	No	No
Indoramin	No	No	No
Methoxyphenamine	No	No	No
CGP 1S 210G	No	No	No
Encainide	No	No	No
Perphenazine	Yes	Yes[e]	Yes
Thioridazine	Yes	Yes[e]	Yes

[a] see Clark et al. 1984; [b] for discussion, see Zekorn et al. 1985; [c] see Siddoway et al. 1987; [d] see Gram et al. 1984; [e] see Dahl 1986

Table 5. Drugs known to be potent inhibitors of P450db1 function in human liver in vitro and in vivo

Inhibitor	Inhibition				
	In vitro			In vivo	
	Substrate	K_i nM	Reference	Substrate	Reference
Antiarrhythmics:					
Quinidine	Sparteine	60	Otton et al. 1984	Metoprolol	Leeman et al. 1986
	Desipramine	270	von Bahr et al. 1985	Sparteine	Brinn et al. 1986
	Bufuralol	150[a]	Zanger et al. 1988	Debrisoquine	Brøsen et al. 1987
	Codeine	15	Dayer et al. 1988	Desipramine	Steiner et al. 1988
Propafenone	Debrisoquine	700	Siddoway et al. 1987	Debrisoquine	Siddoway et al. 1987
	Bufuralol	50[a]	Kroemer et al. 1989	Metoprolol	Wagner et al. 1987a
Neuroleptics:					
Chlorpromazine	Sparteine	7000	Inaba et al. 1985	Nortriptyline, Imipramine	Gram and Overø 1972
Haloperidol	Sparteine	1000	Inaba et al. 1985	Sparteine	Gram et al. 1989
Thioridazine	Desipramine	750	von Bahr et al. 1985	Desipramine	Hirschowitz et al. 1983
				Debrisoquine	Syvählahti et al. 1986
Fluphenazine	Bufuralol	1030[a]	Fonne-Pfister and Meyer 1988	Imipramine	Siris et al. 1982

[a] Kinetics based on a cumene hydroperoxide-mediated reaction

groups (review by Gram and Brøsen, in press). Neuroleptics are frequently added to antidepressant treatment, in particular in elderly, delusional depressed patients, and the interaction appears to be one of the most clinically important drug-drug interactions in relation to the P450db1 isozyme (Gram et al. 1984). Codeine is a special case (Table 2), because no morphine will be formed in EM during combined treatment with quinidine and presumably other potent inhibitors (P. Dayer, personal communication).

Conclusion

The sparteine/debrisoquine oxidation polymorphism is a determinant of the extremes in pharmacokinetic variability of several clinically useful drugs. This monogenically determined variability becomes clinically significant only in those cases where pharmacokinetic variability is considered important relative to the efficacy and clinical safety of the drug. This mean in essence that it is applicable to those drugs for which plasma concentration monitoring is considered useful, and at present the list includes tricyclic antidepressants, certain neuroleptics and possibly flecainide and propafenone. Codeine and possibly other prodrugs, which depend on P450db1 for their conversion to an active metabolite, are exceptions to this general rule. The mere demonstration of genetic polymorphism in the oxidation of a new drug should not of itself lead to discontinuation of its development (Balant et al., in press), nor should detection of genetic polymorphism in the oxidation of a drug which is already on the market lead to discontinuation of its clinical use.

Phenotyping with sparteine, debrisoquine or dextromethorphan before treatment with a tricyclic antidepressant may serve as a safe and simple test to enable clinicians, to select an appropriate initial dose and to reduce interindividual variability in drug concentrations. The test result (MR) is usually not sufficently precise to replace plasma concentration monitoring, but the optimal strategy for blood sampling (time to reach steady-state, dose-dependent kinetics and drug interactions) is different in EM and PM.

Since the test result will apply to several tricyclic antidepressants and phenotyping has to be performed only once in a life-time, the approach should be particularly useful in patients with recurrent depression. Analogous considerations may apply to antipsychotic treatment with neuroleptics, and antiarrhythmic treatment with propafenone and flecainide. As for any clinical test, its introduction into routine use should be implemented under continuous surveillance in a follow-up programme that would ultimately enable our understanding of its potentials and limitations to be refined.

The relative substrate specificity of different cytochrome P450 isozymes affords an opening for new and more rational research on drug-drug interactions. Studies in vitro with microsomal preparations from human liver may be particularly useful in initial screening for interactions of possible clinical importance.

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