Variability in Human Drug Response
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Clinical Aspects of Polymorphic Drug Metabolism

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ABSTRACT

Recent advances in our understanding of the molecular biology and genetic variability of human drug metabolizing enzymes, particularly cytochromes P450, have contributed immensely towards clarifying the pharmacokinetics and pharmacodynamics of many existing drugs, and are increasingly important in the development of new chemical entities. However, while this knowledge has implications for therapeutics, appreciation and application in clinical practice has either been limited or yet to be realised. For example, the debrisoquine polymorphism was discovered 20 years ago, but controlled prospective studies to evaluate its clinical significance are few. The clinical implications of genetic polymorphisms in drug metabolism, as they relate to drug toxicity, and therapeutic failure, are reviewed briefly with specific reference to CYP2D6.

Key words: genetic polymorphism; cytochrome P450; CYP2D6; drug interactions.

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GENETIC POLYMORPHISM IN CYP2D6

It is now 20 years since the observation of distinct bimodality in the frequency distributions of log urinary drug/metabolite ratios of debrisoquine and sparteine led to the discovery of genetic polymorphism in the cytochrome P450 enzyme which was later to be designated CYP2D6 [1-4].

The term 'genetic polymorphism' refers to the inheritance of a trait controlled by a single locus with two alleles, in which the least common allele has a frequency of (arbitrarily) 1% or more. Oxidation by CYP2D6 qualifies as a genetic polymorphism since the PM (poor metaboliser) geno/phenotype occurs in about 7% of Caucasian populations, albeit to a significantly less extent in other racial groups [5,6]. Within the EM (extensive metaboliser) and PM groups further variation occurs in enzyme function as a result of allelic variants,

which does not manifest as distinct modes in the frequency distribution of urinary drug/metabolite ratios [7,8]. At the extreme of the EM distribution gene amplification gives rise to so-called UM's (ultra-rapid metabolisers), these individuals being rare in most Caucasian populations but common in Ethiopians (30%) [9].

PHARMACOKINETIC AND PHARMACODYNAMIC CONSEQUENCES

The pharmacokinetic and pharmacodynamic consequences of the activity of a polymorphic enzyme depend upon whether it mediates metabolism of parent drug or primary metabolite or both, whether parent drug or metabolites or both are active, the overall contribution to clearance from the affected pathway, the potency of active species, and the patency of competing pathways of elimination [10] (Fig. 1).

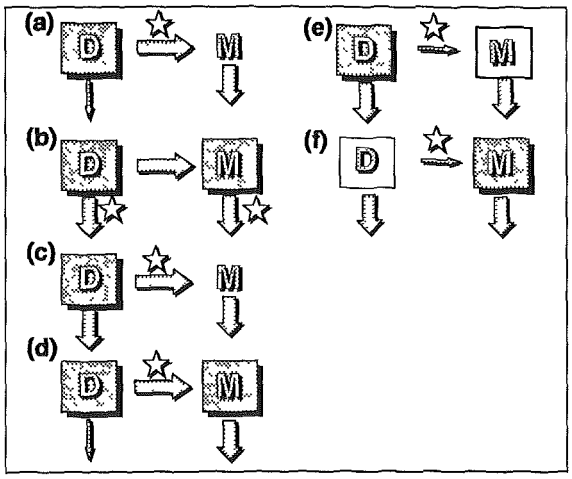

Figure 1. Precursor-product relationships illustrating different pharmacokinetic and pharmacodynamic consequences of polymorphic drug metabolism. [D = parent drug; M = metabolite; large arrow = major pathway; small arrow = minor pathway; star = polymorphic pathway; shaded box = major activity; unshaded box = minor activity; no box = no activity.]

Case (a) in Fig. 1 is where parent drug is the major active moiety and most of its clearance is effected by a polymorphic enzyme. The kinetic consequences of being a PM would be a decrease in first-pass metabolism, increased oral bioavailability and a prolonged elimination half-life. Metoprolol illustrates these features in being converted from a compound with medium to high metabolic clearance in the CYP2D6 EM to a low clearance drug in PM [11]. Accordingly, the latter individuals have more intense and more prolonged β-blockade after standard doses [12]. Case (b) (Fig. 1) is where both drug and metabolite are active and

are metabolised by a polymorphic enzyme, but the conversion from drug to active metabolite is mediated largely by a non-polymorphic enzyme. Imipramine and its metabolite desipramine illustrate these features [13]. Thus, standard doses of imipramine will yield relatively high and low plasma concentrations of both active moieties in CYP2D6 PM and EM subjects, respectively, with implications for therapeutic and toxic response.

Case (c) (Fig. 1) is where the main activity resides in the parent drug and it is cleared principally by both polymorphic metabolism and renal excretion. An example of this is the antiarrhythmic flecainide, the accumulation of which will be particularly marked in PM of CYP2D6 with renal impairment [14].

Case (d) (Fig. 1) is where both drug and a major metabolite produced by a polymorphic enzyme contribute to pharmacological activity. The antiarrhythmics encainide and propafenone illustrate this possibility. Both are metabolised by CYP2D6, the former to the active O-desmethyl product [15] and the latter to the active 5-hydroxy metabolite [16]. In these cases, standard doses in both PM and EM tend to produce similar therapeutic responses because relatively high parent drug concentrations in the former are matched by relatively high active metabolite concentrations in the latter.

Case (e) (Fig. 1) is where the polymorphic enzyme catalyses metabolism through a minor pathway and most activity resides in the parent drug. Thus, although the 4-hydroxylation of propranolol is mediated partly by CYP2D6, this has little influence on the clearance of parent drug and, despite 4-hydroxypropranolol retaining some β-blocking activity, there is no significant difference in response to propranolol in PM and EM [17].

Case (f) (Fig. 1) is where drug is metabolised by a polymorphic enzyme to a quantitatively minor but much more active metabolite. Plasma concentrations of codeine are similar in EM and PM (CYP2D6), but measurable concentrations of morphine, its more analgesic O-demethylation product, are only detectable in EM [18,19].

Inhibition or induction of drug metabolising enzymes may modify the kinetic significance of a polymorphic pathway. There are many examples of drugs that inhibit CYP2D6 whereas there is little evidence, except in association with pregnancy [20], that it is significantly inducible. Clearly, EM subjects will be more susceptible to inhibition interactions than PM's and, when a potent inhibitor is administered (such as quinidine), this can lead to phenocopying (conversion into an apparent PM) [21].

DETERMINANTS OF CLINICAL RELEVANCE

The clinical relevance or otherwise of a genetic polymorphism in drug metabolism will depend upon a number of considerations:

1. For most drugs the polymorphic pathway would need to represent a major contribution to clearance for significant differences in clinical response to be apparent between phenotypes. However, as illustrated in Fig. 1, some active metabolites may be so potent or toxic that a minor polymorphic route has to be considered.

2. Variability in other pharmacokinetic processes and elimination by other routes often causes considerable overlap in unbound plasma drug concentrations between phenotypes receiving the same dose of drug [22]. A difference in genotype or a phenotypic difference in the measurement of a drug to metabolite ratio does not necessarily signify a major difference in plasma drug concentration.

3. Pharmacokinetic differences between phenotypes are most relevant for drugs with low therapeutic indices. For those where variability of plasma concentrations outside the therapeutic range is not associated with dangerous under- or overtreatment, or where usual doses produce effects at the top of the concentration-response relationship in most subjects, polymorphic metabolism will be of less or little concern. However, the perception of what is significant discomfort may differ for patient and doctor when a side-effect is not life-threatening.

4. Pharmacodynamic variability in receptor sensitivity or number or in the turnover of a natural ligand may outweigh any kinetic variability imposed by polymorphic metabolism.

5. If dosage can be titrated by direct clinical monitoring or an alternative drug is available which shows less variability in response, then polymorphic metabolism is of no practical consequence. This does, of course, assume an ideal therapeutic world where patients are not left on homeopathic or toxic doses to suffer or to become noncompliant with treatment!

6. Other risk factors such as drug interactions, the effects of disease on drug disposition and the rare combination of being a PM for more than one enzyme may elevate polymorphic metabolism in the affected individual to clinical significance.

CLINICAL RELEVANCE - IMPLICATIONS AND EVIDENCE

The potential clinical significance of the CYP2D6 polymorphism relates mainly to drugs acting on the cardiovascular and central nervous systems. Those where the implications are most well-documented are discussed below.

Perhexiline

This is a significant example of polymorphic metabolism causing the clinical demise of an otherwise useful drug. Thus, 50% of patients developing peripheral neuropathy while taking this antianginal drug were phenotyped retrospectively as PM [23].

β-*Adrenoceptor Antagonists*

Although there are large phenotypic differences in the pharmacokinetics and β-blocking effects of both metoprolol and timolol [24], these agents are generally considered to have high therapeutic indices and are easily titrated to response. Therefore, many dismiss the clinical relevance of polymorphic metabolism in their clinical use. However, while it is true that adverse effects are rarely life-threatening, such effects can cause discomfort leading to poor compliance, and outpatient assessment of response is not always ideal.

A retrospective analysis found no association between adverse effects from metoprolol and CYP2D6 phenotype [25], but controlled prospective studies are lacking. Lewis *et al.* [26] compared fatigue in normal subjects after single doses of metoprolol and atenolol, the biological fate of the latter being independent of polymorphic metabolism. They concluded that subjective fatigue with β-blocker treatment is unrelated to β-blockade as conventionally measured, and is determined mainly by pharmacodynamic factors with relatively little contribution from genetic variation in metabolism. Thus, in the clinical setting, genetic polymorphism may have little discernable influence on side-effects of metoprolol in cross-sectional studies. Nevertheless, the difference in exercise time and fatigue between atenolol and metoprolol, was inversely related to the ability to metabolise debrisoquine. Therefore,

phenotype may have implications for the choice or dose of β-blocker in individual patients. This would also extend to the choice of dosage form. Clearly, prolonged-release preparations would not be necessary in PM subjects [27].

Inadvertent administration to asthmatics of (S)-timolol eye drops, for the treatment of open-angle glaucoma, can cause severe bronchoconstriction. However, following ocular drug administration phenotypic differences in plasma concentrations of timolol were not observed, and it was concluded that the extensive variability in systemic drug absorption from the eye outweighs any effect of oxidation phenotype as a risk factor [28]. The development of more precise ocular delivery systems might necessitate a reconsideration of this conclusion.

Antiarrhythmic Agents

These drugs have low therapeutic indices and for many of them the associated pro-arrythmic effects have rendered the cure far worse than the disease. Thus, for example, the results of the Cardiac Arrhythmia Suppression Trial (CAST) of flecainide and encainide raised substantial doubts about the clinical safety of this class of antiarrythmic [29]. Since the effects of antiarrhythmic agents are closely related to their plasma concentrations, the possibility arises that the increased mortality seen with encainide and flecainide might be related to CYP2D6 phenotype. As explained earlier, decreased renal function may increase the risk of fatal sustained ventricular tachycardia following administration of flecainide to elderly PM patients [30]. The dose of propafenone required to suppress arrhythmias is similar in EM and PM because of the activity of both drug and metabolite. However, PM have a higher incidence of adverse neurological effects. In addition, the S-isomer of propafenone has weak β-blocking activity, possibly constituting a risk in PM patients with heart failure [16].

Antidepressants and Neuroleptics

Evidence for relationships between the plasma concentrations of tricyclic antidepressants and their active metabolites and therapeutic response is contentious. To date it has not been possible to demonstrate that the higher plasma concentrations of the active species in CYP2D6 PM's are associated with greater amelioration of depression [31]. Thus, the diagnosis and severity of disease seem to be more variable than the kinetics. On the other hand, data for adverse effects associated with psychiatric drug use and CYP2D6 status are more convincing. For example, Chen *et al.* [32] found a significantly higher frequency of alleles associated with deficient CYP2D6 activity in depressed patients with adverse drug reactions than in those without such reactions and normal controls.

This issue is further compounded by polypsychopharmacy and its associated drug-drug interactions. Many antipsychotic drugs, particularly the phenothiazine neuroleptics, are potent inhibitors of CYP2D6. Thus, in a population of schizophrenic patients taking these drugs, 50% were found to have undergone phenocopying to become apparent PM's [33]. Indeed, **fixed** combination products containing both tricylic antidepressants and neuroleptics are extremely common, and there is evidence to suggest that prescribers do not lower dosage relative to single drug formulations [34,35]. Furthermore, data from therapeutic drug monitoring (TDM) of plasma nortriptyline concentrations confirm higher levels relative to dose in patients receiving certain neuroleptics compared to tricylic monotherapy. Again, and despite TDM, combination therapy was not associated with dose reduction [36]. In contrast, the effects of tricyclics on plasma concentrations of neuroleptics appear to be much less significant. Thus, for example, considerable overlap was observed in dose-corrected plasma perphenazine

concentrations in EM's, co-treated EM's and PM's [37]. This probably reflects the fact that tricyclics are much weaker inhibitors of CYP2D6 and that the importance of the enzyme with respect to overall clearance of many substrates diminishes at steady-state owing to enzyme saturation.

Combined therapy with tricyclic antidepressants and the newer specific serotonin reuptake inhibitors (SSRI's) has been used in some patients who respond inadequately to tricyclics alone. However, the use of fluoxetine for this purpose has been associated with a number of case reports of massive increases in the plasma concentrations of tricyclics and severe cardiotoxicity [38]. In retrospect, such interactions are now entirely predictable based upon *in vitro* and *in vivo* studies showing that some of the SSRI's are potent CYP2D6 inhibitors [39-41]. Paroxetine has been shown to potentiate the central nervous system side effects of perphenazine
[42].

Ecstasy

The demethylenation of methylenedioxymethamphetamine (MDMA, Ecstasy) is catalysed to a large extent by CYP2D6 , and the downstream products are known to be serotoninergic and dopaminergic toxins [43]. Possible consequences of this for users of Ecstasy are that PM's may be at greater risk of acute toxicity mediated by parent drug, while EM's may be more susceptible to long-term problems because of greater formation of neurotoxic metabolites. There are also implications with regard to interactions between Ecstasy and inhibitors of CYP2D6. Thus, combination with fluoxetine allegedly increases the duration of effect [44]. Patients taking the HIV protease inhibitor ritonavir, a particularly potent inhibitor of CYP2D6 [45], are likely to be at significant risk of acute toxicity. A recent death in such a patient, who allegedly took only two Ecstasy tablets, was associated with plasma concentrations of MDMA more consistent with the ingestion of 20 tablets [46].

Analgesics and Antitussives

Codeine

Objective and subjective measurements of analgesia have shown that codeine increases experimental pain thresholds in EM's but is without effect in PM's, who do not O-demethylate it to morphine [18,19]. This implies that patients who are PM for CYP2D6 and those who are also taking potent inhibitors of the enzyme might gain no benefit from treatment with codeine. Unfortunately, studies on clinical pain to support this hypothesis are currently lacking, although there are reports indicating that the incidence of non-response to codeine is similar to the frequency of PM's [47]. Further investigations in healthy subjects suggested that PM's may be inherently less tolerant to tonic pain than EM's, possibly because of decreased endogenous synthesis of morphine by CYP2D6 in the brain [48]. However, in contrast to the findings with exogenous codeine showing pronounced phenotypic differences in morphine formation, no differences in endogenous morphine and codeine excretion were detected between EM's and PM's [49].

The diminished production of morphine from exogenous codeine in PM's is associated with significantly reduced respiratory, psychomotor and pupillary effects [50], although another study has shown no clear decrease in the frequency and intensity of adverse events in PM's [47]. A greater decrease in gastrointestinal motility following administration of

codeine to EM's compared to PM's has been claimed [51], but the statistical analysis of these data is questionable.

Tyndale *et al.* [52] have shown that the PM genotype offers significant protection against the risk of developing oral opiate-dependence with codeine and its congeners oxycodone and hydrocodone. Thus, amongst 83 patients dependent on these drugs they found no PM's, compared to frequencies of 4% in 276 never-dependent controls and 6.5% in 93 multi-drug dependent patients (estimated odds ratio >7). Such 'pharmacogenetic protection' may have implications for other drugs of abuse, including many of the 'designer amphetamines' which are also substrates of CYP2D6 [43,53,54].

Dihydrocodeine

In quinidine-induced PM's a significant decrease in dihydromorphine formation was not associated with corresponding decreases in experimental pain thresholds, suggesting that this CYP2D6-mediated reaction is not of clinical importance for analgesia [55].

Tramadol

The analgesic effect of this drug in experimental pain models has been shown to be greater in EM's than in PM's, reflecting higher plasma concentrations in the former of the active (+)-O-desmethyl metabolite [56,57].

Dextromethorphan

Although much higher plasma concentrations of dextromethorphan and lower concentrations of conjugated dextrorphan have been observed in PM's compared to EM's following administration of 30mg doses of dextromethorpan, no difference in capsaicin-induced cough frequency was observed [58]. However, these studies need to be repeated using a validated cough model, shown to be responsive to change in the dose of dextromethorphan. The issue of whether the antitussive activity is mediated by parent drug or metabolite remains unresolved, and there are implications for the use of combinations of dextromethorphan (and codeine) with diphenhydramine, an inhibitor
of CYP2D6 [59].

Fenfluramine and Dexfenfluramine

Evidence linking the use of these drugs to an unacceptable incidence of primary pulmonary hypertension and valvular heart disease [60] has led to their recent withdrawal. Since the clearance of dexfenfluramine in CYP2D6 PM's is half that in EM's [61], it is important to establish retrospectively whether there is an overrepresentation of PM's (real and phenocopies) in the patients who developed serious cardiovascular toxicity.

PROSPECTS

So, what are the clinical perspectives with regard to genetic polymorphism in drug metabolism, specifically with respect to CYP2D6? The issue may be separated into a consideration of old and new drugs.

Understanding the impact of genetic polymorphism in drug metabolism is clearly only part of the task of improving existing therapy. In the metabolic context, environmentally evoked

variability in CYP3A4 activity is just as, if not more important than genetic control of CYP2D6 activity. Nevertheless, there is a need for prospective clinical studies to assess safety and efficacy, particularly in relation to those individuals at the extremes of the CYP2D6 spectrum of activity. The problem is that such studies are difficult to fund, and these days (at least in the UK) it is difficult to find clinical pharmacologists to do them. Perhaps a more realistic strategy is through education. Certainly, a glance through the APBI Data Sheet Compendium and the PDR will indicate significant mention of CYP2D6 polymorphism and associated drug interactions. However, whether the average physician knows what cytochrome P450 is and can relate to this information is debatable; the task of flagging it up would seem to be more appropriate for the pharmacist armed with modern information technology. Another possibility is to assess enzyme activity in the individual patient, In terms of phenotyping this would essentially be an add-on or alternative to TDM (Therapeutic Drug Monitoring). But then, of course, outside of some specialist centres, TDM has never really caught on. Alternatively, the zealots of molecular genetics would argue that everybody should be genotyped and, indeed, the technology is now available for rapid microchip typing for many of the mutations of CYPs 2D6 and 2C19. Thus, the Brave New World would involve entering genotypes on a SMART card for each person, which would then flag out recommendations for individual drug therapy to the health care system as and when needed [62]. Currently, at least with regard to CYP2D6, there are two problems with this. Firstly, the instrumentation needed to read the gene chip is affordable only by the pharmaceutical industry and, secondly, genotype does not necessarily predict phenotype and hence enzyme function and clinical outcome. Although genotyping may be prognostic with regard to the dichotomous distinction between enzyme function in EM's and PM's and with respect to gene replication [63], the ability to predict function from knowledge of allelic variants within the large EM envelope appears to be much less precise [7,8,64].

As far as new drugs are concerned, the way forward is much clearer. The *in vitro* technology is well-developed to understand the enzymology of new chemical entities at an early stage in development [65]. If, for example, CYP2D6 proves to be a major player, it might be possible to de-select the compound or to design out significant involvement of the enzyme. Where this is not feasible it is then essential that the safety and efficacy profile be evaluated with respect to geno/phenotype. Studies with tolterodine, a new antimuscarinic agent for the treatment of bladder dysfunction, illustrate this approach, showing that the clinical impact of the CYP2D6 polymorphism is likely to be minimal because of an additive action of parent drug and the active metabolite produced by the enzyme [66]. Progressing into clinical studies, an optimal way of assessing the impact of variability in drug metabolism would be to use geno/phenotypes as a covariates in sparse sampling - population kinetics methodology. Hence, it should be possible to tell the physician (and, indeed, the regulators) prospectively that genetic polymorphism and variability in drug metabolism is or is not clinically important.

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Discussion: Clinical aspects of polymorphic drug metabolism

P. du Souich:
I think the problems are even greater than what you have shown, because we have not considered the patient, and his compliance, or the obsessive patient who will take everything and who will obviously notice and report every potential side-effect. We have not taken into account the time the physician needs to explain and to listen to the patient. Because the real situation is much more complicated than that we have discussed, we are very far away from reaching the right solution.

G.T. Tucker:
My concern here was to present what science has to offer, and make the point that there is also a problem of medical education.

M. Lader:
I would like to defend prescribing in psychiatry by, firstly, agreeing with what was said. There is a great problem in the large variability, but there are other factors interfering. For example, you mentioned schizophrenic patients and neuroleptics. Somewhere between 30 and 40% of schizophrenic patients are co-morbid for drug abuse. There is very little knowledge of this situation, and even less control over which particular medications they are taking. They are also, almost all of them, inveterate heavy smokers, as an additional factor. In practice, in a particular speciality like psychiatry, the practical problems are really quite immense. Not to say they cannot be resolved, but it is going to be one of the later areas of therapeutics where we can really bring in some sort of rationale.

M. Pirmohamed:
In some diseases such as cystic fibrosis, the same genotype with completely different clinical presentations exist. It is possible that there are modifier genes which modify the effect of an individual gene. It the case of CYP2D6, there may be environmental factors operating or modifier genes on completely different chromosomes, which may be affecting its activity. What is your opinion? Secondly, with regard to other drug reactions in CYP2D6, it may be possible to phenotype or genotype individuals for certain type A adverse drug reactions. But when you come to type B adverse drug reactions, the idiosyncratic ones, there may be only very specific few examples where one can genotype. When you look at the more complex type of reactions, for example hepatotoxicity and skin rashes, it seems that there may be multiple genes which are interacting together, plus the environment, to produce the phenotype or the clinical toxicity. Therefore, it becomes very difficult to be able to genotype or phenotype those individuals prospectively, and to be able to predict that they are going to get the reaction.

G.T. Tucker:
Absolutely, I agree that it is not going to be as simple as some may think in terms of genotyping. There are going to be genes that affect other genes and so on until finally we will have a whole array of genes to look at. And the more we look, the more complicated it becomes, in terms of predicting function.

A.J.J. Wood:
One way to remove the variability would be to administer an inhibitor like quinidine, but we never discuss that. Maybe the Spanish are right in having 99% of subjects with a combination therapy. If we gave everybody quinidine with their CYP2D6 substrate, they all would be poor metabolisers, as the variability would be reduced dramatically. Although the problem would not disappear, but at least the dosage would be more rational. Do you think that is reasonable?

G.T. Tucker:
If you use another drug, you might be affecting another enzyme system which affects another drug. That could introduce an additional problem, another drug interaction completely separate from the one you tried to deal with in the first place.

I.P. Hall:
I think we are being a little bit unfair on the possibilities that pharmacogenetics offer. As I understand it, there is such a large effect with the CYP2D6 that a very strong case can be made for genotyping before treating. Whether or not that is going to be effective in populations with regard to other drugs depends on two things. Firstly, it depends on whether or not there are viable alternative treatments which do not use the same metabolic pathway, and then if there is a perfectly adequate second alternative first-line treatment. The vast majority of pharmacogenetic variability in treatment response is not going to be as clear-cut as CYP2D6. There has to be some threshold to determine when it is worthwhile genotyping. The idea that you might have a chip where you identify a hundred common treatment response genes, genotype your population and then say, if you are going to get hypertension, you get drug X, if you get diabetes, you get drug Y is fine, but the effects have to be large enough. I do not think there are good examples at the moment of other targets where there is such a large big effect as for CYP2D6.

G.T. Tucker:
I guess that is exactly why the chip technology is concentrating initially on polymorphic CYPs. But still the technology has to be shown to have clinical relevance.

E.M. Sellers:
I would like to make a comment concerning the impact of environmental and other factors as possible gene regulators. It is probably important to remember that gene-regulation is organ-specific, and that there is now increasing evidence that the expression of cytochrome P450 in the brain is cell-type specific, and the regulation of those cell types in the brain is also very specific. It is quite easy to demonstrate that you can have cell-specific, cytochrome-specific induction in the brain with absolutely no effect whatsoever on hepatic expression of the cytochromes. So the extent that the central cytochromes are playing a role, either in endogenous-like answered response or whether they actually have a drug-metabolising role, is something that is essentially invisible to us. Therefore, studying clearance is a poor model for this situation.

M.M. Reidenberg:

A lot of us have been proposing for a while the idea that we need to identify which of these sources of variability that we have been discovering are clinically important. We have seen with classic examples, such as the tricyclic antidepressants and the CYP2D6 polymorphism, that people who do know about it and do understand it, do not seem to use this information in their clinical practice. In my opinion, rather than trying to prove the clinical importance of each of these sources of variability that we are identifying, we have to concentrate more on discovering the situations in which knowledge of the existence of a specific source of variability is clinically important. As clinical pharmacologists, we need to discover a lot more of when this variability is important, rather than assume that every one is equally important.

D.C. Brater:

I would like to comment on the example of mibefradil, where it was absolutely predictable that drug interactions were going to be problematic. It is surprising that a highly respected pharmaceutical company did not realize this beforehand and modify their studies and marketing accordingly, instead of having a disaster on their hands. Education about relevance of drug reactions goes beyond demonstrating the clinical relevance to our clinician colleagues.

M. Lader:

Related to all these drug interactions, I would like to consider a simple drug like lithium. With lithium, if you are looking for correlations with clinical response, there is only a broad spectrum of levels that you can look at. And even if you look at the toxicology, when you reach the high levels, you may have somebody who is perfectly comfortable at 1 mM concentration and another person who is going into toxicity at this level. The intra-cellular mechanisms are so important here, even with a simple drug like lithium, that they probably swamp the individual disposition of the compound and the variability in that. Until we know a lot more about what these drugs are actually doing at the cellular level, the concentrations are really a secondary issue.

M.M. Reidenberg:

Your point is well-taken because we do not differentiate drugs that move throughout the body and to the site of action by passive diffusion, from those that are involved in active transport. A basic theory that was developed in the 1940s essentially presupposes that drugs move by passive diffusion. For many organic molecules, this is a reasonable assumption. But when we consider other classes of molecules, then this assumption often breaks down.

T. Salmonson:

Firstly, I want to point out that mibefradil was not approved in Sweden. The problem is we are not today where we may be in the future. The health care system is under severe time and financial pressures and the industry acts accordingly. The drug industry therefore dislikes any type of labelling restriction which makes the drug more difficult to prescribe and/or handle, even if it means only avoiding taking the drug with food. This problem is partly due to lack of easily accessible information at the time of prescribing, and perhaps a lot can be done with modern technology to improve this. Although we should continue to focus on all the sources of variability, we also have to focus on why we are not considering even the most obvious sources of variability that do not need sophisticated measurements, such as gender or weight.

When we have problems correcting for such simple factors, how can we imagine that we will be successful in correcting for genotypes? The challenge is to show that there is a consequence for all these variabilities. We have also to be better at predicting the clinically relevant sources of variability. We are extremely good at detecting potential interactions with today's technology and we at the regulatory side can be blamed for including pharmacokinetically significant interactions on the labelling without considering the clinical relevance. This makes it impossible for the prescriber to consider all of these issues. So we need to be better at identifying clinically relevant interactions and sources of variability. And the challenge for us is how we can stimulate this development and reward knowledge and penalise lack of knowledge, instead of the opposite, which is the present situation.

J. Benítez:

Regarding the mibefradil case, it seems unbelievable and it is surprising that one of the biggest drug companies in the world has made such a mistake, and the FDA allowed it to occur, after removing from the market terfenadine for similar reasons. In about 100 psychiatric patients we studied the importance of CYP2D6 from a clinical point of view. We found that whether the patients were actually smokers or not was the most important factor. When we studied the possible interaction between fluvoxamine and thioridazine, a tremendous inhibition through CYP1A2 was observed, leading us to advise about the possible danger in giving these two drugs together. But apparently most clinical pharmacologists, including myself, did not think of this. A too simplistic view was taken and people were studying their favourite cytochrome, for example, 2D6, 1A2, 3A4. This reminds me of the frustrations related to therapeutic drug monitoring, about which we were very optimistic some years ago but I think it was oversold. If the results have not been as good as expected, it is because we took a too simplistic view, and I think we are making the same mistake again. Much more studies are needed, about how cytochromes interact with each other, how dietary components like caffeine and juice interact together. Too frequently results are not published because there is no clear clinical correlation.

J. Urquhart:

One of the places that might be useful to look at is therapeutic failure. Everything indicates a drug ought to work, but when it does not work then there is some kind of pharmacoescalation, either in drug, in dose or both. Considering this from a logical point of view, three possibilities exist: 1. Clinically unrecognised non-complier; 2. Clinically unrecognised non-absorption or some kind of absorption barrier problem; and 3. Non-responder. The clinical failure situation focuses attention on the resolution of these 3 possibilities, and when the problem is resolved, it should be clear what is happening. However, this does not deal with toxicity, but it at least deals with therapeutic failure.

M.M. Reidenberg:

The same approach can be used for toxicity, and the example I would use is digoxin, where you make the digoxin toxicity diagnosis clinically, looking at the digoxin level. If the digoxin level is very high, you have made a mistake on the renal function. If it is normal, then you look at serum potassium, serum calcium and so on, and it is a very different list. This way of thinking, we do clinically with at least digoxin, so that conceptually I think this process is understood.

A.J.J. Wood:

Anticoagulants could be a good example of our failure to having good end-points with other drugs, because there is certainly a good relationship between the extent of anticoagulation and the risk of haemorrhage, which is a devastating adverse effect but it is pretty easy for people to define. On the contrary, it is a lot harder to define an end-point in psychiatry for distinguishing between efficacy and toxicity. If you feel bad, it could be because you have not had your depression improved, or because your depression might have improved but the drug's toxicity has made you feel worse. Sometimes, the complexity makes it really hard to separate out efficacy from toxicity.

P. du Souich:

Probably we need to improve our pharmacodynamic tools to assess the effects of drugs. If we were able to speak to the physicians on pharmacodynamic grounds, they would understand us much better than when we talk to them about half-lives and clearances.

P.B. Watkins:

I patented the erythromycin breath test and for the last decade have been proposing use of the test to individualize dosing of CYP3A4 substrates with narrow therapeutic indices. My experiences point out some of the problems with gaining acceptance for phenotyping tests. The first drug we targeted was cyclosporin A. This seemed to be a good candidate as it has a narrow therapeutic index and its pharmacokinetics vary substantially among patients. Moreover, the physician must place the patient on a sufficient but nontoxic dose as soon as possible after transplantation. It is therefore not possible to start at a low dose and slowly increase it, which is often the strategy used for dosing other drugs with narrow therapeutic indices. Both clinicians and members of pharmaceutical industry found our studies scientifically appealing. However, one seemed interested in funding or participating in studies that might show the true utility of the test; no once even seemed interested in the concept of reducing the need for blood level monitoring. I have been told that blood level monitoring is more lucrative than the sale of the drug, which may account for this reluctance.

The second category of drugs we are examining are chemotherapies which are CYP3A4 substrates and where pharmacokinetics predict clinical response. Again, it is not desirable to start with a low dose and escalate, as the tumor can develop drug resistance. Alternatively, these drugs are very toxic in high doses. I have participated in several discussions within industry were scientists and clinicians have argued for phenotyping studies, but marketing executives have viewed bundling any sort of special test testing to their drug as a competitive disadvantage. To date, marketing has won these discussions.

U. Klotz:

It would be interesting to know whether all the clinical pharmacologists working in the area of pharmacogenetics and CYP2D6 and in units capable of phenotyping, routinely carry out this analysis. If it is not done by clinical pharmacologists in their own units, you cannot expect it from practitioners or other physicians. For instance, in my hospital we have patients on certain drugs who were not routinely phenotyped. If we do not consider such an important factor for individualisation of dosage, we place ourselves in a weak position.

J. Benítez:

Obviously phenotyping is not done routinely but when there exist special problems with some patients. Phenotyping is not routinely done anywhere as far as I know.

G.T. Tucker:

I mentioned a study, in a major centre of therapeutic drug monitoring showing that the levels of nortriptiline were significantly higher in the presence of neuroleptics. However, physicians using this drug did not lower the dose. If this is true in a leading TDM centre, then it is unlikely that phenotyping will catch on as a routine procedure.

M.M. Reidenberg:

The question I would raise is whether there is any clinical need to act on the situation for these drugs when there was a difference in mean levels but there was not a very steep concentration-effect relationship. At least, the psychiatrists at my university and at the University of Pittsburgh, with whom I have discussed this matter and who are well aware of this clinical pharmacology issue, find that, in practice, it is of little importance. Among all the reasons for variability in the response of depressed patients to treatment, the pharmacokinetic degree of variability in tricyclics is such a small part of the total that it can be ignored without perceiving any detriment.

G.T. Tucker:

That could be true of the desired response, but it may not be true of adverse response, whether overt toxicity or impaired quality of life.