Cytochrome P450 drug interactions: are they clinically relevant?

Jennifer Martin, Clinical Pharmacology Registrar, and Michael Fay, Medical Oncology Registrar, Alfred Hospital, Melbourne

SYNOPSIS

The cytochrome P450 system is an evolutionary system to deal with the breakdown of endogenous and exogenous chemicals in the body. There is an increasing amount of interest in this area as new information is enabling us to understand why people metabolise drugs differently and why there is a spectrum of adverse effects in different people. Understanding the cytochrome P450 system also explains the mechanisms of some drug interactions, and enables us to predict which of these are likely to be relevant in clinical practice.

Index words: pharmacokinetics, drug metabolism, warfarin.

(Aust Prescr 2001;24:10–2)

Introduction

The cytochrome P450 enzyme system is one of several metabolic systems which evolved to enable organisms to deal with lipid-soluble environmental chemicals. Latterly, the importance of the system in metabolising drugs has been recognised. The cytochrome P450 system performs this function by oxidising, hydrolysing or reducing the chemicals. This enables another group of enzymes, conjugation enzymes, to attach polar groups to make the metabolites water soluble so that they can be excreted in the urine. Although there are other enzyme systems that perform similar functions, the cytochrome P450 system is important because it is involved in most clinically relevant metabolic drug interactions.

The cytochrome P450 family

To date, about 55 human isoforms of cytochrome P450 have been discovered. These isoforms are given numbers and letters to signify their common evolutionary families. CYP1, CYP2 and CYP3 are important in drug metabolism. Each member of a family contains similar amino acids. Subfamilies are classified by the protein sequence. The known clinically relevant cytochromes are CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19 and CYP2E1. CYP3A4 is the most abundant enzyme. Most of the enzymes are involved in metabolising endogenous substrates to carry out housekeeping functions. For example, they are involved in the intermediary metabolism of steroids such as testosterone, and of lipids. Other isoforms are responsible mainly for metabolising exogenous chemicals including drugs.

Each of the isoforms has a wide substrate specificity, but each has its own specific substrate profile. This enables the whole range of chemical structures to be metabolised. These isoforms have differing regulatory mechanisms to control their activity. The regulatory mechanisms involve chemicals which induce or inhibit the enzyme. For example, CYP1A2 metabolises some carcinogenic tars in cigarette smoke and is induced by these chemicals. Members of other CYP gene families are induced by drugs such as barbiturates, anticonvulsants and rifampicin.

As well as showing some degree of substrate selectivity, the individual isoforms also show selectivity for inhibitors. For example, sulfaphenazole is a specific inhibitor of CYP2C9 whereas quinidine is a potent and selective inhibitor of the isoform CYP2D6.

Some of the isoforms exhibit genetic polymorphisms. The frequency of these polymorphisms differs markedly between ethnic groups. These genetic differences mean some people have an enzyme with reduced or no activity. Patients who are 'slow metabolisers' may have an increased risk of adverse reactions to a drug metabolised by the affected enzyme. One isoform, CYP2D6, also has alleles that result in 'superfast' metabolisers.

The liver is the main site of drug metabolism. However, isoforms occur in many tissues and CYP3A4, in particular, is found at quite high concentrations in the mucosa of the small intestine. This means that drug substrates for this isoform are subject to metabolism during absorption, while they are passing through the small intestinal mucosa, and during their first pass through the liver. Serious drug interactions resulted in the withdrawal of mibefradil (a T-type calcium channel blocker that inhibits CYP3A4) because of deaths occurring from the concurrent administration of drugs that are CYP3A4 substrates.

Principles

With new knowledge regarding substrate specificity, drug interactions involving the cytochrome P450 system are often predictable. However, they may not necessarily be clinically significant. There are several principles that help predict whether or not a drug interaction will be clinically significant. These include pharmacokinetic (what the body does to the drug) and pharmacodynamic (what the drug does to the body) factors. Other factors such as the wide variability of patient response to the same drug, concomitant medical illness and factors relating to the route and timing of administration may also be important.

Concentration-effect relationship

Clinically significant interactions occur when one drug affects the metabolism of another causing a change in concentration.

This change in concentration can have clinical implications depending on the concentration-effect relationship. A number of factors influence this, including:

- the position of the drug concentration on the dose-response curve at the time of the interaction
- the slope of the concentration-effect curve
- the size of the change in concentration of the drug
- the therapeutic index of the drug.

If the drug concentration is near the top of the response curve, adding a drug that increases its concentration will not increase its efficacy, regardless of the size of the interaction. However, the increase in concentration still may be relevant with respect to toxicity. An example of this is with drugs that increase the concentration of amlodipine. Increasing the concentration beyond a certain point does not increase the hypotensive effect.

As a general rule, if an enzyme inhibitor doubles the concentration, an enhanced drug response can occur. However, even a small increase may be important for medications with a narrow therapeutic index. Likewise a small decrease may be important for medications (such as cyclosporin) that rely on a certain concentration for their efficacy.

Patient factors

Gender, hormonal status, age and pre-existing conditions can all affect whether a drug interaction is likely to be clinically significant. For example, giving high doses of cisapride to someone with a normal heart, or normal doses to someone with a long ECG QT interval, will increase the likelihood of an arrhythmia. Drugs which reduce cisapride metabolism by inhibiting CYP3A4 (e.g. macrolides) can increase its concentration and further increase the chance of a potentially fatal arrhythmia occurring.

Administration

The route of administration and the timing of a dose can be important. Oral administration is more likely to have cytochrome P450 interactions because the drug is then subject to cytochrome P450 interactions in the gut wall as well as in the liver. An example of this is grapefruit juice. When taken at the same time as felodipine, it inhibits gut wall CYP3A4, increasing felodipine absorption across the gut wall and therefore bioavailability.

First-pass metabolism

In general, if a drug has a high first-pass metabolism through the liver one can expect a marked increase in its concentration if it is taken with another drug which inhibits metabolism. Whether or not this change in concentration is clinically significant is related to the factors affecting the concentration-effect relationship. Examples of drugs which undergo first-pass metabolism by CYP3A4 include[1]:

- **very high** first-pass metabolism: buspirone, ergotamine, lovastatin, nimodipine, saquinavir, simvastatin
- **high** first-pass metabolism: oestradiol, atorvastatin, felodipine, indinavir, isradipine, nicardipine, propafenone and tacrolimus
- **intermediate** first-pass metabolism: amiodarone, carbamazepine, carvedilol, cisapride, cyclosporin, diltiazem, ethinyloestradiol, etoposide, losartan, midazolam, nifedipine, nelfinavir, ondansetron, pimozide, sildenafil, triazolam and verapamil.

Significant interactions by drug class

Anticonvulsants

Carbamazepine, oxcarbazepine, and phenytoin reduce the concentration of oral contraceptives by inducing CYP3A4. This has resulted in some women having unplanned pregnancies.[2] Carbamazepine toxicity has occurred with 3A4 inhibitors. Phenytoin reduces the concentrations of many drugs metabolised by the cytochrome P450 system. This results in clinically significant effects for some drugs with a low therapeutic index such as warfarin and cyclosporin**.**

Immunosuppressants

Ketoconazole widely inhibits the cytochrome P450 system and doubles the oral availability of concurrently administered cyclosporin. This interaction has been used to enable patients to be given lower doses of cyclosporin. Other inhibitors of CYP3A4 have been used with similar, but less predictable results.

Tacrolimus is a substrate for CYP3A4. Clinically significant toxicity has been reported when co-administered with CYP3A4 inhibitors, such as diltiazem. CYP3A4 inducers such as carbamazepine reduce tacrolimus concentrations.

St John's wort has caused organ rejection when added to cyclosporin therapy, by inducing CYP3A4.[3]

Protease inhibitors

Ritonavir, a CYP3A4 inhibitor, is often added to saquinavir, a CYP3A4 substrate, as their interaction results in a 33% increase in the maximum concentration of saquinavir. Grapefruit juice can double the bioavailability of saquinavir, although this is not reliable enough to be used clinically. St John's wort, a CYP3A4 inducer, reduces the concentration of indinavir, a CYP3A4 substrate, by 57%. This is clinically significant as the reduction can lead to failure of therapy.[4]

Non-drug

Grapefruit juice, by inhibiting CYP3A4, increases the concentrations of several drugs. This could be clinically relevant especially in older patients, or those with liver failure.[5] Although there is an interaction with felodipine[5], there is no clinically significant effect from the interaction with amlodipine.[6]

Anti-infectives

Ketoconazole and to a lesser extent itraconazole inhibit all cytochrome P450 enzymes. These antifungal drugs can cause many clinically significant interactions by increasing the concentrations of other drugs. Fluconazole has clinically significant interactions only if the other drug has a low therapeutic index, e.g. cyclosporin. Miconazole oral gel increases the INR in patients taking warfarin.[7] Erythromycin has similar interactions to ketoconazole. Rifampicin is an

enzyme inducer and has been reported to reduce the concentration of drugs metabolised by cytochrome P450.

Cardiovascular

Felodipine concentrations are increased by grapefruit juice, erythromycin, and itraconazole, but the change in blood pressure is not usually significant.[8] It is more likely to be a problem in people who cannot tolerate even a small reduction in blood pressure. Diltiazem and verapamil increase the concentration of cyclosporin and, because of cyclosporin's low therapeutic index, this is likely to be clinically significant.

Cisapride and pimozide can cause QT prolongation by themselves if their concentrations are high enough. However, this effect will occur more frequently if the drugs are taken with CYP3A4 inhibitors such as diltiazem, macrolides, ketoconazole or grapefruit juice.

Rhabdomyolysis occurs more frequently with increasing concentration of 'statins'. The risk may be increased when statins such as the predominantly CYP3A4 metabolised lovastatin, simvastatin and atorvastatin are given with CYP3A4 inhibitors like macrolides, diltiazem and grapefruit juice.

Warfarin has a complex metabolic pathway acting as a substrate for a number of cytochrome P450 enzymes. Any change in medication in patients on warfarin requires close monitoring of the INR for a period long enough to ensure the plasma concentrations are at steady state. For example, when amiodarone, which has a half-life of 26–107 days, is added to or subtracted from warfarin it may not have its full impact on the INR for 100–400 days.

Antidepressants

Some selective serotonin reuptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine and fluvoxamine) inhibit CYP2D6. If a patient taking one of these drugs is given codeine, it cannot be converted to morphine. This results in lack of analgesic activity. The same drugs have been reported to prolong the INR when used with warfarin. Paroxetine has also caused a serious interaction by inhibiting the metabolism of perhexilene.[3]

Nefazodone is a substrate and an inhibitor of CYP3A4. It increases the concentration of several CYP3A4 substrates including cisapride, terfenadine, astemizole and pimozide. This may cause arrhythmias. Similarly nefazodone reduces the required doses of triazolam and alprazolam by 75% and 50% respectively.[10] ADRAC has reported a death from rhabdomyolysis due to the addition of nefazodone to simvastatin, a CYP3A4 substrate.[3]

Tricyclic antidepressants and SSRIs should not routinely be used together as the combination can result in a serotonergic syndrome. Most tricyclics are extensively metabolised by CYP2D6 and concentrations will increase if an inhibitory drug, e.g. an SSRI, is co-administered. The addition of fluoxetine, paroxetine or fluvoxamine (CYP2D6 inhibitors) to patients on desipramine, imipramine or nortriptyline results in a clinically significant (but often unpredictable) increase in tricyclic concentration.

Others

The concentration of oral contraceptives may be reduced by enzyme inducers. This interaction is clinically relevant with griseofulvin, rifampicin and carbamazepine. Sildenafil is a substrate of CYP3A4. It should not be prescribed with CYP3A4 inhibitors as they increase its concentration and therefore the likelihood of systemic hypotensive effects.

Conclusion

The safest way of knowing which drugs are likely to have metabolic interactions is to understand the principles behind the interactions. Drugs which induce or inhibit the enzymes of cytochrome P450 should ring alarm bells. Interacting drugs with a low therapeutic index are likely to be affected by even small changes in concentration. The importance of the change in clinical effect (such as organ rejection) also needs to be considered.

ACKNOWLEDGEMENT

We thank Professor Don Birkett for his comments on an earlier draft of this article.

NOTE

For a table of drugs metabolised by cytochrome P450 see http://www.georgetown.edu/departments/pharmacology/davetab.html

REFERENCES

1. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 2000;38:41-57.
2. Wilbur K, Ensom MH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. Clin Pharmacokinet 2000;38:355-65.
3. Drug interactions and adverse drug reactions. Aust Adv Drug React Bull 2000;19:10-2.
4. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort [letter]. Lancet 2000;355:547-8.
5. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998;46:101-10.
6. Josefsson M, Zackrisson AL, Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. Eur J Clin Pharmacol 1996;51:189-93.
7. Shenfield GM, Page M. Potentiation of warfarin action by miconazole oral gel [letter]. Aust N Z J Med 1991;21:928.
8. Edgar B, Bailey D, Bergstrand R, Johnsson G, Regardh CG. Acute effects of drinking grapefruit juice on the pharmacokinetics and dynamics of felodipine – and its potential clinical relevance. Eur J Clin Pharmacol 1992;42:313-7.
9. Kivisto KT, Kroemer HK, Eichelbaum M. The role of human cytochrome P450 enzymes in the metabolism of anticancer agents: implications for drug interactions. Br J Clin Pharmacol 1995;40:523-30.
10. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression [published erratum appears in Lancet 2000;355:2000]. Lancet 2000;355:911-8.

E-mail: j.martin@alfred.org.au

Self-test questions

The following statements are either true or false (answers on page 23)

3. The inhibition of CYP3A4 by grapefruit juice can cause clinically significant drug interactions.
4. Fluoxetine, paroxetine and fluvoxamine can reduce the analgesic effect of codeine.