Variability in Human Drug Response
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Adverse drug reactions: role of enzyme inhibition and induction

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ABSTRACT

Human drug metabolising enzymes can be induced or inhibited by drugs, foodstuffs, and alcohol. which can predispose to toxicity from both endogenous and exogenous substrates. For endogenous substrates, enzyme inhibition can lead to a deficiency of an essential metabolite or accumulation of an otherwise non-toxic compound. Enzyme induction by increasing metabolism of endogenous compounds can lead to a deficiency state, e.g. vitamin D deficiency with phenytoin. With drugs, perturbation of enzyme activity can lead to both type A and type B adverse drug reactions (ADRs) depending on whether phase I or phase II pathways are affected. Thus type A ADRs can result from inhibition or induction of phase I pathways, the toxicity being due to the parent drug or active metabolite, respectively. Type B ADRs result form induction of phase I, or inhibition of phase II pathways, with a resultant imbalance between bioactivation and detoxication. Knowledge of drug effects on metabolic pathways is important so that their potential to cause toxicity can be anticipated. In the long-term, it is important to develop "cleaner" compounds so that the problem of enzyme inhibition and enzyme induction can be eliminated, and together with it, the potential of such drugs to cause ADRs.

Key words: hypersensitivity, idiosyncratic, interaction, toxicity, chemically reactive metabolites.

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INTRODUCTION

An adverse drug reaction (ADR) may be defined as any undersirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use [1]. ADRs are common and account for 2-6% of all hospital admissions [2]. A recent meta-analysis has suggested that ADRs are the fourth commonest cause of death in the USA [3].

In general, ADRs can be divided into two types, type A and type B [1]. Type A reactions represent an augmentation of the pharmacological actions of a drug, are dose-dependent and therefore readily reversible on drug withdrawal, or after dose-reduction. In contrast, type B, or idiosyncratic adverse reactions, are bizarre, and cannot be predicted from the known pharmacology of the drug. Type A reactions account for over 80% of all ADRs.

There are many factors which predispose to ADRs: these have been considered in more detail elsewhere [4,5]. The purpose of this chapter is to evaluate the role of inhibition and induction of enzymes in predisposing to ADRs. When considering the role of either enzyme inhibition or enzyme induction in ADRs, it is important to note that (a) the toxicity may arise as a result of an alteration in the metabolism of either endogenous or exogenous substances (Table 1), and (b) both type A and type B reactions may arise as a result of modulation of enzyme activity.

Table 1
Mechanisms of adverse drug reactions resulting from effects of changes in enzyme activity for endogenous and exogenous substrates

	Endogenous substrates	Exogenous substrates
Enzyme inhibition	· Deficiency of essential metabolite, production of abnormal and biologically inactive metabolites, or accumulation of intermediary products which become toxic when present in excess	· Increased levels of parent drug resulting in dose-dependent toxicity · Decreased bioinactivation of an active metabolite resulting in idiosyncratic toxicity
Enzyme induction	· Increased metabolism of an endogenous substrate resulting in a deficiency state	· Increased production of a toxic metabolite resulting in either dose-dependent (idiosyncratic) toxicity

PHARMACOKINETIC CONSIDERATIONS

The toxiclogical impact of enzyme inhibiton is dependent on

(i) the degree and duration of enzyme inhibition (as determined by the potency of the inhibitor, the nature of inhibition and the pharmacokinetics of the inhibitor), and

(ii) the biological importance of the enzyme and its ability to overcome inhibition by either synthesis of more enzyme or utilization of alternative biochemical pathways.

The impact of enzyme inhibition on drug half-life is very sensitive to the fraction of the dose normally metabolised via the inhibited pathway [6]. Thus, if drug clearance is dependent

on one pathway, then inhibition of that pathway, will lead to supra-pharmacological concentrations of the inhibited drug, and possible toxicity. When drug clearance is dependent on more than one pathway, inhibition of one of the pathways may have little effect on plasma drug concentrations, and thus is unlikely to cause toxicity. The exception to this are drugs with a narrow therapeutic index, such as warfarin and phenytoin, where a relatively modest change in plasma levels may result in a shift from a therapeutic response to a toxic effect [6].

Enzyme induction by increasing drug clearance will lead to a reduction in parent drug concentration, and thus loss of efficacy [7]. Loss of efficacy is not considered as an adverse drug reaction in the context of this chapter, but nevertheless is important, since it can result in re-emergence of the underlying disease process, for example, thrombosis in a patient administered an enzyme inducer while anticoagulated on warfarin. Clearly, the effect of enzyme induction can be overcome by increasing the dose of the drug. Whether the dose needs to be increased and by how much depends on whether drug clearance is dependent on one or more than one metabolic pathway. This has been considered in detail in a recent review [7]. With particular respect to this chapter, more important is a consideration of toxic metabolite formation via the induced pathway. The rate of reactive metabolite formation will increase as a function of the change in the maximal velocity of the reaction (V_{max}). If the reactive metabolite is normally only a minor metabolite (<5%), then the total dose of the toxic metabolite will increase substantially. Such an increase in reactive metabolite formation may be adequate to overcome the detoxication processes, unless these are also induced, resulting in toxicity.

DRUGS AND THE METABOLISM OF ENDOGENOUS SUBSTRATES

Inhibition of the metabolism of endogenous substrates

Various drugs designed as enzyme inhibitors to achieve their therapeutic actions may also result in the interruption of the metabolism of other closely related endogenous compounds or the same endogenous compound but at a different site in the body, resulting in an adverse drug reactions [6]. Examples of enzymes inhibited, the endogenous substrates affected, and the toxicity which results because of the inhibition, are listed in table 2

Prevention of ADRs with some drugs may be possible by developing more selective enzyme inhibitors [1]. Non-steroidal anti-inflammatory drugs best exemplify this. Inhibition of cyclo-oxygenase in the joints is responsible for their therapeutic action, while inhibition of cyclo-oxygenase in extra-articular tissues such as the stomach and kidney, can result in peptic ulceration and renal insufficiency, respectively. The recent discoveries that there are two isoforms of COX (COX-1 and COX-2), and that COX-2 expression is enhanced in inflammatory conditions, has led to the development of selective COX-2 inhibitors based on the hypothesis that sparing of COX-1 activity may prevent toxicity. Preliminary clinical experience has suggested that selective COX-2 inhibitors have both anti-inflammatory and gastrointestinal sparing properties, but whether this is translated into long-term safety will only become evident with clinical experience [8].

Table 2.
Examples of adverse drug reactions produced as a result of inhibition of the metabolism of endogenous substrates

Enzyme	Enzyme inhibitor	Endogenous substrate	Adverse reaction
Angiotensin converting enzyme	ACE inhibitors, e.g. captopril	Bradykinin	Angio-oedema
Cholinesterase	Anti-cholinesterases, e.g. neostigmine	Acetylcholine	Abdominal cramps, salivation and diarrhoea
Cyclo-oxygenase	Non-steroidal anti-inflammatory drugs, e.g. diclofenac	Prostaglandins	Peptic ulceration, nephrotoxicity
Cytochrome P450 enzymes	Ketoconazole	Corticosteroids, testosterone	Adrenal suppression, impotence
Dihydrofolate reductase	Methotrexate	Folic acid	Megaloblastic anaemia
Monoamine oxidase	Iproniazid	Catecholamines	Hypertensive crises

Induction of the metabolism of endogenous substrates

Induction of the metabolism of endogenous substrates such as thyroid hormones and vitamin D may lead to clinically significant deficiency of such substrates. For example, use of phenobarbitone in rats leads to increased glucuronidation of the thyroid hormones, which is followed by functional adaptation of the thyroid gland, with respect to size and activity. Subclinical depression of thyroid hormone concentrations has been reported in epileptics and in patients taking rifampicin, although the incidence of clinical hypothyroidism in such patients is low [7,9]. Enzyme inducers can also perturb the metabolism of steroids and fat-soluble vitamins. Induction of vitamin D metabolism by drugs such as phenytoin can lead to osteomalacia [10].

DRUGS AND THE METABOLISM OF EXOGENOUS SUBSTRATES

The rate of elimination of a lipophilic drug is governed largely by its rate of metabolism. Metabolism via either the phase I oxidation pathways and/or the phase II conjugation pathways is usually associated with an increase in the water solubility of the compound and thus enhanced clearance. Metabolism can also lead to the formation of toxic, chemically reactive metabolites from drugs (a process termed bioactivation), which if not detoxified by detoxication mechanisms in body, can bind to cellular macromolecules and lead to various

forms of idiosyncratic toxicity (such as tissue necrosis, hypersensitivity reactions and teratogenicity) [4,5,11].

Modulation of any of these pathways by either enzyme inhibitors or enzyme inducers can increase the risk of toxicity (table 1). Therefore, an enzyme inhibitor may (a) reduce elimination of the drug leading to dose-dependent toxicity, or (b) by inhibiting the detoxication pathways, decrease inactivation of a toxic metabolite and predispose to idiosyncratic toxicity. Conversely, enzyme induction (of the phase I metabolic pathways) may increase chemically reactive metabolite formation.

Table 3.
Cytochrome P450 isozymes involved in the metabolism of drugs and xenobiotics in man

P450 isoform	Substrates	Inducers	Inhibitors
CYP1A2	Clozapine Theophylline	Cigarette smoke Omeprazole	Ciprofloxacin Furafylline
CYP2A6	Halothane Methoxyflurane	Phenytoin Rifampicin	Tranylcypromine
CYP2C9	Diclofenac Tolbutamide Warfarin	Barbiturates Rifampicin	Sulphaphenazole
CYP2C19	Citalopram Diazepam Omeprazole	Rifampicin	Tranylcypromine
CYP2D6	Codeine Haloperidol Metoprolol Nortriptyline	Not inducible	Quinidine
CYP2E1	Enflurane Halothane Paracetamol	Alcohol (chronic use)	Disulfiram
CYP3A4	Amiodarone Carbamazepine Cyclosporin Terfenadine	Carbamazepine Glucocorticoids Phenytoin Rifampicin	Ketoconazole Erythromycin
CYP4A1	Testosterone	Clofibrate	-

Only few substrates, inhibitors and inducers have been mentioned for each P450 isoform.

The enzymes most liable to undergo inhibition and induction and thereby be involved in ADRs are the cytochrome P450 enzymes. There are many different P450 isoforms, and many of these can be induced and inhibited in a selective fashion, resulting in different forms of drug toxicity [12]. Table 3 provides a summary of the different P450 isoforms together with their inducers and inhibitors.

Enzyme inhibition and dose-dependent adverse drug reactions

The concomitant administration of a drug with a narrow therapeutic index together with an enzyme inhibitor can lead to adverse drug interactions, which can be severe and occasionally fatal. Many such interactions have been reported, and the drugs with a narrow therapeutic index most likely to be involved are the aromatic anticonvulsants, theophylline, cyclosporin, warfarin, terfenadine and cisapride [13]. In all cases, inhibition of the relevant P450 isoform needed for metabolism of these drugs is involved in the pathogenesis of the ADR. The reader is referred elsewhere for a more detailed discussion of such adverse drug reactions [13].

An area which has generated a lot of media interest and has resulted in drug regulatory action is the interaction between non-sedating antihistamines and CYP3A4 inhibitors. Astemizole and terfenadine, both non-sedating antihistamines, have been reported to cause life-threatening cardiac arrhythmias [14]. Attention has primarily focused on terfenadine, which is the most widely used. Terfenadine is a pro-drug that is converted to a carboxylic acid metabolite by CYP3A4 [5]. Terfenadine cannot normally be detected in the plasma, unless taken in overdosage or when its metabolism is inhibited. The latter has been reported to occur by various drugs including ketoconazole, itraconazole, erythromycin and clarithromycin [15]. Grapefruit juice also inhibits the metabolism of terfenadine [16]. When any of these drugs are given together with terfenadine, the elevated plasma terfenadine concentration leads to prolongation of the QT-interval, which in turn, may lead to a polymorphic ventricular tachycardia termed "torsades de pointes" [14]. Both terfenadine and astemizole block the ventricular potassium channels, particularly the rapidly activating component of the delayed rectifier, which increases the duration of the action potential and the QT-interval [17]. In order to reduce the risk of arrhythmias with terfenadine, the legal status of the drug has recently been changed, so that it is now only available as a prescription-only medicine [14]. In addition, its active metabolite (fexofenadine), which does not affect potassium [18], has recently been marketed as a drug in its own right.

Enzyme inhibition and idiosyncratic toxicity

Inhibition of P450 enzymes can actually lead to a reduction in the formation of a toxic or chemically reactive metabolite, and may thereby protect against idiosyncratic toxicity (discussed below). Conversely, inhibition of detoxication enzymes can decrease bioinactivation of the toxic metabolite, and increase the propensity of a drug to cause idiosyncratic toxicity. Given the wide and overlapping substrate specificities of most of the detoxication enzymes, such situations fortunately are uncommon. An area that has caused concern however is the increase in frequency of teratogenicity in patients on combination anti-epileptic therapy which includes valpromide and valproic acid. Both these drugs are inhibitors of microsomal epoxide hydrolase, which catalyses the hydrolysis of various epoxides, including arene oxides. Lindhout *et al.* [19] reported a 58% rate of foetal malformations associated with combination therapy (which included valproic acid); inhibition of foetal microsomal epoxide hydrolase by

valproic acid, thus increasing foetal exposure to reactive epoxides has been suggested to be the mechanism [20].

Enzyme induction and dose-dependent toxicity

Enzyme induction increases the clearance of a drug and therefore should protect against dose-dependent toxicity. However, if the toxicity is due to an active metabolite, then enzyme induction will increase the risk of toxicity. The clearest example of this is paracetamol which causes hepatotoxicity when taken in overdosage, and still causes about 160 deaths per year in the UK [21]. According to the definition of adverse drug reactions given above, paracetamol hepatotoxicity should not be classified as an adverse drug reaction, since the hepatic injury occurs when the drug is used inappropriately. However, it is important to note that the occurrence of liver damage with paracetamol and its severity is a function not only of the dose but also of various host factors [5]. Indeed, paracetamol hepatotoxicity has been reported with therapeutic drug use. For example, a recent study in 67 alcoholics who had sustained liver injury after paracetamol ingestion, showed that 40% had taken less than 4g/day (the maximum recommended therapeutic dose) while another 20% had taken between 4-6g/day (which is also regarded as a non-toxic dose) [22]. In therapeutic dosage, paracetamol is largely metabolised by phase II processes (glucuronidation and sulphation) to stable metabolites, but between 5-10% also undergoes P450 metabolism to the toxic quinoneimine metabolite [23]. This is detoxified by cellular glutathione. In overdosage, saturation of the phase II metabolic pathways results in a greater proportion of the drug undergoing bioactivation. This ultimately leads to depletion of cellular glutathione, and allows the toxic metabolite to bind to hepatic proteins resulting in hepatocellular damage [23]. The use of N-acetylcysteine in the treatment of paracetamol overdosage illustrates the important point that elucidation of the mechanism of drug toxicity can lead to the development of rational therapies which will prevent the toxicity. Alcoholics show increased susceptibility to paracetamol overdosage because excess alcohol consumption results in depletion of glutathione [24] and induction of the P450 isoform CYP2E1 [25]. Recent studies in knockout mice have shown that CYP2E1 is the primary isoform involved in the bioactivation of paracetamol [26]. Patients on enzyme-inducing anticonvulsants (which leads to induction of CYP3A4) are also more susceptible to paracetamol hepatotoxicity, and require treatment with N-acetylcysteine at lower plasma paracetamol concentrations [27].

Dapsone, a drug used in the treatment of leprosy, is associated with dose-dependent methaemoglobinaemia [28]. This is thought to be due to P450-mediated (CYP3A4, CYP2C9 and CYP2E1) activation of dapsone to the hydroxylamine metabolite [29]. The hydroxylamine is taken up by red cells where it is co-oxidised with haemoglobin to form nitroso-dapsone and methaemoglobin. Dapsone is usually co-administered with the potent enzyme inducer rifampicin in the treatment of leprosy. In these patients, it has been shown that rifampicin significantly increases the formation clearance of dapsone hydroxylamine by fourfold and methaemoglobinaemia by 1.7-fold [30].

Enzyme induction and idiosyncratic toxicity

Enzyme induction by increasing drug bioactivation (and hence chemically reactive metabolite formation) may overcome the detoxication processes and lead to idiosyncratic toxicity. However, it is important to note that there is very little direct data to support this. This is partly due to the fact that predisposition to idiosyncratic toxicity is multi-factorial, and

the presence one predisposing factor, i.e. enzyme induction, may be compensated for by the lack of other predisposing factors [1]. The important examples of enzyme induction predisposing to idiosyncratic ADRs include the following:

- Isoniazid by itself causes hepatotoxicity in 1% of patients. Co-administration with rifampicin increases the frequency of hepatitis to 7%; this is thought to be secondary to induction of bioactivation of isoniazid to reactive hydrazine intermediates [31].
- Alcohol is metabolised by alcohol dehydrogenase (80%) and CYP2E1 (20%). Chronic alcoholics have induction of CYP2E1 and thus a higher proportion of alcohol undergoing metabolism via CYP2E1. Metabolism of alcohol by CYP2E1 causes the formation of toxic hydroxyethyl radicals, which have been implicated in the pathogenesis of alcoholic liver disease. Thus, autoinduction of its own metabolism by alcohol may increase the risk of liver injury [5].
- Carbamazepine causes generalised hypersensitivity in small number (1:1000-5000) of patients taking the drug. Bioactivation of carbamazepine by CYP3A4 to a toxic arene oxide metabolite is thought to be the initial step in the pathogenesis of toxicity [32]. Carbamazepine induces CYP3A4, and therefore bioactivation to the arene oxide metabolite [33]. However, there is varaibility in induction at the same dose levels, which may serve as a factor in predisposing to this form of idiosyncratic toxicity [34].

PREVENTION OF ADVERSE DRUG REACTIONS BY MODULATION OF ENZYME ACTIVITY

If induction of P450 enzymes predisposes to drug toxicity, then it would seem logical to suppose that therapeutic use of an enzyme inhibitor may prevent toxicity. Using this rationale, and dapsone-induced methaemoglobinaemia as the paradigm, we were able to show that its conversion to dapsone hydroxylamine, and thus methaemoglobinaemia, could be prevented *in vitro* [35], *in vivo* in volunteers [36] and in patients with dermatitis herpetiformis [37], by cimetidine, a P450 inhibitor. The use of disulfiram, a CYP2E1 inhibitor, before halothane anaesthesia has also been suggested (but not yet proven) as a way of preventing halothane hepatitis [38].

Induction of detoxication enzymes may also protect against toxicity, although this has not been used therapeutically. Vegetables such as broccoli contain potent inducers of quinone reductase and glutathione transferase; this has been put forward as the explanation why consumption of vegetables reduces the risk of cancer [39]. Oltipraz, which is an inducer of phase II enzymes (quinone reductase, glutathione transferase and glucuronyl transferase), has been shown to protect against the acute toxicities of many xenobiotics, and inhibits experimental carcinogenesis [40].

CONCLUSION

Human drug metabolising enzymes can be induced or inhibited by a variety of xenobiotics. This contributes to the intra-individual and inter-individual variation in the rate and route of metabolism of xenobiotics, which in some instances, predisposes to an ADR. Any type of

ADR (i.e. type A or type B) can result from a change in enzyme activity. Through knowledge of the metabolic pathways, and the properties of any co-administered drug, it may be possible to anticipate and avoid type A ADRs. For type B ADRs, this is more difficult, since even knowledge of the pathway affected by a concomitantly administered drug does not necessarily allow accurate prediction of the toxicity. The ultimate aim in the future must be to develop pharmacologically "cleaner" drugs so that the problem of enzyme inhibition and enzyme induction can be prevented, and at least some of the factors causing ADRs avoided.

REFERENCES

1. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions: current status. Br Med J 1998;316:1295-1298.
2. Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993;27:832-840.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients - A meta-analysis of prospective studies. JAMA 1998;279:1200-1205.
4. Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. Br J Clin Pharmacol 1992;34:377-395.
5. Pirmohamed M, Kitteringham NR, Park BK. The role of active metabolites in drug toxicity. Drug Saf 1994;11:114-144.
6. Pirmohamed M, Park BK. Enzyme inhibition-mediated toxic effects of drugs. In: Sandler M, Smith J (eds.) Design of enzyme inhibitors as drugs. Oxford: OUP, 1994:800-818.
7. Park BK, Kitteringham NR, Pirmohamed M, Tucker GT. Relevance of induction of human drug-metabolizing enzymes: pharmacological and toxicological implications. Br J Clin Pharmacol 1996;41:477-491.
8. Yeomans ND, Cook GA, Giraud AS. Selective COX-2 inhibitors: Are they safe for the stomach? Gastroenterology 1998;115:227-229.
9. Larkin JG, Macphee GJA, Beastall GH, Brodie MJ. Thyroid hormone concentrations in epileptic patients. Eur J Clin Pharmacol 1989;36:213-216.
10. Park BK, Kitteringham NR. Assessment of enzyme induction and enzyme inhibition in humans: toxicological implications. Xenobiotica 1990;20:1171-1185.
11. Pirmohamed M, Madden S, Park BK. Idiosyncratic drug reactions: metabolic bioactivation as a pathogenic mechanism. Clin Pharmacokin 1996;31:215-230.
12. Kitteringham NR, Pirmohamed M, Park BK. The pharmacology of the cytochrome P450 enzyme system. Baill Clin Anaesthesiol 1998;in press.
13. Pirmohamed M, Orme ML'E. Drug interactions of clinical importance. In: Davies DM, Ferner RE, de Glanville H (eds.) Textbook of Adverse Drug Reactions. London: Chapman & Hall, 1998:888-912.
14. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. Lancet 1997;350:1115-1116.
15. Ament PW, Paterson A. Drug interactions with the nonsedating antihistamines. American Family Physician 1997;56:223.
16. Benton RE, Honig PK, Zamani K, Cantilena LR, Woosley RL. Grapefruit juice alters terfenadine pharmacokinetics resulting in prolongation of repolarization on the electrocardiogram. Clin Pharmacol Ther 1996;59:383-388.

17. Salata JJ, Jurkiewicz NK, Wallace AA, Stupienski RF, Guinosso PJ, Lynch JJ. Cardiac electrophysiological actions of the histamine h-1-receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. Circ Res 1995;76:110-119.
18. Woosley RL, Chen YW, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993;269:1532-1536.
19. Lindhout D, Hoppener RJEA, Meinardi H. Teratogenecity of anti-epileptic drug combinations with special emphasis on epoxidation (of carbamazepine). Epilepsia 1984;25:77-83.
20. Kerr BM, Rettie AE, Eddy C, *et al.* Inhibition of human liver microsomal epoxide hydrolase by valproate and valpromide: *in vitro/in vivo* correlation. Clin Pharmacol Ther 1989;46:82-93.
21. Bray GP. Liver failure induced by paracetamol. Br Med J 1993;306:157-158.
22. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995;22:767-773.
23. Nelson SD. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. Semin Liver Dis 1990;10:267-278.
24. Lauterburg BH, Velez ME. Glutathione deficiency in alcoholics: Risk factor for paracetamol hepatotoxicity. Gut 1988;29:1153-1157.
25. Raucy JL, Lasker JM, Lieber CS, Black M. Acetaminophen activation by human liver cytochromes P-450IIE1 and P-450IA2. Arch Biochem Biophys 1989;271:270-283.
26. Lee SST, Buters JTM, Pineau T, Fernandezsalguero P, Gonzalez FJ. Role of cyp2e1 in the hepatotoxicity of acetaminophen. J Biol Chem 1996;271:12063-12067.
27. Bray GP, Harrison PM, O'Grady JG, Tredger JM, Williams R. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. Hum Exp Toxicol 1992;11:265-270.
28. Park BK, Pirmohamed M, Tingle MD, Madden S, Kitteringham NR. Bioactivation and bioinactivation of drugs and drug metabolites: relevance to adverse drug reactions. Tox in vitro 1994;8:613-621.
29. Gill HJ, Tingle MD, Park BK. N-hydroxylation of dapsone by multiple enzymes of cytochrome P450: implications for inhibition of haemotoxicity. Br J Clin Pharmacol 1995;40:531-539.
30. Occhipinti DJ, Choi A, Deyo K, Danziger LH, Fischer JH. Influence of rifampicin and clarithromycin on dapsone disposition and methemoglobin concentrations. Clin Pharmacol Ther 1995;57:163.
31. Pirmohamed M, Park BK. Mechanisms of hypertransaminemia. In: Cameron RG, Feuer G, de la Iglesia FA (eds.) Drug-Induced Hepatotoxicity. Berlin: Springer-Verlag, 1996:341-366.
32. Madden S, Maggs JL, Park BK. Bioactivation of carbamazepine in the rat in-vivo - evidence for the formation of reactive arene oxide(s). Drug Metab Dispos 1996;24:469-479.
33. Pirmohamed M, Kitteringham NR, Breckenridge AM, Park BK. The effect of enzyme induction on the cytochrome P450-mediated bioactivation of carbamazepine by mouse liver microsomes. Biochem Pharmacol 1992;44:2307-2314.

34. Pirmohamed M, Allott R, Kitteringham NR, Choonara I, Breckenridge AM, Park BK. Lymphocyte microsomal epoxide hydrolase activity in patients on chronic anticonvulsant therapy. Br J Clin Pharmacol 1993;36:159P.
35. Tingle MD, Coleman MD, Park BK. The effect of preincubation with cimetidine on the N-hydroxylation of dapsone by human liver microsomes. Br J Clin Pharmacol 1991;32:120-123.
36. Coleman MD, Scott AK, Breckenridge AM, Park BK. The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. Br J Clin Pharmacol 1990;30:761-767.
37. Rhodes LE, Tingle MD, Park BK, Chu P, Verbov JL, Friedmann PS. Cimetidine improves the therapeutic toxic ratio of dapsone in patients on chronic dapsone therapy. Br J Dermatol 1995;132:257-262.
38. Kharasch ED, Hankins D, Mautz D, Thummel KE. Identification of the enzyme responsible for oxidative halothane metabolism - implications for prevention of halothane hepatitis. Lancet 1996;347:1367-1371.
39. Zhang H, Zdolsek JM, Brunk UT. Alloxan cytotoxicity involves lysosomal damage. Apmis 1992;100:309-316.
40. Egner PA, Kensler TW, Prestera T, *et al.* Regulation of phase 2 enzyme-induction by oltipraz and other dithiolethiones. Carcinogenesis 1994;15:177-181.

Discussion: Adverse drug reactions: Role of enzyme inhibition and induction

H.K. Kroemer:

Terfenadine interaction is a good example, because its metabolism could be explained from the *in vitro* data. But it would not have occurred to anyone that this parent compound, which is basically inactive in terms of H_1 blockade, would block specifically the potassium channel in the heart. The current problem is to predict how relevant the QT prolongation is. A lot of studies have shown that there is an inhibition of the metabolism of some drugs by ketoconazole leading to QT_C prolongation at a specific percentage but it would be difficult to set the threshold. Secondly, from my point of view, it is time to discard the term idiosyncrasy. Maybe 10 years ago we would have attached this term, for example, to many of these CYP2D6-dependent reactions, which we understand nowadays. Idiosyncrasy should define a type of adverse drug reaction which we cannot explain based on our current knowledge.

M. Pirmohamed:

An idiosyncratic reaction is a functional term which does not imply any specific aetiology and for which we do not understand the mechanism. With regard to your first comment, there is a pharmacodynamic variance for these effects and a lot of drug companies are screening for drug actions on potassium channels. Through the knowledge basis we are obtaining of the metabolic and pharmacodynamic profile, hopefully in the future, it will be possible to prevent these kinds of severe interactions from occurring in clinical practice.

L. Aarons:

To actually describe idiosyncratic reactions as dose-independent seems to deny causality, and I suspect the real reason is that, as you just said, you do not have the information to describe the dose-response relationship.

M. Pirmohamed:

It is apparently dose-independent, but what we are looking at is the external dose. The internal dose is unknown as is the dose of the reactive metabolite formed in the body. If one was able to measure the reactive metabolite being formed accurately, then one may be able to say they are dose-independent in terms of the reactive metabolite itself, but dose-independent in terms of the parent drug.

A.J.J. Wood:

The term idiopathic might be better than idiosyncratic which is a moving target. It reflects our lack of knowledge now or in the past but it is not necessarily applicable to the present. Cough following ACE-inhibitors would have been idiosyncratic, I guess, in the absence of an explanation. In the presence of an explanation, it is not. I suspect the dose-effect depends on the concentration of bradykinin. It is knowledge of what the compound is that produces the effect, that presumably is dose-related, not necessarily the dose of the parent drug. For this reason I am not even sure that that is a very helpful definition any more, either.

M.M. Reidenberg:

These definitions are really contingent upon present knowledge. I think, as much as we dislike the term idiosyncratic, it is so well-established throughout medicine that it would be difficult to abolish the term now. We might gain more by defining it clearly in the way we have done: an adverse reaction that, based on present knowledge, is both not predictable and not understood.

M. Pirmohamed:

The term hypersensitivity also causes a lot of problems and is often misused. There needs to be some kind of definition which everybody uses, because different people tend to use the term hypersensitivity or idiosyncrasy differently in different contexts.

D.A. Smith:

The comment I wanted to make was about the specificity of the toxicity, and in particular when teratogenicity exists. Some toxic reactions, for example, a skin rash, some sort of blood dyscrasia, etc., are often associated for the sort of compounds you were describing. But considering teratogenicity, it always seems to me a very specific target because always the same sort of malformations are present. It is a specific set of syndromes which must occur by an interaction at a specific time in the growth of the foetus. I think this is difficult to relate this to the reactive metabolite theory because this theory holds that there is a specific target, one particular receptor or one particular gene.

M. Pirmohamed:

Not necessarily, because what one could hypothesise also is that it depends when, during foetal development, you actually take the drug, or what is the concentration of the drug or its reactive metabolite at that particular point because different organs are developed at different times. If one can interfere with the development of a particular organ, then one can develop a specific form of toxicity. If you examine different forms for teratogenicity, they do have similar features. The exact nature of the teratogenicity will depend on when that particular drug was taken during pregnancy and what particular target was hit at the time. That does not go against the reactive metabolite theory but clearly what one needs to do is to identify which particular target proteins, or target DNA system or target receptors are being hit by that particular reactive metabolite or parent drug.