The cytochrome P450 (CYP) enzyme family plays a dominant role in the biotransformation of a vast number of structurally diverse drugs. There are several factors that influence CYP activity directly or at enzyme regulation level. Many drug interactions are a result of inhibition or induction of CYP enzymes. Inhibition based drug interactions form a major part of clinically significant drug interactions. Six isoenzymes of the CYP enzyme system are mainly involved in metabolism of most of the drugs. CYP3A4 isoenzyme is the most predominant isoenzyme in the liver and is involved in the metabolism of approximately 30-40% of drugs.

The advances in the identification, isolation and characterisation of different isoenzymes of CYP enzyme system made it possible to correlate a specific isoenzyme activity with the metabolism of a specific drug. This will help in prediction of in vivo drug interactions of new drugs based on their in vitro interaction data. Based on knowledge of CYP isoenzymes involved in the metabolism of drugs, physicians may better anticipate drug interactions. This will enhance the use of rational drug therapy and better drug combinations.

**KEYWORDS**

Cytochrome P450  
isoenzymes  
drug interactions

**INTRODUCTION**

The cytochrome P450 (CYP) enzyme system consists of a superfamily of hemoproteins that catalyse the oxidative metabolism of a wide variety of exogenous chemicals including drugs, carcinogens, toxins and endogenous compounds such as steroids, fatty acids and prostaglandins. The CYP enzyme family plays an important role in phase-I metabolism of many drugs. The broad range of drugs that undergo CYP mediated oxidative biotransformation is responsible for the large number of clinically significant drug interactions during multiple drug therapy.

Clinical case reports or studies usually provide the first evidence of interaction between drugs. Several recent studies discuss such drug interactions at the molecular or enzyme level and therefore constitute an important link between clinical and experimental research. Central to this approach is an understanding of the catalytic importance of individual CYP isoenzymes in particular metabolic pathways.

**NOMENCLATURE OF CYP**

Nomenclature of CYP enzyme system has been established by CYP nomenclature committee. The name cytochrome P450 is derived from the fact that these proteins have a heme group and an unusual spectrum. These enzymes are characterised by a maximum absorption wavelength of 450 nm in the reduced state in the presence of carbon monoxide. Naming a cytochrome P450 gene include root symbol “CYP” for humans (“Cyp” for mouse and Drosophila), an Arabic numeral denoting the CYP family (e.g. CYP1, CYP2), letters A, B, C indicating subfamily (e.g. CYP3A, CYP3C) and another Arabic numeral representing the individual gene/isoenzyme/isozyme/isoform (e.g. CYP3A4, CYP3A5). Of the 74 gene families so far described, 14 exist in all mammals. These 14 families comprise of 26 mammalian subfamilies.

Each isoenzyme of CYP is a specific gene product with characteristic substrate specificity. Isoenzymes in the same family must have >40% homology in their
amino acid sequence and members of the same sub-
family must have >55% homology. In the human liver
there are at least 12 distinct CYP enzymes. At present
it appears that from about 30 isozymes, only six isoen-
zymes from the families CYP1, 2 and 3 are involved
in the hepatic metabolism of most of the drugs. These
include CYP1A2, 3A4, 2C9, 2C19, 2D6 and 2E1.

**DRUG INTERACTIONS**

Metabolic drug interactions between drugs represent
a major concern for the pharmaceutical industry, for
regulatory agencies and clinically for health care pro-
fessionals and their patients. It has been estimated
that drug interactions may be fourth to sixth leading
cause of death in hospitalised patients in United
States (U.S.). During the past few years a revolution
has taken place in our understanding of drug inter-
actions, mostly as a result of advances in the mo-
olecular biology of the CYP enzyme system. Sev-
eral factors directly or indirectly influence the CYP
activity. Many drug interactions are a result of induc-
ion or inhibition of CYP enzymes.

**Enzyme inhibition:** Inhibition based drug interac-
tions constitute the major proportion of clinically im-
portant drug interactions. A drug may inhibit the CYP
isoenzyme whether or not it is a substrate for that
isoenzyme. If the two drugs are substrate for the
same CYP isoenzyme then metabolism of one or both
the drugs may be delayed. Erythromycin and mida-
zolam both are substrates for 3A4 isoenzyme so,
there is competition for enzyme sites and metabo-
lism of midazolam is inhibited. Fluoroquinolones
antimicrobials and azole antifungals, although not
metabolised by CYP3A4 isoenzyme, cause rapid
reversible inhibition of CYP3A4 isoenzyme. Macrolide
antimicrobials, fluoxetine, lidocaine and amiodarone
cause slowly reversible inhibition of CYP
isoenzymes. These drugs are converted through
multiple CYP dependent steps to nitroso derivatives
that bind with high affinity to the reduced form of CYP
enzymes. Thus CYP enzymes are unavailable for
further oxidation and synthesis of new enzymes is
therefore the only means by which activity can be
restored and this may take several days. Cimetidine
and macrolide antimicrobials directly form complex
with heme moiety of CYP isoenzyme. Cimetidine,
amiodarone and stiripentol are non-specific inhibi-
tors of CYP450 enzyme system. Reversible inhibi-
tion can be competitive or non-competitive.

The most selective CYP inhibitors generally fall into
the category known as mechanism based inhibitors.
These drugs are substrates for the target CYP and
are converted to reactive species that covalently bind
to CYP isoenzymes leading to their inactivation. This
type of inhibition is known as irreversible or mecha-

**Enzyme induction:** Drug interactions involving en-
zyme induction are not as common as inhibition based
drug interactions but equally profound and clin-
ically important. Exposure to environmental pol-
lutants as well as large number of lipophilic drugs
can result in induction of CYP enzymes. The most
common mechanism is transcriptional activation lead-
ing to increased synthesis of more CYP enzyme pro-
teins. If a drug induces its own metabolism, it is
called autoinduction as is the case with carbama-
zepine. If induction is by other compounds it is called
foreign induction. Metabolism of the affected drug is increased leading to decreased intensity and duration of drug effects. If the drug is a prodrug or it is metabolised to an active or toxic metabolite then the effect or toxicity is increased. It is somewhat difficult to predict the time course of enzyme induction because several factors including the half-life of drug and enzyme turnover determine the time course of induction\textsuperscript{13,14}. Understanding these mechanisms of enzyme induction and inhibition is extremely important in order to give appropriate multiple drug therapy.

**Isoenzymes and drug interactions:** The advances in CYP enzyme system has made it possible to associate specific enzyme activity with the formation of a particular metabolite and in some cases to identify the major isoenzyme responsible for the total clearance of a drug. Presently we know the individual isoenzymes involved in the metabolism of large number of important drugs. Induction or inhibition of these isoenzymes leads to clinically significant drug interactions. Individual isoenzymes and their drug interactions are as follows:

**3A Isoenzymes:** Members of the 3A subfamily are the most abundant CYP enzymes in the liver and account for about 30% of CYP proteins in the liver. High levels are also present in the small intestinal epithelium and thus makes it a major contributor to presystemic elimination of orally administered drugs\textsuperscript{14}. There is considerable interindividual variability in hepatic and intestinal CYP3A activity\textsuperscript{(about 5-10 fold)}\textsuperscript{1}. Since 40-50% of drugs used in humans involve 3A mediated oxidation to some extent, the members of this subfamily are involved in many clinically important drug interactions\textsuperscript{8}. 3A4 is the major isoenzyme in the liver. 3A5 is present in the kidneys. Inducers of 3A4 usually do not upregulate 3A5 activity\textsuperscript{6,8}.

Important drug interactions of 3A4 are listed in Table 1. Noteworthy is high concentration of terfenadine, astemizole and cisapride when these drugs are taken concomitantly with azole antifungals or macrolide antibiotics or fluoxetine or fluvoxamine. High concentration of these drugs lead to life threatening cardiac arrhythmias like torsades de pointes and ventricular fibrillation\textsuperscript{15,16,18,27}. Terfenadine has been withdrawn in USA and the European Union\textsuperscript{32}. Fexofenadine, the active metabolite of terfenadine, is now marketed as a noncardiotoxic alternative to terfenadine. U.S. Food and Drug Administration(FDA) is currently considering to contraindicate the use of selective serotonin reuptake inhibitors(SSRI) with the non-sedating antihistamines\textsuperscript{41}. Mibefradil, a newer calcium channel blocker, that preferentially blocks T-type calcium channels, has already been voluntarily withdrawn from the market because of large number of drug interactions\textsuperscript{42}.

Grapefruit juice(GFJ) is often taken at breakfast in the western countries when drugs are also often taken. GFJ contains bioflavonoids mainly naringin and furacoumarin which cause mechanism based inhibition of presystemic elimination of a number of drugs and increase their bioavailability\textsuperscript{43,45}.

An important interaction involving induction of 3A is the reduction in efficacy of oral contraceptives by rifampicin and rifabutin, because of an induction of the 3A mediated metabolism of estradiol and norethisterone, the components of oral contraceptives\textsuperscript{58}.

**2D6:** This isoenzyme represents <5% of total CYP proteins\textsuperscript{47}. It has aroused great interest because of its large number of substrates(30-50 drugs) and its genetic polymorphism\textsuperscript{3}. It is also called debrisoquine hydroxylase after the drug that led to the discovery of its genetic deficiency. Many psychotropic, antiarrhythmic and β-adrenergic receptor blocker drugs are substrates as well as inhibitors of 2D6\textsuperscript{5,8}. Important drug interactions of 2D6 are listed in Table 2.

**IA2:** This is the only isoenzyme affected by tobacco. Cigarette smoking may lead to threefold increase in 1A2 activity. Theophylline is metabolised in part by 1A2, which explains why smokers require higher doses of theophylline than non-smokers\textsuperscript{70}. Alcohol inhibits metabolism of caffeine, a substrate of 1A2. Alcohol has been reported to mask the 1A2 inducing potential of smoking\textsuperscript{71}. Exposure to polyaromatic hydrocarbons found in charbroiled food can also induce this isoenzyme. This isoenzyme also causes metabolic activation of procarcinogens to carcinogens e.g. aromatic and heterocyclic amines\textsuperscript{72}. Interactions involving 1A2 are shown in Table 2.

**2C9:** S-warfarin and phenytoin, both involved in large number of drug interactions, are metabolised mainly by 2C9\textsuperscript{73,74}. St John’s wart a herbal antidepressant has been reported to decrease levels of warfarin by induction of 2C9\textsuperscript{74}. Interactions of 2C9 are shown in Table 2.
Table 1. Drug interactions involving CYP3A4 isoenzymes.

<table>
<thead>
<tr>
<th>Drugs affected (substrates)</th>
<th>INHIBITORS</th>
<th>INDUCERS</th>
</tr>
</thead>
</table>

### INHIBITORS

#### Azole antifungals:
- **Itraconazole**: Cisapride, quinidine, astemizole, midazolam, triazolam, buspirone, atorvastatin, alprazolam, midazolam, terfenadine, cyclosporin, carbamazepine, simvastatin, alprazolam, estradiol, norgesterol, lidocaine, zopiclone, zolpidem, ondansetron.
- **Fluconazole**: Terfenadine, astemizole, cyclosporin, triazolam, alprazolam.

#### Macrolide antimicrobials:
- **Erythromycin**: Carbamazepine, triazolam, buspirone, terfenadine, simvastatin.
- **Clarithromycin**: Pimozide, cyclosporin, midazolam.

#### Selective serotonin re-uptake inhibitors (SSRIs):
- **Fluoxetine**: Diazepam, alprazolam, midazolam, terfenadine, simvastatin.
- **Paroxetine**: Alprazolam.

#### Calcium channel blockers:
- **Verapamil**: Simvastatin, carbamazepine, cyclosporine, triazolam, carbamazepine, cyclosporine, quinidine, simvastatin, midazolam, alfentanil.
- **Nifedipine**: Midazolam.

#### Protease inhibitors:
- **Itraconazole**: Cisapride, quinidine, astemizole, midazolam, triazolam, buspirone, atorvastatin, alprazolam, midazolam, terfenadine, cyclosporin, carbamazepine, simvastatin, verapamil, prednisolone, ethinylestradiol, artemether.

#### Ciprofloxacin:
- **Tacrolimus**, carbamazepine, cyclosporine.

#### Cimetidine:
- **Carbamazepine**, quinidine, cyclosporine, calcium channel blockers, benzodiazepines.

#### Propofol:
- **Midazolam**.

#### Nafimidone, omeprazole:
- **Carbamazepine**.

### INDUCERS

#### Rifampicin:
- **Protease inhibitors**, diazepam, triazolam, midazolam, estradiol, norgesterol, lidocaine, zopiclone, zolpidem, ondansetron.

#### Rifabutin:
- **Protease inhibitors**, estradiol, norgesterol.

#### Carbamazepine:
- **Protease inhibitors**, midazolam, itraconazole, vincristine.

#### Phenytoin, Phenobarbital:
- **Midazolam**, vincristine, carbamazepine.

**2C19**: This isoenzyme also exhibits genetic polymorphism. It is involved in metabolism of a number of clinically important drugs e.g. omeprazole, diazepam, antidepressants and antimalarials. Important interactions are listed in Table 2.

**2E1**: This isoenzyme is involved in metabolism of low molecular weight toxins, fluorinated ether volatile anesthetics and procarcinogens. This isoenzyme is inducible by ethanol and is responsible in part for metabolism of acetaminophen. The metabolite of acetaminophen formed is highly reactive and hepatotoxic. Alcohol dependent patients may be at increased risk of acetaminophen hepatotoxicity because of induction of 2E1 by alcohol. Isoniazid has biphasic effect on 2E1 activity, a direct inhibitory
Table 2. Drug interactions involving CYP2D6 isoenzymes.

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>INHIBITORS</th>
<th>Drugs affected (substrates)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs:</strong></td>
<td>Fluoxetine</td>
<td>Imipramine, clomipramine, theophylline, caffeine, clozapine&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>Fluoxetine&lt;sup&gt;64&lt;/sup&gt;, tacrine, imipramine, clomipramine, theophylline, caffeine, clozapine&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Propranolol, quinidine&lt;sup&gt;47&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Theophylline&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Terbinafine</td>
<td>Theophylline&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Theophylline&lt;sup&gt;70&lt;/sup&gt;</td>
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</tbody>
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<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>INHIBITORS</th>
<th>Drugs affected (substrates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>Melatonin&lt;sup&gt;64&lt;/sup&gt;, tacrine, imipramine, clomipramine, theophylline, caffeine, clozapine&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>Clozapine&lt;sup&gt;66&lt;/sup&gt;, desipramine&lt;sup&gt;33,34&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>Caffeine, theophylline, antipyrine&lt;sup&gt;4&lt;/sup&gt;, tacrolimus&lt;sup&gt;46&lt;/sup&gt;, clozapine&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Grapefruit juice</td>
<td>Caffeine&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Theophylline, warfarin&lt;sup&gt;47&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Verapamil, diltiazem</td>
<td>Antipyrine&lt;sup&gt;47&lt;/sup&gt;, theophylline&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Estradiol, levonorgestrel</td>
<td>Tacrine&lt;sup&gt;49&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Omeprazole</td>
<td>Theophylline&lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Tobacco</td>
<td>Theophylline&lt;sup&gt;70&lt;/sup&gt;</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2C9</th>
<th>INHIBITORS</th>
<th>Drugs affected (substrates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketoconazole, metronidazole</td>
<td>S-warfarin&lt;sup&gt;70,73&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Phenytoin&lt;sup&gt;3&lt;/sup&gt;, S-warfarin&lt;sup&gt;73&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Amiodarone, benzbromarone, Cimetidine, stripentol</td>
<td>S-warfarin&lt;sup&gt;63,75&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>INDUCER</td>
<td>Phenytoin&lt;sup&gt;3,47&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>Phenytoin&lt;sup&gt;53&lt;/sup&gt;</td>
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<table>
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<tr>
<th>CYP2C19</th>
<th>INHIBITORS</th>
<th>Drugs affected (substrates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>Imipramine, clomipramine, amitriptyline, diazepam, chloroguanide&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>Imipramine, diazepam&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td>Diazepam&lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine</td>
<td>Phenytoin&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Imipramine, benzodiazepines&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Omeprazole&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>INDUCER</td>
<td>Omeprazole&lt;sup&gt;77&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Artemisinin</td>
<td>Omeprazole&lt;sup&gt;77&lt;/sup&gt;</td>
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<tr>
<th>CYP2E1</th>
<th>INHIBITORS</th>
<th>Drugs affected (substrates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disulfiram, isoniazid</td>
<td>Chloroxazone&lt;sup&gt;78&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>INDUCER</td>
<td>Acetaminophen&lt;sup&gt;79&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
effect immediately after its administration followed by an inducing effect because of CYP protein stabilisation. Important interactions of 2E1 are listed in Table 2.

Knowledge of substrates, inhibitors and inducers of CYP isoenzymes assists in predicting clinically significant drug interactions.

Other factors affecting the expression of CYP proteins: Apart from drugs, the following factors may affect expression of CYP proteins and lead to significant alterations in drug interactions.

Age: Activity of CYP enzymes decreases with advancing age in both the sexes. Metabolism of antipyrine (metabolised by at least 10 CYP isoenzymes, CYP1A2, 2A6, 3A4, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6 and 2E1), lidocaine, diazepam and theophylline decreases in the elderly. In vivo activities of CYP1A2, 3A4, 2C9 and 2D6 have been reported to be low at birth, but maximally increased at the young adult stage and decreased in old age.

Gender: Gender-based differences in metabolic activity of hepatic CYP isoenzymes have been identified in humans. Women exhibit higher baseline 3A4 activity than men and therefore a greater extent of interactions on average. Clearance of diazepam and prednisolone is more in women, but clearance of some drugs like propranolol are more in men. Male subjects typically have been used in most drug studies. US FDA now encourages inclusion of women in clinical trials and one of the reasons for this inclusion is variation in drug metabolising enzymes.

Hormones: Testosterone deficiency decreases CYP activity. This may be the reason for decreased activity of CYP enzymes in the elderly. Estrogen has been found to decrease oxidation of some drugs e.g. imipramine. Oral contraceptives (estrogen/progesterone combination preparations) were reported to decrease clearance of diazepam and chlor Diazepoxide. Menstrual cycle phases have variable effect on CYP activity. Theophylline clearance was found to be decreased in luteal phase. Increased metabolism of antipyrine was reported near the time of ovulation. No effect of menstrual cycle phases was found on the clearance of paracetamol, nitrazepam, salicylates and propranolol. Pituitary-liver axis is thought to be an important regulator of CYP expression. Growth hormone deficiency may lead to down regulation of CYP enzymes.

Genetic polymorphism: As each isoenzyme is a specific gene product, genetic variations influence the expression of isoenzymes in different individuals and hence the capacity of the individual to metabolise drugs. Genetic polymorphism with clinical implications has been described for 2D6, 2C19, 2C9 and 1A2. These isoenzymes exhibit polymorphism with number of allelic variants, the frequency of which often varies between different populations.

About 5-10% of Caucasians and 1% of Asians are poor metabolisers of drugs metabolised by 2D6. The frequency of poor metabolisers in Indian population is about 2-4.8%. Poor metabolisers are more prone to adverse drug reactions because metabolism is decreased and blood levels are high. CYP2D6 is involved in O-demethylation of codeine to morphine. Hence poor metabolisers exhibit impaired or no analgesia after codeine administration. Polymorphism of 2D6 contributes to the pronounced interindividual variability observed in the elimination of important drugs including tricyclic antidepressants, antipsychotics, mexiletine and several β-adrenergic receptor blockers. About 5% of whites and 20% of Asians are poor metabolisers of drugs metabolised by 2C19. The frequency of poor metabolisers in Indian population is about 11-20%. The Chinese are poor metabolisers of 2C19 and are more prone to sedative effect of diazepam and they are prescribed lower doses of diazepam. In case of 1A2 only 3-4% of white population is poor metaboliser.

An area of growing interest is that relating to consequences of inhibitory interactions of drugs subjected to isoenzyme polymorphism. Dual drug therapy for eradication of Helicobacter pylori is more beneficial in poor metabolisers of 2C19 than extensive metabolisers. This is because of decreased metabolism of omeprazole in poor metabolisers and inhibition of omeprazole metabolism by clarithromycin. Poor metabolisers of phenytoin (less 2C19 activity) will require lower doses of phenytoin and chances of interaction between phenytoin and felbamate will be less. Species variation in expression of these isoenzymes may create difficulty in extrapolating results of drug interactions from animals to humans. For example, in humans there is only one active 2D CYP isoenzyme, the 2D6 isoenzyme. In rats there are 5 or 6 different 2D isoenzymes. So, studying the effect of a drug interactions in rats may not be relevant to humans.
Hepatic disease: Many studies have shown effect of liver disease on CYP enzymes. In cirrhotic patients expression of 1A2, 2E1 and 3A isoenzymes was decreased. There are reports of alteration of clearance of drugs metabolised by 3A4 in patients of cirrhosis. Activity of 2C19 was reported to be decreased in patients of liver disease, but activity of 2D6 was unaltered. Levels of 2C subfamily have been reported to be upregulated in patients of hepatic carcinoma. Detailed knowledge of these isoenzymes affected in disease states would be used to enhance the design of rational drug therapy.

Inflammation: Acute phase response inflammatory mediators have been reported to suppress CYP activity in humans. This inhibition can lead to abnormally high plasma levels and toxicity of drugs that are metabolised by CYP dependent enzymes and have low therapeutic ratio. This phenomenon has been observed with oral anticoagulants in herpes zoster, theophylline in acute respiratory viral infection, nifedipine in acute febrile infection and quinine in malaria. Tumour necrosis factor and interleukin-1, two major inflammatory cytokines probably play a role. These factors have been reported to inhibit CYP enzymes in rats and mice.

Nutrition: Starvation and obesity are known to induce CYP enzymes in rodents, but in humans these conditions inhibit CYP enzymes. Obesity has been reported to increase metabolism of enflurane and sevoflurane in humans.

Environmental factors: Cigarette smoking is known to induce CYP enzymes. Smoking has been found to increase clearance of phenacetin and theophylline. Charbroiled food can induce CYP enzymes.

Pregnancy: Pregnancy may induce CYP enzymes. Increased metabolism of metoprolol was found in pregnant women due to induction of 2D6 isoenzyme.

Keeping in view the above factors the dose of the substrate for affected isoenzymes must be altered.

PREDICTION OF INTERACTIONS

The prediction of inhibition based interactions has been possible for new drug candidates as a result of identification of CYP isoenzymes and an increased awareness of their in vitro and in vivo behaviour. For any new drug the spectrum of drug interactions can be predicted even before the drug reaches the clinical phase of development. These predictions are based on the following principles:

If the drug of interest is substrate: In vivo and in vitro inhibition is isoenzymes specific and substrate independent. Metabolism of all drugs that are metabolised by the same isoenzyme is inhibited by inhibitors of that isoenzyme. Therefore, these drugs exhibit the same spectrum of interactions. For example phenytoin, warfarin and tolbutamide are metabolised by the same isoenzyme and exhibit a similar spectrum of interactions, even though these drugs are unrelated chemically, pharmacologically and therapeutically.

If the drug of interest is inhibitor: The potential for any new drug to inhibit the various isoenzymes of CYP can be assessed in vitro using probes. If the new drug inhibits one isoenzyme at therapeutic concentration, we can predict that it will interact with any substrate of that isoenzyme. It is important to note that a drug may inhibit an isoenzyme whether or not it is a substrate of that isoenzyme. For example, fluconazole inhibits the major isoenzyme (2C9) metabolising phenytoin, but it is not a substrate for that isoenzyme. In fact, its major route of elimination is renal. In principle, the situation for rapidly reversible inhibition is relatively straightforward i.e. the degree of inhibition depends only on the dose and elimination kinetics of the inhibitor and its affinity for the isoenzyme. However, for slowly reversible or mechanism based inhibition the situation is more complex, since not only are these factors important but in addition the rate of enzyme complexation/inactivation and synthesis as well as the degradation of the holoenzyme are determinants. Accordingly in vivo prediction of these types of inhibition is difficult. A critical aspect of any a priori prediction concerns the accuracy of the Ki determined in vitro. Experimental conditions such as incubation time, concentration of drug at the enzyme site and non-hepatic metabolism limit the ability of in vitro system to predict in vivo interactions. Although most of the predictions are still at the qualitative level, quantitative predictions have been achieved in some situations to estimate the extent of in vivo interactions from in vitro data. For example, midazolam is almost completely
metabolised by 3A4 isoenzyme. In vitro interactions by ketoconazole reveal that Ki is <0.1 µM/L. Knowing this Ki value and achievable plasma concentration of ketoconazole (>1 µg/L), one could predict from in vitro model developed by Rowland and Martin that clearance of midazolam after oral administration of ketoconazole is decreased by 95%. This prediction was confirmed by a clinical study in which midazolam clearance was decreased by 94% after ketoconazole administration.

CONCLUSION

Drug interactions involving inhibition and induction of CYP enzymes will undoubtedly continue to be of scientific interest and clinical importance simply because of enzyme’s role in metabolism of currently available and future drugs. Mibefradil, terfenadine and cisapride provide classical examples indicating the critical importance of CYP enzyme mediated drug interactions in the development, regulation and ultimate economic success of drugs. Our knowledge of the isoenzymes involved in metabolism of drugs will allow a prediction of interactions of these drugs with new drugs, to be developed in the future. Indeed an editorial from US FDA suggests that this type of information will be required for future new drugs.

By understanding the unique functions and characteristics of CYP enzymes, physicians may better anticipate and manage drug interactions. This practice will increase in future and will result in the formation of a rational information base that would indicate drug combinations to be avoided. For example inhibitors or inducers of 3A4 isoenzyme would not be given along with substrates of 3A4 and instead will receive alternative drugs that are not inhibitors or inducers of 3A4. This will improve rational drug use and facilitate better selection of drug combinations.

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