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Review Article

Role of CYP pharmacogenetics and drug–drug interactions in the efficacy and safety of atypical and other antipsychotic agents

Michael Murray

Abstract

Cytochrome P450 (CYP) drug oxidases play a pivotal role in the elimination of antipsychotic agents, and therefore influence the toxicity and efficacy of these drugs. Factors that affect CYP function and expression have a major impact on treatment outcomes with antipsychotic agents. In particular, aspects of CYP pharmacogenetics, and the processes of CYP induction and inhibition all influence in-vivo rates of drug elimination. Certain CYPs that mediate the oxidation of antipsychotic drugs exhibit genetic variants that may influence in-vivo activity. Thus, single nucleotide polymorphisms (SNPs) in CYP genes have been shown to encode enzymes that have decreased drug oxidation capacity. Additionally, psychopharmacotherapy has the potential for drug–drug inhibitory interactions involving CYPs, as well as drug-mediated CYP induction. Literature evidence supports a role for CYP1A2 in the clearance of the atypical antipsychotics clozapine and olanzapine; CYP1A2 is inducible by certain drugs and environmental chemicals. Recent studies have suggested that specific CYP1A2 variants possessing individual SNPs, and possibly also SNP combinations (haplotypes), in the 5′-regulatory regions may respond differently to inducing chemicals. CYP2D6 is an important catalyst of the oxidation of chlorpromazine, thioridazine, risperidone and haloperidol. Certain CYP2D6 allelic variants that encode enzymes with decreased drug oxidation capacity are more common in particular ethnic groups, which may lead to adverse effects with standard doses of psychoactive drugs. Thus, genotyping may be useful for dose optimization with certain psychoactive drugs that are substrates for CYP2D6. However, genotyping for inducible CYPs is unlikely to be sufficient to direct therapy with all antipsychotic agents. In-vivo CYP phenotyping with cocktails of drug substrates may assist at the commencement of therapy, but this approach could be complicated by pharmacokinetic interactions if applied when an antipsychotic drug regimen is ongoing.

Introduction

The incidence of schizophrenia is approximately 1% in the general population (Kessler et al 1994). Antipsychotic agents (or neuroleptics) have been used in the management of schizophrenia since the middle of the last century. Although beneficial in many patients, conventional antipsychotics induce a high incidence of extrapyramidal neurological effects, such as tardive dyskinesia and dystonias, and the development of parkinsonian symptoms, including tremor, rigidity and akathisia. Over the last 15 years the pharmacologic management of this illness has changed markedly with decreased use of the typical antipsychotic agents, that include phenothiazines, thioxanthenes and butyrophenones, and the advent of the atypical antipsychotic drugs, such as clozapine, olanzapine, risperidone and other agents (Burns 2001; Berk & Dodd 2005). Whereas typical antipsychotics are effective in the treatment of the positive signs of schizophrenia (such as hallucinations and delusions) they are less effective against the negative signs (including social withdrawal and avolition). Atypical agents are effective against both positive and negative signs of schizophrenia. The high incidence of extrapyramidal side-effects and tardive dyskinesia that is seen with the typical antipsychotic drugs results in poor compliance and treatment failure. The atypical antipsychotics are better tolerated and so compliance with drug dosage regimens is also greater. Despite these advantages, some atypical antipsychotic agents exhibit significant toxicity in patients, including clozapine neutropenia and cardiotoxicity (Baldessarini & Frankenburg 1991), and extrapyramidal effects and other adverse

Pharmacogenomics and Drug Development Group, Faculty of Pharmacy, University of Sydney, NSW 2006, Australia

M. Murray

Correspondence: M. Murray, Pharmacogenomics and Drug Development Group, Faculty of Pharmacy, University of Sydney, NSW 2006, Australia. E-mail: michaelm@pharm.usyd.edu.au

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reactions with risperidone (de Leon et al 2005). Clinical evidence is increasing that the incidence of some of these adverse effects is related to the pharmacokinetic factors of drug biotransformation and elimination. This review will discuss the role of the cytochrome P450 (CYP) drug oxidation enzyme system in the safety and efficacy of major neuroleptic agents, with emphasis on the role of CYP pharmacogenetics and drug–drug interactions in the incidence of adverse effects.

Role of CYPs in the oxidative biotransformation of drugs

Hepatic phase I oxidation, catalysed principally by the CYPs, represents the major pathway of elimination of antipsychotic drugs. The CYP mixed-function oxidases are versatile haemoprotein catalysts that activate molecular oxygen for biotransformation of a wide range of drug substrates. CYPs are members of a complex multigene family. Each CYP enzyme is encoded by an individual gene; the amino acid sequence of the encoded polypeptide determines CYP substrate specificity (Nelson et al 1996). Functional CYPs are holoenzymes that also contain a ferroprotoporphyrin IX prosthetic group at which oxygen activation occurs (Ortiz de Montellano 1995). Some drug oxidations are catalysed by multiple CYPs but others may be attributed to the activities of individual CYPs. Thus, the clearance of certain drugs may be useful surrogate markers of the in-vivo activity of specific CYP enzymes.

According to the accepted nomenclature, CYPs that are at least 40% related at the amino acid sequence level are grouped within the same family, and those that are at least 55% related are members of a subfamily (Nelson et al 1996). For example, CYP2D6 is the human enzyme that is a member of subfamily D within family 2. However, the complete nomenclature also includes CYPs from all species and CYPs 2D1–2D5 are subfamily CYP2D enzymes that are very similar to CYP2D6, but are expressed in non-human species.

CYP pharmacogenetics and drug–drug interactions

There is considerable variation in CYP expression between individuals (Roots et al 2004). Single nucleotide polymorphisms (SNPs) in CYP2D6 or CYP2C19 genes give rise to defective variant proteins or, in some cases, no protein. Subjects who possess inactive alleles are termed poor metabolizers (PMs) in the oxidation of certain drugs that are substrates for the encoded CYPs (Roots et al 2004). By comparison, extensive metabolizer (EM) subjects eliminate drugs at normal rates because their CYP alleles encode enzymes that are fully functional. Ultrarapid metabolizers eliminate CYP2D6 substrates very rapidly because they possess multiple copies of the gene and high level enzyme expression. There is a high incidence of CYP2D6 gene duplication in middle eastern populations, although this genotype is also evident in other ethnic groups (Zanger et al 2001). Indeed, differences in CYP allelic variation are significant factors in individual variation in drug response and safety in different ethnic populations. Asian populations generally exhibit a lower incidence of PM and ultrarapid phenotypes than in Caucasian populations (Zanger et al 2004). However, although there is a higher incidence of the active CYP2D6*10 allele in Asian subjects the encoded enzyme is less active in drug oxidation than the CYP2D6*1 gene product (Lam et al 2001; Yu et al 2002). These issues are especially relevant in psychopharmacology because CYP2D6 is an important catalyst in the biotransformation of typical antipsychotics, certain atypical antipsychotics and the tricyclic antidepressants (Table 1). A suitable therapeutic regimen should be devised that takes CYP2D6 genotype into account. Indeed, recent

Table 1 CYPs with major roles in the in-vivo clearance of antipsychotic agents

CYP	Antipsychotic drug	Alternate drug substrates and inhibitors that may be used in psychotic patients	Inducers	Number of allelic variants
1A2	Clozapine Olanzapine	Omeprazole	Omeprazole Cigarette smoke Barbecued meats	24 plus wild-type (also 9 predicted haplotypes)
2D6	Risperidone Chlorpromazine Thioridazine	Dextromethorphan Codeine Imipramine Nortriptyline Paroxetine	None	94 plus wild-type
3A4	Ziprasidone Quetiapine Aripiprazole Haloperidol	Erythromycin Diltiazem Ciclosporin Ethinyl estradiol	Rifampicin Carbamazepine Phenytoin Dexamethasone	38 plus wild-type

microarray-based systems for CYP2D6 genotyping could gain increasing acceptance for the future individualization of therapy with a number of psychoactive drugs (de Leon et al 2005).

CYPs accommodate many drug substrates, and so the potential for inhibitory interactions is great. Most individuals with schizophrenia take combinations of psychoactive agents for prolonged periods and many also receive additional medications from time to time. Thus, the potential risks of adverse effects from polypharmacy are highly significant in these subjects. Inhibitory drug interactions involving CYPs may involve reversible or irreversible mechanisms. In the case of reversible inhibition, CYP function is rapidly restored after the inhibitory agent has been cleared by hepatic biotransformation but, in the case of irreversible inhibition, new enzyme must be synthesized for the recovery of CYP activity (Murray & Reidy 1990). Many CNS active drugs possess significant CYP inhibition potential.

Apart from the inhibition of CYP activity, certain drugs upregulate CYP gene expression in liver (Lin & Lu 1998). Many clinical studies have implicated drugs like rifampicin, carbamazepine and phenytoin in the induction of CYPs that eliminate psychoactive drugs. In addition, certain environmental chemicals, including constituents of cigarette smoke, may also activate CYP gene transcription in cells. Important inducible CYPs that have a role in the metabolism of atypical antipsychotic drugs are CYP1A2, CYP2C9, CYP2C19 and CYP3A4 (Spina et al 2003).

The molecular mechanisms by which CYP induction occurs in response to drug and chemical exposure are becoming clearer. The aryl hydrocarbon receptor accommodates large planar aromatic hydrocarbons, such as benzo[a]pyrene, and activates the transcription of target genes, including CYP1A2 (Denison et al 1988). Certain drugs may also function as ligands for members of the nuclear hormone receptor superfamily, including the pregnane X receptor (PXR) and constitutive androstane receptor (CAR). The PXR is activated by a wide range of chemicals, including dexamethasone, rifampicin and carbamazepine, and induces CYPs 3A (Xie et al 2000; Watkins et al 2001). CYP2B genes are inducible by phenobarbital, orphenadrine and other drugs that activate the CAR (Murray et al 2003; Wang & Negishi 2003). In principle, SNPs in 5′-upstream regulatory regions in CYP genes may influence the extent of induction by altering the binding of ligand-activated transcription factors to important regulatory elements.

Pharmacokinetic variables of antipsychotic agents

The clearance rates of most antipsychotics are quite slow and their volumes of distribution in the body are large because the drugs are highly lipophilic and extensively bound to plasma and tissue proteins. Unbound concentrations of these drugs are most relevant for interpreting their interactions with CYPs. The biotransformation of antipsychotic drugs is complex and may involve several CYP-dependent pathways. Moreover, some metabolites of antipsychotic drugs are pharmacologically active and may themselves inhibit CYP enzymes with potencies that are similar to or greater than the parent drugs. Thus, there are several processes that influence CYP function that may contribute to the overall complexity of antipsychotic drug pharmacokinetics and pharmacodynamics.

In-vivo phenotyping approaches with marker substrates for particular CYPs may be useful in directing therapy with potent and toxic drugs. The Pittsburg cocktail (Frye et al 1997) uses single doses of five drugs (caffeine, chlorzoxazone, dapsone, debrisoquine and mephenytoin) as probes to the activities of CYPs 1A2, 2E1, 3A4, 2D6 and 2C19, whereas the Karolinska cocktail (Christensen et al 2003) employs a different combination of five drugs (caffeine, losartan, omeprazole, debrisoquine and quinine) as in-vivo probes of the activities of CYPs 1A2, 2C9, 2C19, 2D6 and 3A4. Several variations on this approach have also appeared. In-vivo CYPs are often inducible or readily inhibited by co-administered drugs and so a phenotyping approach is necessary; genotyping for these CYPs alone would provide incomplete information. However, phenotyping may also be problematic in psychotic patients on existing drug therapy because of the likelihood of pharmacokinetic interactions between the drugs in the phenotyping cocktail and therapeutic agents.

Before the commencement of antipsychotic therapy may be the optimal time for the application of CYP phenotyping approaches.

Clinically important atypical antipsychotic drugs: clozapine

Clozapine (Figure 1) is important because it is effective in many patients who are unresponsive to typical antipsychotics, but toxicity limits its wider use; the emergence of toxicity frequently necessitates the termination of therapy (Baldessarini & Frankenburg 1991). Although other atypical agents are less toxic they do not have the same efficacy as clozapine in all patients so that the value of the drug remains significant. Continuation of therapy with clozapine may be possible in patients suffering from drug-induced neutropenia (Esposito et al 2005). From these considerations it is clear that greater insight into the factors associated with its optimal use is critically important.

Dose itself is not a good predictor of serum concentrations. Instead, factors relating to CYP biotransformation have pronounced effects on circulating concentrations of the drug. For example, the threshold for effective serum clozapine concentrations is approximately $1.2\,\mu$M ($\sim 400\,\text{ng mL}^{-1}$), but above $3.0\,\mu$M ($1000\,\text{ng mL}^{-1}$) the risk of adverse effects is greatly increased in most individuals (Freeman & Oyewumi 1997). To an extent, monitoring of serum concentrations of clozapine has improved its safety but toxicity remains unacceptably high (Hiemke et al 2004).

As the first atypical antipsychotic released for clinical use, there is more information on the biotransformation

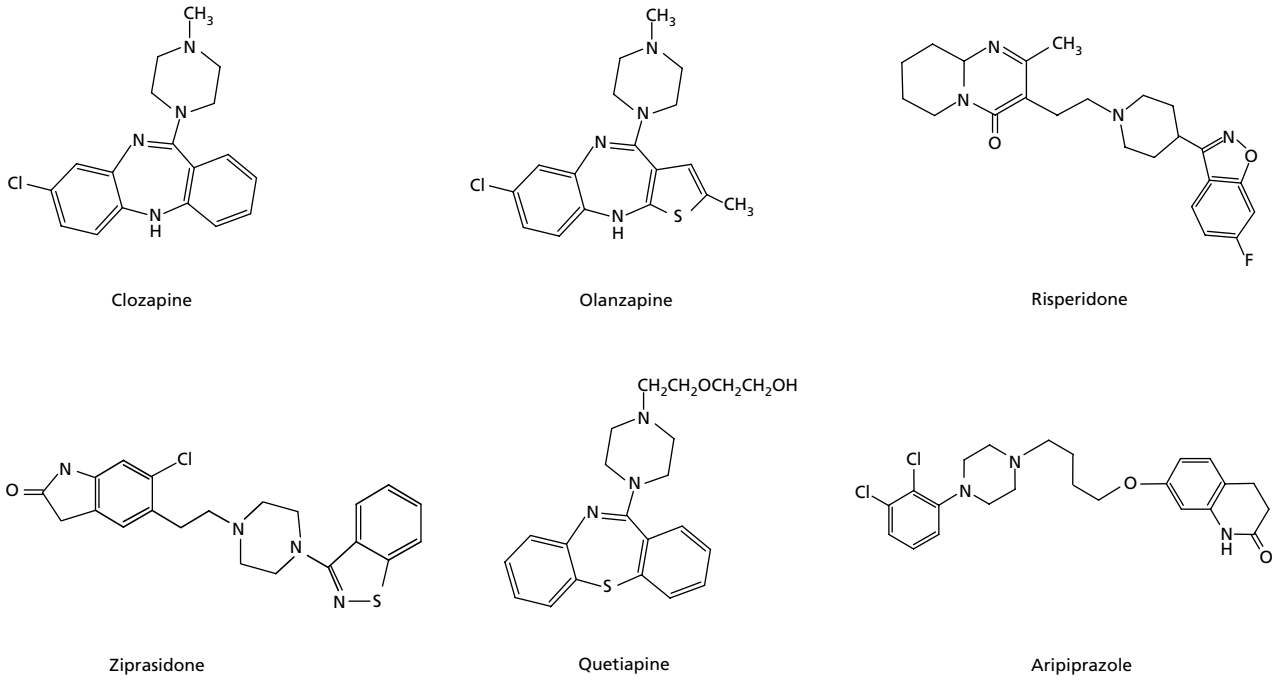

Figure 1 Structures of atypical antipsychotic drugs.

of clozapine than other atypical agents (Byerly & DeVane 1996; Taylor 1997). Clozapine is oxidized extensively to the major *N*-desmethyl- (norclozapine) and *N*-oxide metabolites, and to minor mono- and dihydroxylated products (Dain et al 1997; Figure 2). Norclozapine, but not clozapine *N*-oxide, is pharmacologically active; there is no information on the pharmacological activity of minor metabolites. The drug has a long half-life (11–105 h) that varies widely amongst individuals. Factors that influence biotransformation capacity, such as diet, age and disease, in addition to CYP pharmacogenetics and exposure to exogenous inducers and inhibitors of CYP enzymes, are highly significant. Newer pharmacogenetic approaches that take into account CYP genotype and/or phenotype may eventually assist in the optimization of therapy by individualizing treatment regimen. Critical to the development of such approaches is an appreciation of the importance of CYP-dependent biotransformation in the safety and duration of action of clozapine.

Impact of CYP1A2 activity on the safety and efficacy of clozapine therapy

CYP1A2 appears to have a major role in the metabolism of clozapine (Eiermann et al 1997; Tugnait et al 1999), although there is also evidence for the involvement of other CYPs. Such information comes from in-vitro studies in human liver microsomes and related systems, as well as from in-vivo studies, including phenotyping approaches with the alternate CYP1A2 substrate caffeine. Most individuals who cleared caffeine readily also exhibited

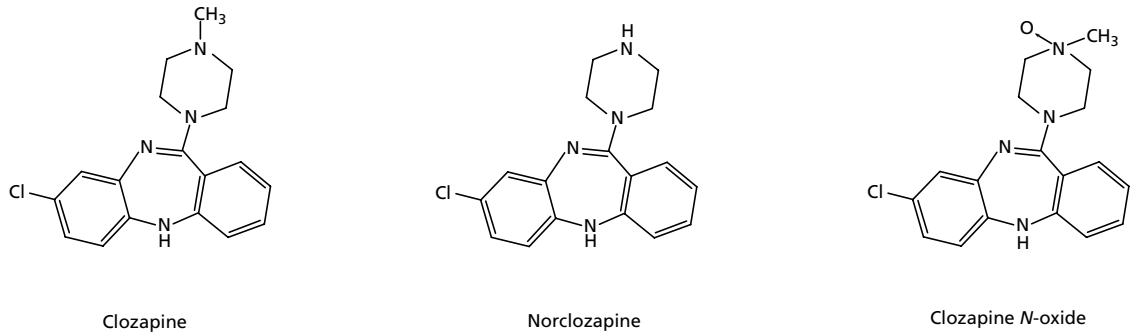

Figure 2 Structures of clozapine and its principal CYP-derived metabolites, norclozapine and clozapine *N*-oxide.

relatively low serum levels of clozapine after administration of a single dose of the drug (Bertilsson et al 1994; Raaska et al 2004). In these approaches, caffeine is employed because it is a well tolerated surrogate marker for CYP1A2. Quantification of caffeine and its metabolites in patient samples thus provides information on CYP1A2 activity in-vivo that may be of value in directing clozapine therapy.

Further data supporting a role for CYP1A2 in the biotransformation of clozapine comes from clinical studies of the inhibitory effects of fluoroquinolone antibiotics: an 80% increase in serum clozapine levels occurred after co-administration of these agents (Batty et al 1995; Markowitz et al 1997). Thus, schizophrenic patients who were stabilized on clozapine experienced significant increases in plasma clozapine and norclozapine concentrations when treated with concurrent ciprofloxacin; these increases correlated with blood concentrations of the antibiotic (Raaska & Neuvonen 2000; Gex-Fabry et al 2001).

Increased serum levels of clozapine and norclozapine during concurrent treatment with fluvoxamine have been reported in several studies (Hiemke et al 1994; DuMortier et al 1996). Schizophrenic patients who were treated with fluvoxamine for two weeks experienced greater sedation, consistent with impaired clearance of clozapine (Hiemke et al 1994); moreover the elimination half-life of clozapine was threefold longer (DuMortier et al 1996). The extent of this effect on elimination half-life varied greatly between individuals (1.7–6-fold for clozapine and 1.1–5.9-fold for norclozapine), which suggested that the further disposition of norclozapine could also be dependent on CYP1A2.

Although the interaction between clozapine and the SSRI fluvoxamine may complicate concurrent therapy, beneficial effects may arise in some instances. Thus, therapeutic serum levels were achieved in patients with lower doses of clozapine when fluvoxamine was co-administered (Lammers et al 1999). In a similar study, patients were stabilized on clozapine (100 mg daily), and after fluvoxamine was added to the regimen experienced significant increases in clozapine serum levels that coincided with more optimal clinical responses and fewer adverse effects (Lu et al 2000). Similarly, in two patients who exhibited low serum clozapine concentrations with standard doses of the drug, rapid elimination of clozapine was improved by coadministration of fluvoxamine (Alfaro et al 2001). Thus, the combination of clozapine and fluvoxamine can facilitate therapeutic control in some patients.

Further support for a clinically relevant role of CYP1A2 in clozapine clearance comes from case reports of clozapine toxicity after ingestion of caffeine (Odom-White & de Leon 1996; Carillo et al 1998). Serum levels of clozapine and norclozapine in patients were approximately 2.5- and 2-fold higher compared with the levels after removal of caffeine. There have been similar reports of acute psychotic episodes after ingestion of coffee or diet coke by clozapine patients (Carillo et al 1998). Indeed, there is growing evidence that interactions between clozapine and caffeine may produce exaggerated therapeutic effects and the emergence of extrapyramidal symptoms; substitution with decaffeinated beverages resolved this situation (Vanier & Chouinard 1994).

Drug- and chemical-mediated induction of CYP1A2 can significantly influence clozapine therapy (Campbell et al 1987; Faber & Fuhr 2004). Thus, serum levels of clozapine are generally lower in smokers than in non-smokers (Seppala et al 1999; Desai et al 2000) and in individuals who received omeprazole (Frick et al 2003; Mookhoek & Loonen 2004) or rifampicin (Wietholtz et al 1995). Removal of the inducing agent may have a pronounced effect on therapeutic control with clozapine. Smokers who were stabilized on clozapine experienced seizures and even coma on cessation of smoking, which appeared to be due to rebound elevation of serum clozapine concentrations (McCarthy 1994; Skogh et al 1999). Replacement of rifampicin with ciprofloxacin increased the serum concentrations of clozapine to 160% of pre-rifampicin levels and also improved the antipsychotic effect (Joos et al 1998). Interestingly, this therapeutic adjustment replaced an inducer of CYP1A2 with an inhibitor of the same enzyme. The suggestion that CYP1A2 is induced by rifampicin warrants further investigation because this drug is widely considered to induce CYP3A4 by acting as a PXR ligand. The possibility that inducible CYPs other than CYP1A2, such as CYP3A4, may contribute to clozapine clearance in some individuals is worthy of consideration.

There is evidence that CYP1A2 pharmacogenetics may also play a role in induction processes impacting on therapy with clozapine. Figure 3 shows the organization of the CYP1A2 gene and the locations of known SNPs that give rise to allelic variants. Two variant alleles have been reported to influence the extent of induction of CYP1A2 by cigarette smoke. From clinical reports of plasma concentrations of clozapine and caffeine, the CYP1A2*1F allele (−164C→A) appears to be more readily induced than the wild-type allele (Sachse et al 1999; Eap et al 2004) while the CYP1A2*1C allele (−3860G→A) could be less inducible (Nakajima et al 1999). Another CYP1A2 variant – the *7 allele – is characterized by an SNP at an mRNA splicing site in intron 6 and is associated with impaired RNA processing and decreased translation of CYP1A2 protein (Allorge et al 2003). However, these assertions have not been substantiated in further clinical studies with clozapine, so that the

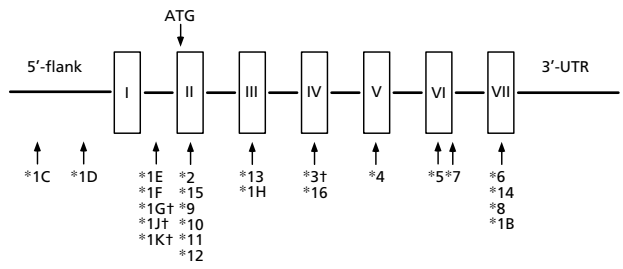

Figure 3 Genomic organization of the human CYP1A2 gene, showing the seven exons (exon I is non-coding) and locations of SNPs that give rise to allelic variants. †Indicates that these variants possess multiple SNPs. ATG, start codon; UTR, untranslated region.

association between serum concentrations of clozapine and CYP1A2 genotype in schizophrenic patients may be quite complex (Kootstra-Ros et al 2005). Indeed, in experimental studies undertaken in transfected cells, a particular arrangement of SNPs in the CYP1A2 regulatory region (the *1K haplotype) was less responsive to a chemical inducer of CYP1A2 gene expression (Aklillu et al 2003). Clinical studies are now required to evaluate the relevance of these findings to patients on clozapine.

Clozapine biotransformation by other CYPs

Evidence for the involvement of other CYPs in clozapine oxidation has been provided by in-vitro studies. Thus, CYPs 2C19 and 3A4 have been shown to catalyse clozapine *N*-demethylation, and CYP3A4 and the flavin-containing monooxygenase to mediate clozapine *N*-oxidation (Linnet & Olesen 1997; Olesen & Linnet 2001). Some, but not all, in-vitro studies with microsomal fractions and cDNA-expressed CYPs have also implicated CYP2D6 in clozapine oxidation (Fischer et al 1992). However, a relationship between CYP2D6 phenotype and the in-vitro oxidation of clozapine was not found in one study (Pirmohamed et al 1995). Despite such negative findings, in-vivo drug interactions with SSRI antidepressants have also implicated CYP2D6 in clozapine elimination. Thus, serum levels of clozapine were increased in patients who also received the SSRIs paroxetine, fluoxetine and sertraline (Wetzel et al 1998). Such effects have not been observed uniformly in clinical studies so that their general applicability remains unclear (Arranz et al 1995; Joos et al 1997).

There have been occasional reports of adverse effects in schizophrenic patients who received concurrent clozapine and risperidone (Koreen et al 1995; Tyson et al 1995; Chong et al 1996). Some of these studies reported that plasma clozapine concentrations were increased by co-administered risperidone (Koreen et al 1995; Tyson et al 1995). This has been explained in terms of a CYP2D6 interaction, although the weight of evidence is against a significant role for this enzyme in clozapine biotransformation in most individuals and the combination was well tolerated in more recent studies (Raskin et al 2000). An interesting possibility that could account for these apparently disparate findings is that individuals who are EMs for CYP2D6, and who are deficient in CYP1A2, may utilize CYP2D6 for clozapine clearance. Such individuals may well be more susceptible to interactions from co-administered drugs that are alternate substrates of CYP2D6.

Evidence for the involvement of CYP3A4 in in-vivo studies of clozapine clearance is also somewhat equivocal. In an early study, the macrolide antibiotic erythromycin (a CYP3A inhibitor) increased serum clozapine to ~2-fold of steady-state concentrations (Funderberg et al 1994), which resolved after removal of the antibiotic. However, another study found no significant difference in the clearance of serum clozapine after erythromycin co-administration (Haag et al 1999). The CYP3A4 inhibitor nefazodone elicited a dose-related increase in serum clozapine concentrations (Khan & Preskorn 2001), but the clinical significance of this interaction has been questioned (Taylor et al 1999). Co-administration of fluoxetine also led to a moderate elevation in serum levels of both clozapine and norclozapine (Centorrino et al 1996), whereas itraconazole did not significantly affect clozapine concentrations in serum (Raaska & Neuvonen 1998). Considered together, CYP3A4 seems to be of minor importance in the disposition of clozapine in man at least when a single dose of the drug is administered.

CYP inhibitory interactions involving clozapine

The in-vitro capacity of the SSRI drug fluvoxamine to inhibit five CYPs involved in clozapine oxidation has been evaluated. The K_i values ranged from 41 nM for inhibition of CYP1A2 to 24 μM for inhibition of CYP3A4; the K_i values against CYPs 2C19, 2C9 and 2D6 were in the range 0.09–4.9 μM (Olesen & Linnet 2000). These findings were largely in agreement with the work of von Moltke et al (1995, 1996), who also reported high potency inhibition of CYP1A2 by fluvoxamine, with lesser susceptibilities of CYPs 2D6 and 3A4 (higher K_i values). From these studies it was proposed that fluvoxamine may inhibit low K_i enzymes involved in clozapine oxidation in-vivo at lower serum concentrations, with more generalized inhibition at higher serum concentrations of the drug. There may be a spectrum of CYP inhibition during fluvoxamine administration, ranging from short-term generalized CYP inhibition to CYP1A2 selectivity as serum concentrations decline.

From in-vitro studies, clozapine has some capacity to inhibit the microsomal activity of CYP2C9 and CYP2D6, but exhibited only low potency against activity mediated by CYPs 1A2, 2C19 and 3A (Ring et al 1996a). A doubling of the serum levels of nortriptyline (a CYP2D6 substrate) occurred in one patient after commencing clozapine therapy (Smith & Risken 1994). The elimination half-life of clozapine was reported to increase during multiple dosage regimens (Choc et al 1990), which suggests that CYP autoinhibitory metabolites may accumulate during therapy. However, to date the potential role of clozapine metabolites in pharmacokinetic interactions does not appear to have been studied directly.

Cytotoxicity of clozapine: role of biotransformation

Clozapine exerts a range of toxic effects in cells and organs, such as agranulocytosis and cardiotoxicity. Peroxidases, including myeloperoxidase which is highly active in neutrophils, convert clozapine to a reactive nitrenium metabolite that has been implicated in the toxic mechanism (Fischer et al 1991). The nitrenium ion was detected bound to neutrophils (Liu & Uetrecht 1995) and bone marrow cells (Maggs et al 1995). The half-life for the clozapine nitrenium ion is relatively long due to delocalization of its positive charge, which could be a significant factor in the cytotoxic mechanism (Liu & Uetrecht 1995).

Some workers have suggested that a hapten reaction contributes to the mechanism of clozapine toxicity. Thus, it is held that the clozapine nitrenium ion may form protein adducts against which a cellular antibody is raised. Indeed, there have been reports of anti-neutrophil

antibodies circulating in serum of clozapine-treated patients (Pisciotta et al 1992), although their pathogenicity is yet to be established. Maggs et al (1995) have proposed that neutrophils and bone marrow cells can also be haptenated by reactive clozapine metabolites, which is followed by immune recognition and initiation of an immune response; this is manifest clinically as neutropenia and agranulocytosis.

Role of CYPs in the biotransformation of other atypical antipsychotic agents

Olanzapine

Olanzapine is an atypical antipsychotic agent that is structurally similar to clozapine, but possesses a thiophene ring in place of one of the carbocyclic systems of clozapine (Figure 1). This drug also has a long half-life of 21–54 h and is 90% bound to serum albumin (Callaghan et al 1999). Metabolites of olanzapine include the 2-hydroxymethyl-, 7-hydroxy-, 4′-*N*-oxide and 4′-*N*-desmethyl derivatives, as well as the *N*-glucuronide conjugate that is formed by phase II metabolism. CYP-dependent metabolism of olanzapine has been studied in human liver microsomes with K_m values for metabolite formation of 30–75 μM (Ring et al 1996b). These values exceed the usual free concentrations of drug in serum, and so the operative CYPs are unlikely to be saturated during therapy with the drug.

The flavin-containing monooxygenase has been implicated in *N*-oxide formation, as is also the case with clozapine. CYP1A2 has a major role in formation of the *N*-desmethyl and 7-hydroxy metabolites whereas CYP2D6 appears responsible for the 2-hydroxymethyl metabolite (Ring et al 1996b). In clinical trials a close concordance between olanzapine and caffeine clearance was observed, which underscores the apparent importance of CYP1A2 in the elimination of olanzapine (Shirley et al 2003).

In-vivo administration of fluvoxamine increased serum levels of olanzapine and decreased its clearance, whereas serum levels of the *N*-desmethyl metabolite were decreased (Maenpaa et al 1997; Weigmann et al 2001). The AUC of olanzapine was increased by fluvoxamine (Sathirakul et al 2003; Chiu et al 2004) and further support for a significant role for CYP1A2 in olanzapine clearance in-vivo is the observation that smokers had lower serum levels and higher clearance rates of the drug (Carillo et al 2003). Carbamazepine and indinavir also increased the clearance of olanzapine, which is consistent with induction of CYP1A2 and/or UDP-glucuronosyl transferase conjugation enzymes (Lucas et al 1998; Penzak et al 2002). In contrast, a recent study indicated that administration of fluvoxamine (25 mg/day) enabled the dose of olanzapine to be decreased by ~25% (Albers et al 2005). Monitoring of serum olanzapine concentrations is recommended during such combination therapy to avoid drug toxicity (Hiemke et al 2002).

The structural requirements for nitrenium ion formation by clozapine analogues have been studied. Like clozapine, olanzapine is oxidized by hypochlorous acid – the oxidant utilized by myeloperoxidase – to the corresponding nitrenium ion, but this has a lower toxic potential than the clozapine nitrenium ion. Moreover, the concentrations of olanzapine that are required for reactive metabolite formation are unlikely to be achieved during therapy with the drug (Albers et al 2005); these factors contribute to the relative safety of olanzapine over clozapine.

Risperidone

The substituted pyrimidinone risperidone (Figure 1) undergoes extensive presystemic elimination, involving high first-pass hepatic extraction by CYPs that decreases its bioavailability to ~70% (Byerly & DeVane 1996). The active 9-hydroxy metabolite acts at D2/5HT2 receptors with a potency similar to that of the parent drug (Leysen et al 1994). The half-life of the active moiety (risperidone and active metabolite) is approximately 20 h and plasma protein binding is 90% for risperidone and 70% for 9-hydroxyrisperidone.

CYP2D6 mediates the formation of the 9-hydroxy metabolite, whereas other metabolites arise by *N*-dealkylation at the piperidine nitrogen and by 7-hydroxylation on the pyrimidinone ring system (Byerly & DeVane 1996). There is a deficiency of information on the CYP enzymes involved in these pathways.

Several studies have attempted to correlate CYP2D6 polymorphic status with serum levels of risperidone and 9-hydroxyrisperidone. In one report a correlation was observed between CYP2D6 phenotype and the formation of 9-hydroxyrisperidone (Berecz et al 2002). In accord with this finding CYP2D6 PM subjects had an increased ratio of risperidone to 9-hydroxyrisperidone but no overall difference in the concentration of the active moiety (Olesen et al 1998). However, possibly as a result of the pharmacological activity of 9-hydroxyrisperidone, the significance of the CYP2D6 phenotype for the safety and efficacy of the drug remains unclear (Scordo et al 1999; Berecz et al 2004).

The debrisoquine metabolic ratio (an in-vivo marker of CYP2D6 activity) and the number of active CYP2D6 genes have been related to steady-state plasma concentrations of risperidone in patients (Berecz et al 2004). Recently, a large study of 136 schizophrenic patients who received risperidone was concluded (Kakihara et al 2005). There was a positive correlation between plasma levels of the active moiety and clinical scores during treatment, but no differences in the risperidone/9-hydroxyrisperidone ratio, clinical improvement or extrapyramidal symptoms among CYP2D6 genotypes. The incidence of adverse effects leading to discontinuation of risperidone therapy was increased in CYP2D6 PM subjects (de Leon et al 2005). On the other hand, CYP2D6 ultrarapid metabolizers exhibited low serum risperidone concentrations and may be difficult to control with the drug (Guzey et al 2000).

In a small study of patients, the CYP2D6 inhibitor paroxetine increased serum concentrations of risperidone, but not those of the 9-hydroxy metabolite (Spina et al 2001a); one patient suffered from extrapyramidal effects. Plasma concentrations of risperidone were increased by

fluoxetine co-administration to approximately fourfold of control, while the levels of 9-hydroxyrisperidone were not significantly affected (Spina et al 2002). The incidence of parkinsonian symptoms increased during longer-term therapy with fluoxetine. Thus, fluoxetine, a potent inhibitor of CYP2D6, and to a lesser extent CYP3A4, decreased risperidone clearance which led to toxic plasma concentrations.

Other CYPs may also participate in risperidone biotransformation. Risperidone 9-hydroxylation activity correlated with CYP3A4-mediated testosterone 6β-hydroxylation in human liver microsomes (Fang et al 1999). Inhibitors and inducers of CYP3A4 also influenced the serum levels of risperidone in some patients and have been associated with drug toxicity (Bork et al 1999, Jover et al 2002). Co-administration of the CYP3A4 inducer carbamazepine to a CYP2D6 EM subject suppressed serum concentrations of risperidone and increased circulating concentrations of the active 9-hydroxy metabolite over a two-week period of treatment (de Leon & Bork 1997, 1998). Removal of carbamazepine may elicit rebound increases in circulating risperidone concentrations which precipitated severe akathisia (Spina et al 2000; Takahashi et al 2001; Ono et al 2002). Plasma levels of both risperidone and 9-hydroxyrisperidone were decreased and psychotic symptoms were exacerbated by administration of carbamazepine to a CYP2D6 PM subject (Spina et al 2001b). Taken together, these relatively limited reports suggest that some individuals may rely on other CYPs for clearance of risperidone and that this may be associated with unanticipated interactions during therapy with co-administered agents.

Ziprasidone

Ziprasidone (Figure 1) is another atypical neuroleptic that also exhibits a long half-life of ~10 h and is extensively bound to plasma proteins (>99%) (Prakash et al 2000). Metabolism occurs primarily to ziprasidone sulphoxide and sulphone, benzisothiazole piperazine sulphoxide and sulphone, and *S*-methyldihydroziprasidone sulphoxide. Studies using human liver microsomes, CYP-specific inhibitors and recombinant enzymes have implicated CYP3A4, but not CYP1A2, CYP2C9, CYP2C19 or CYP2D6, in the in-vitro oxidation of ziprasidone (Prakash et al 2000). The non-CYP enzyme aldehyde oxidase has a predominant role in ziprasidone biotransformation via the reductive cleavage of the heterocyclic S-N bond of the benzoisothiazole ring to generate the dihydro analogue (Beedham et al 2003). Consistent with a significant role for CYP3A4 in ziprasidone biotransformation, co-administration of ketoconazole decreased clearance and increased serum concentrations of the drug (Miceli et al 2000a). On the other hand, administration of the CYP3A4 inducer carbamazepine elicited a modest decrease in ziprasidone C_{max} values of 27–36% (Miceli et al 2000b). Ziprasidone also inhibited oxidation reactions mediated by CYP2D6 and CYP3A4 in-vitro, but the K_i values were quite high in relation to the serum concentrations of the drug usually attained during therapy. In support of this contention, ziprasidone had minimal effect on the clearance of the CYP2D6 substrate dextromethorphan in-vivo (Wilner et al 2000).

Quetiapine

Quetiapine (Figure 1) is also metabolized principally by CYP3A4 (Prior et al 1999). Eleven metabolites formed by hepatic oxidation have been identified, including oxidation in the alkyl side chain, carbocyclic ring and heterocyclic sulphur atom, as well as phase II conjugation (DeVane & Nemeroff 2001). Two of these metabolites are pharmacologically active, but are present in plasma at only 2–12% of the concentration of the parent drug and appear unlikely to contribute substantially to the overall pharmacological effect. Quetiapine did not inhibit the in-vitro activity of CYPs 1A2, 2C9, 2C19, 2D6 or 3A4 when studied at clinically relevant concentrations, or the in-vivo clearance of antipyrine. The CYP3A4 inhibitors ketoconazole and metronidazole decreased the in-vivo clearance of quetiapine (Shelton et al 2000; DeVane & Nemeroff 2001), but cimetidine, haloperidol, risperidone and imipramine did not influence the pharmacokinetics of the drug (DeVane & Nemeroff 2001; Strakowski et al 2002). Quetiapine dosage adjustment may be necessary when co-administered with phenytoin (Wong et al 2001), thioridazine or other potent CYP3A4 inducers or inhibitors (DeVane & Nemeroff 2001).

Aripiprazole

Aripiprazole (Figure 1) is oxidized to the pharmacologically active dehydro metabolite by CYPs 2D6 and 3A4, and also forms *N*-dealkylated and hydroxylated metabolites. The drug has an extremely long half-life of up to 75 h and is extensively protein bound (99%), but the half-life is somewhat shorter on extended dosing (Swainston-Harrison & Perry 2004). Whether this involves CYP autoinduction is an interesting possibility that has not yet been evaluated. Clearance is also slower in PM subjects of CYP2D6, in whom the elimination half-life is approximately doubled (Swainston-Harrison & Perry 2004). A recent report confirmed the importance of CYP2D6 genotype on aripiprazole pharmacokinetics (Kubo et al 2005). Co-administration of the CYP3A4 inhibitor itraconazole did not produce significant adverse effects, despite decreased clearance of the antipsychotic agent (Kubo et al 2005).

Role of CYP biotransformation in the efficacy and safety of major typical neuroleptics

The phenothiazine derivatives: chlorpromazine and thioridazine

Chlorpromazine has a long and variable in-vivo half-life of 12–36 h, is highly protein bound (~99%), has a large volume of distribution and undergoes complex biotransformation to a range of metabolites. Oxidation of the heterocyclic sulphur atom of chlorpromazine (Figure 4) is mediated by CYP3A4 in human hepatic microsomes (Cashman et al 1993). 7-Hydroxylation and *N*-oxidation of chlorpromazine may involve CYP2D6 and 1A2

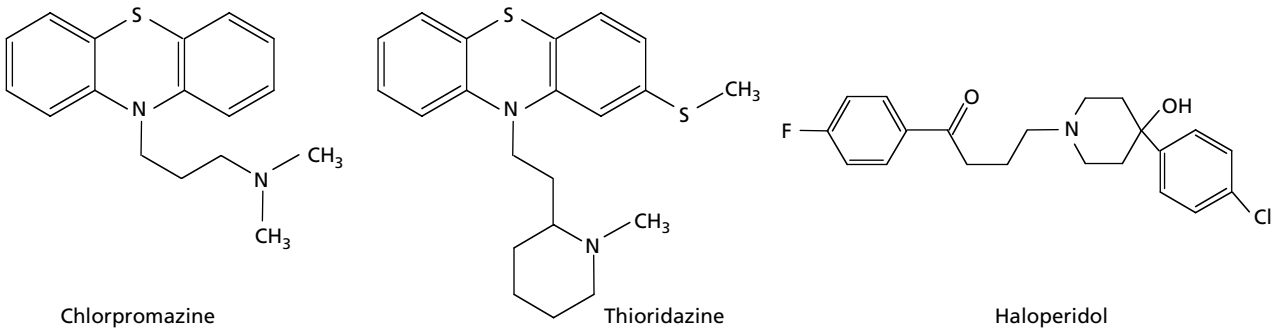

Figure 4 Structures of the major typical antipsychotic agents chlorpromazine, thioridazine and haloperidol.

(Cashman et al 1993, Yoshii et al 2000). Indeed, chlorpromazine inhibits CYP2D6 activity in microsomes in-vitro (von Bahr et al 1991; Dayer et al 1992) and also impaired the clearance of propranolol and debrisoquine in-vivo (Peet et al 1980; Miller & Rampling 1982; Syvahlahti et al 1986).

The pharmacokinetics of thioridazine are similar to those of chlorpromazine. Its biotransformation is extremely complex because the 2′-carbon atom of the piperidino substituent is also a chiral centre (Figure 4). Thus, twelve metabolites of thioridazine are formed by oxidation at the methylthio-substituent to generate the corresponding sulphoxide and sulphone metabolites, oxidation at the side chain nitrogen atom, oxidation of the heterocyclic phenothiazine sulphur atom and oxidation of the piperidino moiety (Lin et al 1993).

CYP2D6 is involved in the 2-sulphoxidation of thioridazine to mesoridazine, which is a pharmacologically active metabolite, and the further oxidation of mesoridazine to the sulphone sulforidazine (von Bahr et al 1991; Blake et al 1995; Eap et al 1996). From clinical studies the steady-state plasma concentration of thioridazine appears to be related to the number of functional CYP2D6 alleles (Berecz et al 2003). Smoking may also impact on thioridazine clearance, but the mechanism underlying this effect is unclear because a major role for CYP1A2 in thioridazine clearance seems unlikely in most subjects, and CYP2D6 is not inducible. It may be that CYP1A2 is usually a minor contributor to the clearance of thioridazine, except in those subjects who are deficient in the more important CYP2D6 enzyme of thioridazine oxidation. In support of this possibility, a role for other CYPs is suggested by the observations of Carillo et al (1999), who found that fluvoxamine decreased thioridazine clearance, and implicated CYPs 1A2 or 2C19 as ancillary enzymes of thioridazine biotransformation.

Thioridazine inhibits CYP2D6-dependent desipramine 2-hydroxylation, dextromethorphan *O*-demethylation and-codeine *O*-demethylation in human liver microsomes (Hirschowitz et al 1983; Syvahlahti et al 1986; Shin et al 1999). Activity mediated by CYPs 1A2, 2C9, 2C19 and 3A was uninhibited (Shin et al 1999). After administration of a standard dosage regimen over a 10-day period, thioridazine decreased dextromethorphan elimination in CYP2D6 EM subjects to rates comparable with those observed in PM individuals (Baumann et al 1992). Similarly, serum nortriptyline concentrations were increased in patients after co-administration of thioridazine and either nortriptyline or its precursor amitriptyline. Low dose thioridazine increased the steady-state plasma concentration of risperidone and decreased the circulating levels of the 9-hydroxy metabolite, which is consistent with the role of CYP2D6 in the biotransformation of both drugs. The interaction appeared to be particularly prominent in patients who possessed two active CYP2D6 alleles (Nakagami et al 2005). However, only twelve patients were included in the study and further investigation is required to confirm the findings. Nevertheless, cessation of thioridazine is recommended before therapy is initiated with agents that are metabolized extensively by CYP2D6. Such pharmacokinetic interactions may well be more likely in CYP2D6 EM subjects or ultrarapid metabolizers.

Haloperidol

The butyrophenone neuroleptic haloperidol (Figure 4) has a half-life in patients of approximately 18 h and is ~92% bound to plasma proteins (Froemming et al 1989). The drug is converted to haloperidol-1,2,3,4-tetrahydropyridine (reduced haloperidol) in part by CYP3A4, and is oxidized to the corresponding neurotoxic haloperidol pyridinium species by the same CYP (Usuki et al 1996; Fang et al 1997). UDP-glucuronosyltransferases mediate the phase II conjugation of haloperidol and a carbonyl reductase also contributes to the conversion of haloperidol to reduced haloperidol (Someya et al 1992). *N*-Dealkylation of haloperidol is a prominent pathway of biotransformation (Figure 5) and is mediated by CYPs 3A4 and 2D6.

In-vivo studies have supported a major role for CYP3A4 in haloperidol metabolism. Plasma concentrations of the drug were decreased in patients who had received phenytoin, phenobarbital or carbamazepine (Linnoila et al 1980; Jann et al 1989), a finding that is consistent with CYP3A4 induction by the anticonvulsants. A rebound increase in serum haloperidol concentrations to toxic levels occurred on removal of carbamazepine from the therapeutic regimen (Jann et al 1989). On the other hand, haloperidol administration increased serum levels of carbamazepine in patients to ~140% of steady-state concentrations (Iwahashi et al 1995), which suggests that haloperidol may also inhibit CYP3A4 activity in-vivo.

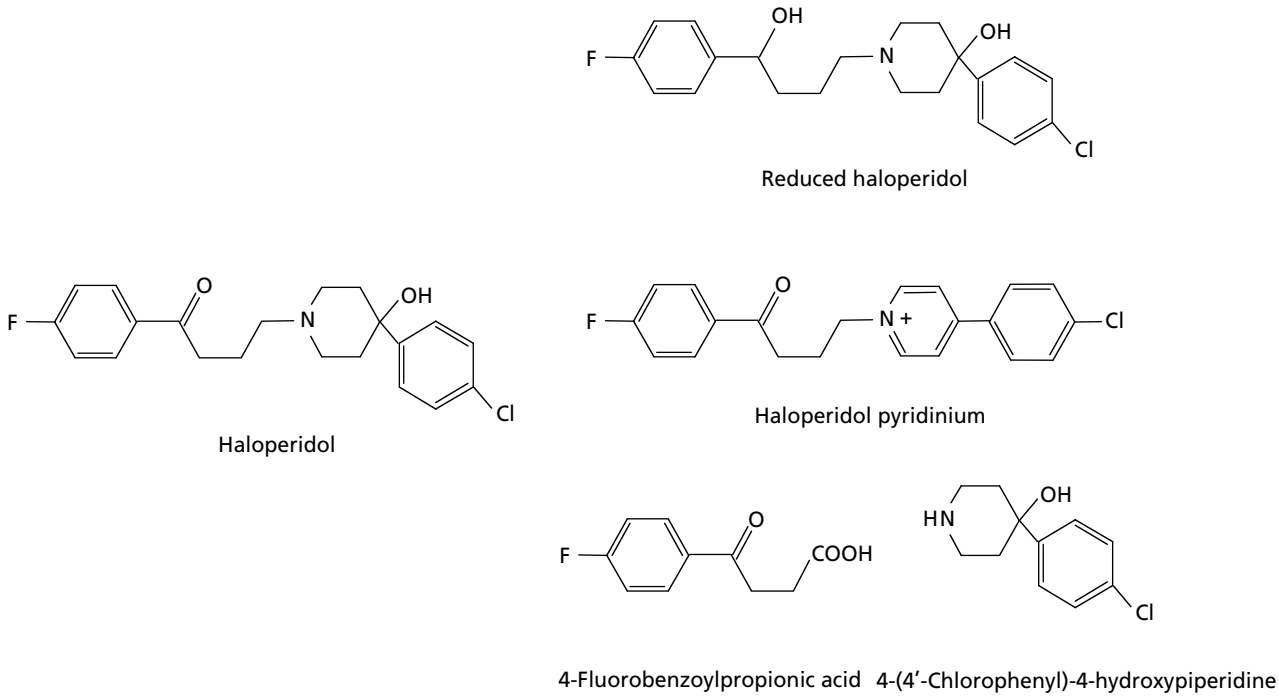

Figure 5 Structures of the principal metabolites of haloperidol.

Haloperidol inhibited CYP2D6-mediated bufuralol 1′-hydroxylation and dextromethorphan *O*-demethylation in human liver microsomes in-vitro (Fonne-Pfister & Meyer 1988; Shin et al 1999). In accord with these findings, the drug also impaired the in-vivo elimination of debrisoquine (Bock et al 1983; Syvahlahti et al 1986; Baumann et al 1992) and sparteine (Gram et al 1989). Thus, there is an association between CYP2D6 phenotype and the biotransformation of haloperidol.

Haloperidol and chlorpromazine may be used concurrently in patients. Suzuki et al (2001) studied the impact of CYP2D6 genotype on the safety of the combination. The relationship between plasma concentrations of haloperidol and the CYP2D6 genotypes *1/*1, *1/*10, *10/*10, *1/*5, and *5/*10 was evaluated in patients who also received chlorpromazine. There was a greater increase in plasma haloperidol concentrations caused by concurrent chlorpromazine in individuals with the CYP2D6*1/*1 genotype than in those with the CYP2D6*5 allele. This is consistent with the diminished activity of the CYP2D6*5 allele in the oxidation of these drugs and suggests that drug interactions may be less significant in individuals who possess that allele. It was recommended that treatment with haloperidol should be avoided in extremely slow and extremely rapid metabolizers of CYP2D6 substrates.

Conclusions

Interpretation of the mechanisms by which genetic factors and co-administered drugs may influence therapeutic efficacy and safety of atypical antipsychotic agents is increasing. The majority of experimental and clinical studies have implicated particular CYPs in the oxidative elimination of important psychoactive drugs. CYPs 1A2, 3A4 and 2D6 have emerged as possibly the most important catalysts in the oxidative biotransformation of typical and atypical antipsychotic agents. However, there is also a significant number of reports of unexpected drug–drug interactions that occur during therapy with antipsychotic agents and other drugs. Recent biochemical and molecular studies offer some insights that may account for such observations. A picture is emerging that there may be alternate CYP pathways that operate in antipsychotic drug elimination in certain individuals, particularly those with diminished metabolic capacity along the major CYP pathways. The prediction of in-vivo CYP activity profiles may prove to be valuable in directing therapeutic regimen. These reports have illustrated that CYP phenotypic and allelic differences between subjects may give rise to significant variation in the biotransformation of neuroleptics. Considered in this light it is now important to apply new pharmacogenetic (e.g. CYP2D6 microarray-based genotyping) and clinical phenotyping approaches for optimizing psychoactive drug therapy in individual patients where possible. These combined approaches are necessary to gain a proper appreciation of the in-vivo capacities of individuals to clear these potent and potentially toxic agents. It is also important to consider the possible impact of CYP genotype and phenotype as factors that may influence the incidence of pharmacokinetic interactions in different ethnic populations.

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