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Editorial

Cytochromes and Psychotropic Drug Interactions

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The cytochrome p450 enzymes in the liver were discovered about 40 years ago. Soon after, it was found that these enzymes could be induced by various drugs whose metabolism would then be accelerated. Over the years, more and more subtypes of cytochromes have been characterised. A recent listing contained over 30 (Guengerich, 1992). Of these, a few appear to be of particular importance in the metabolism of commonly-used psychotropic drugs (von Moltke *et al*, 1994). Furthermore, predictions can now be made concerning potentially troublesome drug interactions (Murray, 1992), especially those involving antidepressants.

p450–2D6

This cytochrome is implicated in the metabolism of the antidepressants desipramine, nortriptyline, imipramine, amitriptyline and clomipramine, and the antipsychotic drugs thioridazine, fluphenazine, perphenazine and clozapine (Fischer *et al*, 1992). Many non-psychotic drugs are also metabolised mainly via 2D6 mechanisms including beta-blockers, analgesics, antiarrhythmic agents and antitussives. This enzyme is subject to genetic polymorphism, with a minority of the population (5–10%) being slow metabolisers (Cholerton *et al*, 1992). These people are at risk of developing high, potentially toxic concentrations of various drugs and of suffering hazardous drug interactions. Slow metabolisers can be identified by the administration of a test compound such as debrisoquine or dextromethorphan, followed by estimation of parent to metabolite ratio in the urine. In normal metabolisers, metabolite predominates; in slow metabolisers, the parent compound persists. However, the parent compound may then be metabolised along other metabolic routes and may result in toxicity (Watkins, 1990).

The 2D6 system is susceptible to inhibition by some drugs, quinidine being the prime example. This can result in the slow metabolism of other drugs in normal metabolisers but has little effect in slow metabolisers because the liver is already deficient in this function.

Interest has recently increased in the 2D6 system because of the demonstration that some (but not all) of the selective serotonin reuptake inhibitor (SSRI) antidepressants can inhibit this enzyme *in vitro*. The most powerful was paroxetine ($K_i = 0.15$ μM). Citalopram and fluvoxamine were weak inhibitors as were clomipramine, desipramine and amitriptyline (Crewe *et al*, 1992). Thus, paroxetine, fluoxetine and sertraline might be involved in interactions with other drugs metabolised by the 2D6 cytochrome system.

Enough is now known of the molecular configuration of the active site of the 2D6 protein to allow computer modelling. This is not possible yet with most other cytochromes.

p450–3A family

This comprises mainly two closely related cytochromes, 3A3 and 3A4. The psychotropic drugs mainly metabolised by this group include midazolam (Gorski *et al*, 1994), triazolam and alprazolam (von Moltke *et al*, 1993), and it is involved in the demethylation of imipramine, amitriptyline and clomipramine to desipramine, nortriptyline and desclomipramine, respectively. These enzymes do not show genetic polymorphism and are found in the intestinal mucosa as well as the liver. Other drugs metabolised via this system include nifedipine, quinidine, terfenadine and cyclosporin. Ketoconazole, an antifungal agent, is a powerful inhibitor of the 3A enzymes. The SSRIs also have some effect but much less than on the 2D6 system.

p450–1A2

This cytochrome is also involved in the demethylation of imipramine, and in the metabolism of caffeine (Slaughter & Edwards, 1995) and theophylline (Rasmussen *et al*, 1995). It is induced by smoking. Fluvoxamine is a very potent inhibitor of this system (K_i ranging from 0.12–0.24 μM) (Brøsen *et al*, 1993). Paroxetine is a weak inhibitor, citalopram and fluoxetine have almost no effect. Propranolol, clomipramine and amitriptyline accumulate markedly when given concomitantly with

fluvoxamine suggesting that these drugs are also metabolised by the 1A2 system.

In vitro techniques

Extracts from human liver can yield the drug metabolising fraction by ultracentrifugation and can be used to assess biotransformations of various drugs (e.g. Gascon & Dayer, 1991). The addition of selective chemical inhibitors can help elucidate the specific cytochrome systems involved. Thus, inhibition of a reaction by quinidine suggests the participation of the 2D6 system, by ketoconazole of the 3A system. Another technique is to neutralise the cytochrome protein using specific antisera, and to examine the effect on the metabolic reaction of interest (Kronbach *et al*, 1989). Finally, pure human cytochromes can be produced using bacterial or yeast expression systems; already about 40 genes coding various cytochromes have been identified.

Practical implications

All of the currently available SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) have been implicated in adverse drug interactions thought to involve cytochrome p450–2D6. Most of these relate to the elevation of plasma concentrations of tricyclic antidepressants and the occasionally serious adverse effects which result (e.g. seizures (Preskorn *et al*, 1990)). Fluoxetine is most frequently implicated. There are numerous case reports of interactions in the literature and at least one prospective study describing a four-fold increase in plasma desipramine concentrations (Preskorn *et al*, 1994). Information on other SSRIs is much more limited. Paroxetine appears to elevate desipramine levels to a similar extent as that seen with fluoxetine (Alderman *et al*, 1994) and fluvoxamine has been reported to increase substantially serum levels of a number of tricyclic compounds (Hartter *et al*, 1993; Maskall & Lam, 1993), although this may, at least in part, be due to inhibition of other p450 enzymes. Sertraline may have a less profound effect on 2D6 (Alderman *et al*, 1994) but one case report described a 250% increase in desipramine levels when sertraline was given concurrently (Barros & Asnis, 1993). Based on *in vitro* studies, citalopram may be the least likely of the SSRIs to give rise to adverse drug interactions caused by inhibition of 2D6. However, citalopram has been shown to prolong to a small extent the plasma elimination half life of desipramine (Gram *et al*, 1993).

These reports of adverse interactions have two important clinical consequences. Firstly, SSRIs and tricyclic antidepressants should probably not be given concurrently unless facilities for plasma level monitoring of tricyclics are available. Patients should also be carefully monitored for tricyclic-related adverse effects. Secondly, transferring patients from a tricyclic to an SSRI should be undertaken with some caution. The tricyclic should generally be withdrawn slowly over a period of weeks and the SSRI introduced towards the end of the decremental schedule. Problems may also occur when starting a tricyclic after withdrawing fluoxetine (Hahn & Griffin, 1991) which has a much longer duration of action than the other SSRIs. After withdrawing fluoxetine, the tricyclic should be introduced at a low dose (10–25 mg) and increased very slowly according to patient tolerance.

Inhibition of cytochrome p450–2D6 by SSRIs may also provoke interactions with other drugs. As already mentioned, several antipsychotic drugs are at least partly metabolised by 2D6. Fluoxetine has been reported to increase plasma clozapine levels by around 80% (Centorrino *et al*, 1994); levels are known to be directly related to serious adverse effects such as seizures (Simpson & Cooper, 1978). Case reports in the literature also seem to suggest pharmacokinetic potentiation of other antipsychotics such as fluphenazine (Ketai, 1993). Fluoxetine should therefore be used cautiously in patients taking antipsychotic medication and perhaps avoided in those taking clozapine. There is a dearth of reports of interactions involving other SSRIs, perhaps because they have been more recently introduced. Nevertheless, they too should be used carefully. *In vitro* data favour the use of citalopram where inhibition of p450–2D6 would be dangerous.

Some SSRIs may show clinically relevant inhibition of other cytochrome enzymes. Fluvoxamine inhibits theophylline metabolism by p450–1A2 *in vitro* (Rasmussen *et al*, 1995) and may cause substantial elevation of theophylline serum levels when the two drugs are given together (Thomson *et al*, 1992). This combination should be avoided. Cytochrome p450–1A2 is also responsible for caffeine metabolism (Slaughter & Edwards, 1995) and so an increase in the adverse effects of caffeine might be expected in patients taking fluvoxamine. The importance of fluvoxamine's inhibition of 1A2 in the reported interactions with tricyclics is not yet known but the drug does seem to inhibit more than one route of metabolism *in vivo* (Hartter *et al*, 1993).

Fluoxetine may inhibit cytochrome p450–3A3/4 (Preskorn & Magnus, 1994) since it raises

alprazolam plasma concentrations by 30% when the two drugs are given together (Lasher *et al*, 1991). Increased psychomotor impairment may result. In addition, two recent case reports seem to confirm fluoxetine's inhibitory effect on p450–3A4. Horton & Bonser (1995) described substantial elevation of cyclosporin plasma levels soon after starting fluoxetine therapy. Administration of fluoxetine also appeared to be responsible for QT_c abnormalities observed in a patient also taking terfenadine (Marchiando & Cook, 1995).

Cimetidine and ketoconazole are strong inhibitors of p450 enzymes (Murray, 1992) and they are involved in a number of clinically relevant interactions with psychotropic drugs. However, their use is rarely necessary: ranitidine substitutes for cimetidine and fluconazole for ketoconazole. These alternatives are less likely to interact with psychotropic agents. Quinidine is also a potent inhibitor of p450–2D6 but is now rarely used clinically as there are a number of suitable alternatives (digoxin, disopyramide, amiodarone).

The cytochrome-mediated adverse drug interactions described here were, in general, discovered by chance and involved significant patient morbidity before discovery. As knowledge of the mechanisms of adverse interaction has advanced, *in vitro* methods have been developed and used to estimate the potential for interaction. Newer drugs (e.g. citalopram) have been tested for interactions with other psychotropics metabolised by p450 enzymes. In the future, adverse interactions may be predicted by computer modelling and molecular modelling techniques. This latter method has already been used to predict routes of metabolism mediated via p450–2D6 (Slaughter & Edwards, 1995).

Thus, *in vitro* techniques can predict potential drug interactions involving cytochrome p450-mediated metabolic pathways. This focuses clinical research activity towards direct evaluations of drug interactions in normal subjects and patients. The prescriber can then be provided with accurate information to improve the safety of patient care.

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