

Graylands Hospital Drug Bulletin

Cytochromes and Psychotropics

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Introduction

The liver is the primary site for metabolism of most psychotropic drugs. Hepatic biotransformation is via oxidation and conjugation metabolic reactions in the liver.¹ Oxidation reactions involve the cytochrome P450 (CYP) monooxygenases, a group of enzymes located in hepatocytes.¹ CYP enzymes are also present in the enterocytes of the small intestine, kidneys, lungs and brain.¹

Not every psychotropic medication is metabolised by the CYP450 system, e.g. lithium (renal), lamotrigine, lorazepam, temazepam (glucuronidation)^{1,2}

Cytochrome P450 isoenzymes

Cytochrome P450 isoenzymes are grouped into families and subfamilies based on the similarity in amino acid sequence.¹ Enzyme members of the same family are greater than 40% identical in amino acid sequence and have the same numeral prefix (e.g. CYP2). Members of the same subfamily are more than 55% identical in sequence (e.g. CYP2D). The last digit designates the individual isoenzyme (e.g. CYP2D6).¹ A total of 57 different CYP enzymes have been identified² (14 families of cytochrome enzymes are common to all mammals¹), however only six of these enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A3/4) are currently thought to be important in psychotropic drug metabolism.^{1,2}

Uridine diphosphate-glucuronosyltransferases

Uridine diphosphate-glucuronosyltransferases (UGT) are enzymes involved in the glucuronidation of medications. They produce products that are more water-soluble, less toxic and more readily excreted than the parent drug. UGTs are less well understood than the CYP enzyme system^{3,4} but are grouped into families and sub-families similar to cytochrome enzymes.

CYP Genetic Polymorphism

Variability in the DNA sequencing can result in the production of CYP450 enzymes that have increased, normal, decreased or no activity respectively.^{2,5,6}

Increased enzyme activity occurs either because of gene duplication or because a single-nucleotide polymorphism (SNP) makes the enzyme more inducible. Multiple gene copies result in a greater production of an enzyme.^{2,6}

There are 4 categories of inherited metaboliser status described: ultra-rapid metabolisers (UMs), extensive metabolisers (EMs), intermediate metabolisers (IMs) and poor metabolisers (PMs).⁶

Patients who are taking medications and are known to be significant inhibitors or inducers can have their inherited metaboliser status modified.² A person who is a poor metaboliser will not have their enzyme activity greatly changed by substances that are inhibitors or inducers. Alternatively, extensive and ultra metabolisers could become poor metabolisers when taking enzyme inhibitors.⁶

The response of individual patients to the same drug and dose administered can therefore vary considerably.⁶ Many patients will achieve the desired outcome, while others may experience no effect at all or may exhibit severe adverse effects.⁶

Genotyping is primarily of value where there is an established history of poor tolerance or lack of response to medications known to be metabolised by CYP.³ Genotyping is currently rarely used in psychiatric practice and at Graylands Hospital there have been only a few tests ordered. Despite the cost of each test (around \$250) and the fact that published evidence to date does not support ordering genotyping on a wide scale, it may become part of the future of treating psychiatric illness as a predictor of drug metabolism.^{2,6}

Features of psychotropic drug metabolism

Antipsychotics

First generation antipsychotics

Phenothiazines are generally metabolised by CYP2D6 but CYP1A2 and 3A4 can also contribute.⁷

Chlorpromazine's metabolism is complex. There is extensive first-pass metabolism after oral administration, accounting for a low oral bioavailability of unchanged drug, especially at

Table 1: Cytochrome P450 Interactions - Psychotropic medications ^{1, 3, 5, 8-13}

CYP	Substrates		Inhibitors	Inducers
1A2	Amitriptyline Caffeine Clomipramine Clozapine Fluvoxamine	Haloperidol Imipramine Mirtazapine Olanzapine Propranolol	Fluvoxamine Fluoxetine*	Tobacco smoke Modafinil
2B6	Methadone Bupropion			
2C9	Amitriptyline Fluoxetine		Fluvoxamine Fluoxetine*	
2C19	Amitriptyline Citalopram Clomipramine Diazepam	Escitalopram Fluoxetine Imipramine Moclobemide Sertraline	Fluoxetine Fluvoxamine Oxcarbazepine Topiramate	Carbamazepine
2D6	Amitriptyline Aripiprazole Atomoxetine Chlorpromazine Citalopram Clomipramine Duloxetine Escitalopram Fluoxetine Fluvoxamine Haloperidol	Mirtazapine Moclobemide Nortriptyline Olanzapine Paroxetine Phenothiazines Risperidone Sertraline Thioridazine Venlafaxine Zuclopenthixol	Bupropion Citalopram Duloxetine Escitalopram Fluoxetine Paroxetine	
3A4	Alprazolam Amitriptyline Aripiprazole Bupropion Carbamazepine Citalopram Clomipramine Diazepam Haloperidol	Methadone Midazolam Mirtazapine Pimozide Quetiapine Reboxetine Risperidone Ziprasidone Zolpidem	Fluoxetine Fluvoxamine Grapefruit juice	Carbamazepine Oxcarbazepine Modafinil St John's Wort

low oral doses. Over 150 metabolites have been postulated.⁸ The main enzyme involved is CYP2D6. Similarly, 2D6 is the main enzyme involved in the metabolism of zuclopenthixol.

Haloperidol is primarily metabolised by CYP3A4 but CYP2D6 and 1A2 also contribute. One of haloperidol's metabolites can also inhibit CYP2D6.⁷

Second generation antipsychotics

Amisulpride undergoes little metabolism and the enzymes involved in its biotransformation are yet unidentified. Amisulpride is therefore almost free of clinically relevant hepatic mediated interactions.^{4, 8}

Aripiprazole is extensively metabolised by CYP2D6 and 3A4^{4, 7}, forming an active metabolite, dehydroaripiprazole.⁴ It lacks inhibitory and inducing capabilities.⁷

Clozapine's hepatic metabolism involves multiple CYP isoenzymes. Current evidence indicates that CYP1A2 plays a major role in metabolism, though CYP2C19, 2D6, 3A4 and 2C9 also contribute.⁴

Norclozapine, which has limited pharmacological activity and clozapine N-oxide are the two major metabolites formed.⁴ Once the ratio of clozapine to norclozapine has been established for a patient it can be used as an aid to interpreting compliance from clozapine blood levels. If the ratio is significantly increased from what is normal for that patient, then the level is probably a peak level and the results interpreted accordingly.

Olanzapine is primarily metabolised by CYP1A2 and glucuronidation, with a minor effect through CYP2D6.⁷

Quetiapine is mainly metabolised by CYP3A4, forming norquetiapine. Norquetiapine is primarily eliminated via CYP3A4. CYP2D6 and CYP2C9 are also involved in quetiapine metabolism.⁸ Quetiapine

and several of its metabolites (including norquetiapine) were found to be weak to modest inhibitors 3A4, 2C19, 2D6, 1A2 and 2C9 activities in vitro, but only at very high concentrations. Based on these in vitro results it is unlikely that coadministration of quetiapine with other medicines will result in clinically significant drug inhibition of these enzymes.⁸

Risperidone is metabolised by the CYP2D6 pathway to form 9-hydroxyrisperidone (paliperidone).⁵ *Paliperidone* is primarily cleared renally⁵ and is not significantly metabolised via hepatic enzymes.

Antidepressants

Selective Serotonin Reuptake Inhibitors

Citalopram is metabolised by CYP2C19, 2D6 and 3A4 and is likely a mild to moderate inhibitor of 2D6⁷ and a weak inhibitor of 1A2 and 2C19.⁸

Escitalopram's pharmacokinetic features are essentially the same⁷ as it is the S-enantiomer of the racemate (citalopram).⁸

Fluoxetine is metabolised by CYP2C9, 2C19, 2D6 and 3A4. Fluoxetine and its metabolite norfluoxetine, potently inhibit CYP2D6 and mildly/moderately inhibit 1A2, 2B6, 2C9, 2C19 and 3A4.⁷

Fluvoxamine is primarily metabolised by CYP1A2 with some involvement by 2D6. It is a potent inhibitor of CYP1A2 and 2C19, and is a mild/moderate inhibitor of 2B6, 2C9, 2D6 and 3A4.⁷

Paroxetine is metabolised mainly by CYP2D6 and secondarily by 3A4. It also inhibits 2D6.⁷

Sertraline is a substrate of multiple cytochrome enzymes and has a mildly active metabolite, desmethylsertraline.⁷ It inhibits CYP2D6 in a dose dependent manner. Sertraline may also inhibit UGT1A4, resulting in increased lamotrigine concentrations.⁷

Serotonin & Noradrenaline Reuptake Inhibitor

Venlafaxine is metabolised to its active metabolite, *desvenlafaxine*, via CYP2D6. *Desvenlafaxine* is primarily metabolised by the UGT isoenzyme system.⁸

Duloxetine is a moderate inhibitor of 2D6.^{7, 8} Both CYP2D6 and CYP1A2 catalyse the formation of the initial oxidation steps to form 4, 5 and 6-hydroxy duloxetine. The metabolites circulating in plasma are in the conjugated form and are not pharmacologically active.⁸

Other antidepressants

Mirtazapine is metabolised by CYP2D6 and 1A2 to form the 8-hydroxy metabolite of mirtazapine, while 3A4 is considered to be responsible for the formation of the N-demethyl (pharmacologically active) and N-oxide metabolites.⁸ Mirtazapine is

present as a racemate, and clearance of the two enantiomers is via different metabolic processes.⁸

Agomelatine is rapidly oxidized by CYP1A2 (90%) and CYP2C9/ CYP2C19 (10%).⁸ The major metabolites, hydroxylated and demethylated agomelatine, are not pharmacologically active and are rapidly conjugated and eliminated in the urine.⁸

Mood Stabilisers

Carbamazepine is primarily metabolised by CYP3A4 but this enzyme is also potently induced by carbamazepine. It also induces CYP1A2, 2B6, 2C9.⁷

Lamotrigine is metabolised mostly by UGT1A4, however one or more CYP enzymes not yet identified are also involved in metabolism. The CYP pathway leads to the production of toxic metabolites. In the presence of a UGT1A4 inhibitor such as valproate, a greater percentage of lamotrigine is metabolised via the CYP pathway, leading to a greater production of toxic metabolites leading to increased adverse effects.⁷

Lithium is not metabolised hepatically. It is purely renally cleared and does not affect the metabolism of other medications.⁷

Valproate's metabolism is complex. The major elimination pathway is via glucuronidation (40 to 60%). The remainder is largely metabolised via oxidation pathways, β -oxidation accounting for 30 to 40% and ω -oxidation (CYP3A4 dependent), the remaining fraction.⁸

Significant Drug Interactions in Psychiatry

Clozapine + Lithium

Lithium increases the total white blood cell (WBC) and neutrophil count both acutely and chronically.¹⁴ Lithium has been used to increase the WBC count in patients who have developed neutropenia whilst taking clozapine, allowing clozapine treatment to continue.¹⁴ The use of lithium is not recommended to increase the WBC count in patients with clear clozapine-induced neutropenia, but has been used to elevate WBCs in cases of neutropenia not thought to be related to clozapine.¹⁴

Clozapine + Fluvoxamine

Co-administration of clozapine and fluvoxamine results in increased clozapine levels, due to fluvoxamine inhibiting metabolism of clozapine via CYP1A2. Close monitoring is required as the interaction has great variability between patients. This interaction has been used in some patients to increase clozapine levels when it has been

suspected that the patient is a PM or EM. It should be noted that increased clozapine blood levels achieved by this interaction carry the same potential for side effects as if the dose had been increased.

Clozapine, Olanzapine + Smoking

Smoking is a potent inducer of CYP1A2, which results in smokers having significantly reduced plasma concentrations of clozapine and olanzapine compared to non-smokers.¹⁵ Some constituents of tobacco smoke are potent inducers of CYP1A2,¹⁵ but nicotine replacement therapy products do not produce the same effects.

At similar doses, 20-40% lower mean clozapine concentrations have been seen in smokers compared to non-smokers.¹⁵ When patients taking clozapine have ceased smoking, clozapine levels in clinical trials have risen 13-260%.¹⁶ Clozapine metabolism can be highly variable, therefore it is difficult to predict the significance smoking cessation may have on the drug concentration.

This increase in clozapine levels is of particular significance in inpatient settings, where smoking is prohibited and therefore sudden smoking cessation can occur. In these circumstances, close monitoring of the clozapine level as well as side effects is recommended. Of particular concern is the situation when a patient is stabilised on a dose of clozapine or olanzapine in hospital where they have not been smoking. On discharge, many patients restart smoking, experience induction of CYP enzymes and risk reduction in drug levels with consequent decompensation.

Intramuscular olanzapine + intramuscular benzodiazepine

Intramuscular (IM) immediate acting olanzapine must be spaced one hour apart from IM benzodiazepines due to the risk of excessive sedation and cardiorespiratory depression.⁸ No benzodiazepines are indicated for IM administration in Australia, though clonazepam injection is used IM in acute agitation.

Sodium valproate + Lamotrigine

Sodium valproate inhibits the metabolism of lamotrigine via the UGT isoenzymes. Lamotrigine has been associated with severe, life-threatening rashes, particularly at the start of treatment when the dose is increased too rapidly.⁸

For patients already stabilised on sodium valproate, lamotrigine must be started at a lower dose and dose increases must occur more slowly than standard recommendations.⁸

Alcohol

Alcohol, or ethanol, is both a substrate and inducer of CYP2E1.⁵ This pharmacokinetic interaction does not significantly alter the metabolism of any psychotropic medications, however co-administration with other central nervous system (CNS) depressant medications can result in enhanced CNS depression. Chronic, high volume alcohol consumption can lead to cirrhosis.⁵

Antipsychotics + Coffee or Tea

Tea and coffee can cause some drugs to precipitate out of solution in vitro, but so far there is no clinical evidence to show neither that this normally affects the bioavailability of these drugs nor that it has a detrimental effect on treatment.³

It was originally reported in 1981 that phenothiazines form precipitates with tea and coffee due to the formation of a drug-tannin complex.¹⁷ Subsequent studies showed that the drug-tannin complex gives up the drug into solution if it becomes acidified, as in the stomach.¹⁸ Moreover, clinical studies of this interaction found that the plasma levels of chlorpromazine, fluphenazine, trifluoperazine and haloperidol were unaffected by the consumption of tea or coffee and the behaviour of patients also remained unchanged.¹⁸ Therefore, there appears to be little or no direct evidence that this physicochemical interaction is normally of any clinical importance.¹⁸

However, the complex formed by risperidone oral solution and tannins in tea and cola (but not coffee) does significantly reduce absorption of the drug.⁸ Olanzapine wafers should not be dispersed in cola for the same reason.¹⁹

Conclusion

Drug interactions with psychotropic medications can result in poor tolerability or reduced efficacy, both of which can affect the patient's willingness to take the medication.⁵ This bulletin has looked primarily at genetic variations of cytochrome enzymes, psychotropic metabolism and some important pharmacokinetic interactions. Pharmacodynamic interactions, such as additive sedation and anticholinergic effects, can also be important and significantly affect tolerability.

This Drug Bulletin was written by Katie Walker and Darren Schwartz and was reviewed by the Graylands Pharmacy Department and Dr Mircea Schineanu

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Comments are welcome at the email address:
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