REVIEW ARTICLE

DRUG THERAPY

Drug Metabolism and Variability among Patients in Drug Response

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Physicians prescribe drugs on the basis of the characteristics of the medications and on the probability that reliable and reproducible clinical effects will result. However, differences in drug response among patients are common, often leading to challenges in optimizing a dosage regimen for an individual patient. Most major drugs are effective in only 25 to 60 percent of patients,[1] and more than 2 million cases of adverse drug reactions occur annually in the United States, including 100,000 deaths.[2] Such variability in drug response among patients is multifactorial, including environmental, genetic, and disease determinants that affect the disposition (absorption, distribution, metabolism, and excretion) of a given drug. The interplay of these factors determines the profile of the plasma concentration over time for a drug and, therefore, its elicited pharmacologic effect at the site of interaction with targets (such as receptors and enzymes). Too little exposure leads to an ineffective drug regimen, and too much creates the potential for adverse effects. Recognition of such general relationships is long-standing, and information about some drugs is extensive. In contrast, the application of the information is often less than ideal.

There is now, however, a general understanding of the many differences among patients in the disposition and clinical consequences of drugs, especially when cytochrome P-450 enzymes, a superfamily of microsomal drug-metabolizing enzymes, are involved in the metabolism of a drug. The characteristics of the various cytochrome P-450 enzymes are well established, and the involvement of these enzymes in the metabolism of most commonly used drugs is known. This knowledge may provide a basis for understanding and predicting individual differences in drug response, which can be caused by drug interactions and genetic variability.

Drugs may be metabolized by a variety of sequential or competitive chemical processes involving oxidation, reduction, and hydrolysis (phase I reactions) or glucuronidation, sulfation, acetylation, and methylation (phase II reactions). Generally, the water solubility of the resulting metabolites is greater, thus enhancing their removal. This review will focus on cytochrome P-450 enzymes that are important in oxidative drug metabolism.

Cytochrome P-450

Cytochrome P-450 enzymes (CYPs) are important in the biosynthesis and degradation of endogenous compounds such as steroids, lipids, and vitamins. They metabolize many chemicals present in the diet and environment, as well as medications.[3] Cytochrome P-450 enzymes reduce or alter the pharmacologic activity of many drugs and facilitate their elimination. Individual cytochrome P-450 enzymes are classified by their amino acid similarities and are designated by a family number, a subfamily letter, a number for an individual enzyme within the subfamily, and an asterisk followed by a number and a letter for each genetic (allelic) variant (more information is available at www.imm.ki.se/

CYPalleles/). For example, the *CYP2D6*1a* gene, identified in 1989,[4] encodes the wild-type protein CYP2D6.1.

In humans, 57 cytochrome P-450 genes have been identified, but only a relatively small number of the encoded proteins, mainly in the CYP1, CYP2, and CYP3 families, appear to contribute to the metabolism of drugs. Collectively, the cytochrome P-450 enzymes emphasized in this article are involved in approximately 80 percent of oxidative drug metabolism and account for almost 50 percent of the overall elimination of commonly used drugs. Individual cytochrome P-450 enzymes each have a unique substrate specificity, often to a particular region of a drug molecule, to a particular enantiomer, or to both. However, considerable overlap may also be present. Thus, a single cytochrome P-450 enzyme may be largely responsible for all the oxidative metabolism of a given drug, or a variety of cytochrome P-450 enzymes may contribute.

The liver is the major site of cytochrome P-450–mediated metabolism, but the enterocytes in the epithelium of the small intestine are also a potentially important site. CYP3A, in particular, is present in these enterocytes. Thus, after oral administration of a drug, cytochrome P-450 enzymes located in the intestine and in the liver may reduce the portion of the dose that reaches the systemic circulation (i.e., the bioavailability) and, subsequently, may influence the drug effects (Fig. 1 and 2) — a phenomenon termed first-pass metabolism.[7] Less than half the administered oral dose of about 40 percent of commonly used drugs is bioavailable because of limited absorption, first-pass metabolism, or both (Table 1). Drug interactions resulting in either inhibition or induction of the involved enzymes, especially those in the intestinal epithelium, can markedly alter oral bioavailability (Fig. 1 and 3). Differences among patients in drug metabolism in the intestine and liver are common, are often marked, and are frequently major contributors to differences in drug response, including adverse effects.

DRUG METABOLISM BY CYP3A

The CYP3A family of P-450 enzymes collectively describes metabolism that occurs essentially by means of two enzymes with substrate specificities so similar that they cannot be easily distinguished — CYP3A4 and, to a lesser extent, CYP3A5. (The activity of other members of the CYP3A family, such as CYP3A43, is either extremely low or, in the case of CYP3A7, present primarily in fetuses but not in adults.) CYP3A is probably the most important of all drug-metabolizing enzymes because it is abundant in both the intestinal epithelium and in the liver, where it accounts for nearly 50 percent of the cytochrome P-450 enzymes, and because it has the ability to metabolize a multitude of chemically unrelated drugs from almost every drug class (Table 2). It is likely that CYP3A is involved in the metabolism of more than half the therapeutic agents that undergo alteration by oxidation.

The activity of CYP3A can vary markedly among members of a given population, but its distribution is continuous and unimodal. This suggests that multiple genes are involved in its regulation but that individual genetic factors play a minor role. Though constitutive variability is about fivefold, CYP3A activity is readily modulated by several factors, including drug administration.

Drug interactions may reduce CYP3A activity through inhibition or may increase metabolic activity through induction. Such interactions can expand the range of variability to about 400-fold.[9,10] However, such differences in metabolism, together with associated differences in plasma drug concentrations, do not translate into linear differences in drug effects, which depend on the relationship between drug concentration and the response.

Variability in drug levels of this magnitude, if not recognized and understood, potentially presents a major therapeutic problem in dosage optimization. For example, dosage of the immunosuppressive drug cyclosporine generally must be reduced by about 75 percent in order to prevent unacceptably high drug levels (and cyclosporine toxicity) in patients concomitantly receiving the antifungal agent ketoconazole. (This increase in the level of cyclosporine, which is often monitored clinically, is so predictable that coadministration of ketoconazole with cyclosporine has at times been advocated in order to reduce the cost of long-term immunotherapy.[9,10]) In contrast, patients on a regimen that includes cyclosporine who require rifampin for tuberculosis therapy or prophylaxis may require an increase in their cyclosporine dose by a factor of two or three to achieve the same therapeutic level of cyclosporine present before they received the rifampin.

Fortunately, the identification and classification of many CYP3A substrates, inhibitors, and inducers of major clinical importance are now known (Table 2) and can be used to arrive at an appropriate

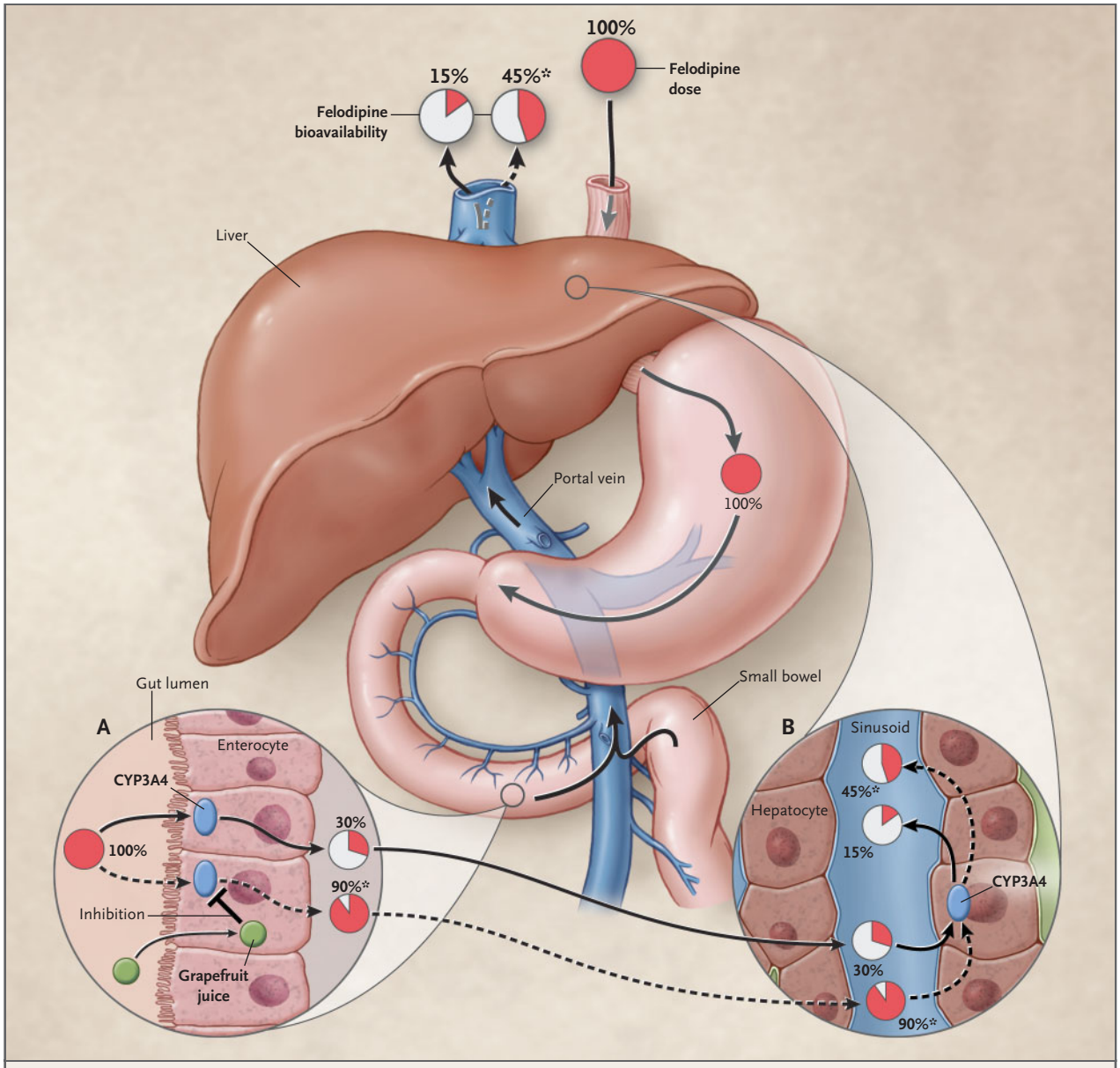

Figure 1. First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice.

CYP3A enzymes (e.g., CYP3A4) present in enterocytes of the intestinal epithelium extensively metabolize felodipine during its absorption, and on average only 30 percent of the administered dose enters the portal vein (solid line). Subsequently, CYP3A enzymes in the liver further metabolize the drug so that only 15 percent of the dose is bioavailable and finally reaches the systemic circulation and is able to exert its effects. Grapefruit juice selectively inhibits CYP3A in the enterocyte, with the net result being an increase in the oral bioavailability of felodipine by a factor of three, denoted by the asterisks and the dashed lines.

dosage strategy for clinical situations. Moreover, updated information about drug interactions is available on a number of Web sites (e.g., www.themedicalletter.com, www.drug-interactions.com, www.depts.washington.edu/didbase/, and www.imm.ki.se/CYPalleles/).

DRUG INTERACTIONS INVOLVING INHIBITION OF CYP3A

Inhibition of the metabolism of one drug by the addition of another causes problems, since plasma drug concentrations may rapidly increase after one

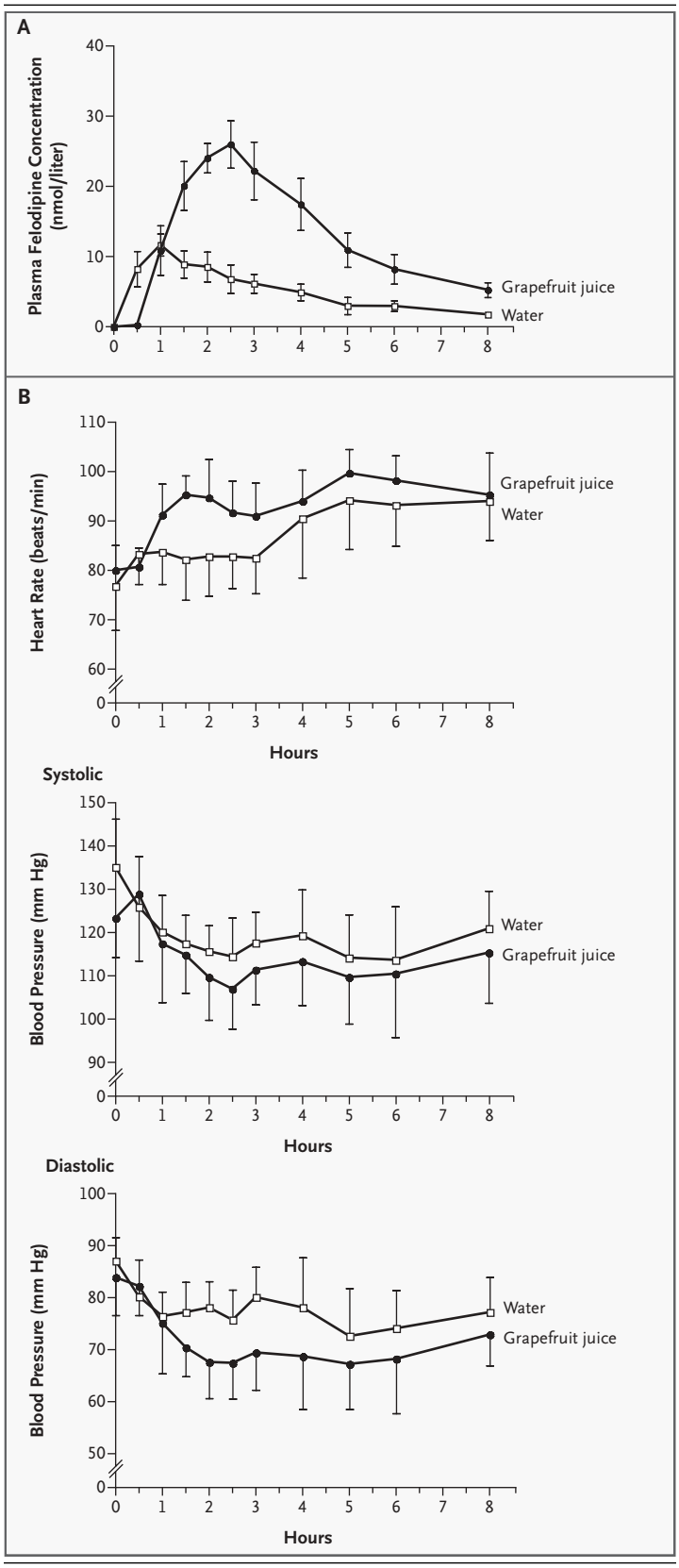

Figure 2. Consequences of the Inhibition of First-Pass Metabolism, as Exemplified by the Interaction between Felodipine and Grapefruit Juice.

The increase in the plasma concentration of felodipine as a result of the concomitant ingestion of grapefruit juice (Panel A; I bars denote SEs) leads to increases in the cardiovascular effects of the drug (Panel B; I bars denote SDs). Blood pressure and heart rate were measured while the patients were standing. Adapted from Bailey et al.,[5,6] with the permission of the publisher.

or two doses of the drug that was added. Thus, the possibility of an adverse effect caused by the interaction of the new agent with the original drug immediately increases, despite a previously stable course on that medication.[9,10]

The problem of drug interactions can be serious, as exemplified by the interaction of erythromycin, a drug that is extensively metabolized by CYP3A, and inhibitory drugs such as nitroimidazole antifungal agents, diltiazem, verapamil, and troleandomycin. Increased erythromycin levels may develop in a patient taking both erythromycin and one of these inhibitors. In turn, since erythromycin prolongs cardiac repolarization, sudden death caused by torsades de pointes may occur.[11] When an orally administered drug undergoes extensive first-pass metabolism, its bioavailability in the face of CYP3A inhibition may increase severalfold, whereas the rate of elimination may be reduced, thus prolonging the presence of the drug in the body.[7]

When a drug is administered by mouth, intestinal CYP3A enzymes are exposed to higher levels of the interacting drug and are inhibited to a greater extent than are hepatic CYP3A enzymes, which may be unaffected. The interaction between grapefruit juice and CYP3A substrates is such a situation[5,6,12] — peak drug levels may be increased by a factor of three without any change in the half-life of the medication. However, the magnitude of this phenomenon is unpredictable and varies widely among patients.

A single 8-oz (250-ml) glass of grapefruit juice can cause CYP3A inhibition for 24 to 48 hours, and regular consumption may continually inhibit intestinal CYP3A activity. For these reasons, grapefruit juice is contraindicated in patients receiving drugs that are extensively metabolized by CYP3A, and especially in patients receiving drugs with a small therapeutic window. The mechanism of this interaction probably involves direct inhibition of CYP3A

activity as well as destruction of the CYP3A enzymes by phytochemicals in grapefruit juice.

Ingestion of the calcium-channel antagonist felodipine with one or two glasses of grapefruit juice leads to an enhanced reduction in blood pressure, an increase in heart rate, and an increase in the frequency of vasodilatory adverse effects (e.g., headache), as compared with the administration of felodipine with water (Fig. 2B). Other calcium-channel antagonists (particularly amlodipine, verapamil, and diltiazem but also nisoldipine, nimodipine, nitrendipine, and pranidipine) seem to cause far smaller hemodynamic alterations and, thus, fewer and less consequential adverse effects. Other classes of medication can be affected. For example, trough blood concentrations of cyclosporine have been reported to increase by a factor of nearly two in patients who ingest grapefruit juice on a regular basis.[12]

In addition to the previously mentioned drugs, there are many other known potent inhibitors of CYP3A that, even when administered at customary doses, are likely to increase the plasma concentrations of drugs metabolized by CYP3A enzymes (Table 2). Adverse effects are predictable, unless a dosage adjustment is made. However, drugs that inhibit CYP3A activity can, at times, be used to therapeutic advantage. For example, ritonavir markedly reduces the CYP3A-mediated first-pass metabolism of certain inhibitors of human immunodeficiency virus (HIV)–encoded protease and substantially increases their levels in plasma (Table 1). This phenomenon, in fact, forms the basis for combining ritonavir with other protease inhibitors in the treatment of infection with HIV type 1.[13]

CYP3A inhibition is usually reversible, typically within two to three days, once the interacting drug is discontinued. In the case of some inhibitors (e.g., diltiazem, macrolide antibiotics, mifepristone, and delavirdine), however, the effect may last much longer, because CYP3A is destroyed and new CYP3A enzyme must be synthesized.[9]

Table 1. Some Common Drugs with Low Oral Bioavailability and Susceptibility to First-Pass Drug Interactions.

Drug	Metabolizing Enzyme	Bioavailability*
		percent
Amiodarone	CYP3A	46±22
Amitriptyline	CYP2D6, CYP3A	48±11
Aspirin	Esterases	68±3
Bromocriptine	CYP3A	3–6
Captopril	S-methyltransferase	~75
Codeine	Glucuronosyltransferase	50±7
Cyclosporine	CYP2C9, CYP3A	28±18
Desipramine	CYP2D6	38±13
Diclofenac	CYP2C9	54±2
Diltiazem	CYP3A	38±11
Erythromycin	CYP3A	35±25
Felodipine	CYP3A	15±8
Imipramine	CYP1A2, CYP2D6, CYP3A	42±3
Labetalol	Glucuronosyltransferase	18±5
Losartan	CYP2C9, CYP3A	36±15
Lovastatin	CYP3A	<5
6-Mercaptopurine	TPMT	12±7
Metoprolol	CYP2D6	38±14
Midazolam	CYP3A	44±17
Morphine	Glucuronosyltransferase	24±12
Naloxone	Glucuronosyltransferase	~2
Nefazodone	CYP2C9, CYP3A	15–23
Nicardipine	CYP3A	18±11
Nimodipine	CYP3A	10±4
Omeprazole	CYP2C19, CYP3A	53±29
Propafenone	CYP2D6	5–10
Propranolol	CYP2D6, CYP1A2	26±10
Saquinavir	CYP3A	4–13
Spironolactone	Thioesterase	25±9
Tacrine	CYP1A2	17±3
Tacrolimus	CYP3A	25±10
Terbutaline	Sulfotransferase	14±2
Triazolam	CYP3A	44
Venlafaxine	CYP2D6, CYP3A	10–45
Verapamil	CYP3A	22±8

* Plus–minus values are means ±SD.

DRUG INTERACTIONS INVOLVING INDUCTION OF CYP3A

Treatment with drugs such as the rifamycins and some anticonvulsants predictably results in a marked reduction (up to 95 percent) in the plasma concentrations of certain drugs administered concurrently (Fig. 3). Such drug interactions involve up-regulation (induction) of several proteins important in drug disposition. However, CYP3A activity is especially sensitive to such modulation,[9] and the metabolism of CYP3A substrates is particularly affected by treatment with these inducing agents (Table 2). In this situation, previously effective drug

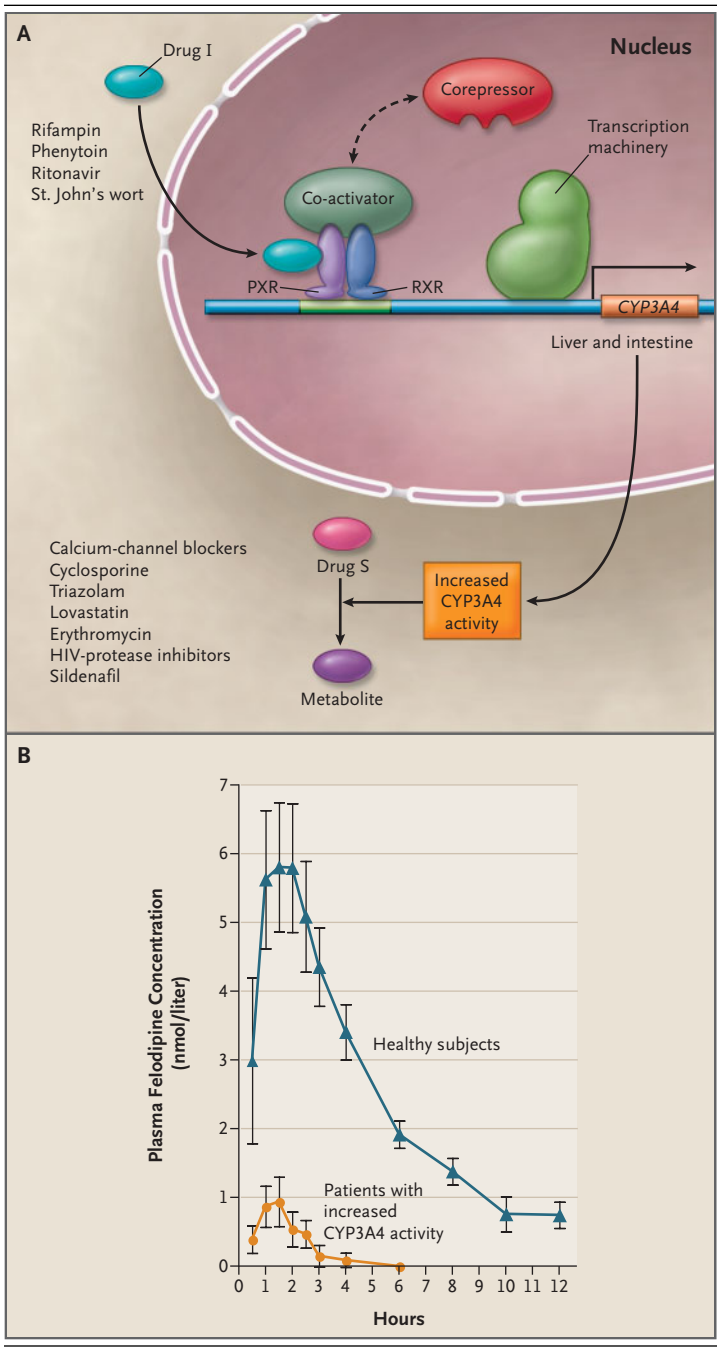

Figure 3. Mechanism of Induction of CYP3A4-Mediated Metabolism of Drug Substrates (Panel A) and the Resulting Reduced Plasma Drug Concentration (Panel B).

In Panel A, an inducing agent (Drug I) interacts with the nuclear receptor PXR (pregnane X receptor), which forms a heterodimer with the retinoid X receptor (RXR), which in turn binds to cognate recognition sites in the 5' regulatory region of the *CYP3A4* gene. As a result, transcription of DNA is up-regulated, leading to increased synthesis of CYP3A4 enzyme and enhanced oxidative metabolism of its substrates (Drug S). This causes a reduction in the plasma drug concentration as exemplified by felodipine (Panel B) and, subsequently, decreased drug effects. The same molecular mechanism is also responsible for the induction of other metabolizing enzymes and membrane transporters important in drug disposition. Comparison of the plasma felodipine concentration–time profiles in Panel B with those in Figure 2A indicates the wide range of CYP3A activity that is possible. I bars denote SEs. Panel B was adapted from Capewell et. al.,[8] with the permission of the publisher.

dosages become ineffective. For example, patients taking oral contraceptives may have breakthrough vaginal bleeding and may become pregnant if they ingest inducing agents; these may be in the form of either prescription drugs or nonprescription products such as those used in alternative medicine (e.g., St. John's wort[14]). St. John's wort is a potent inducer of CYP3A; thus, when a patient receiving cyclosporine or HIV-protease inhibitors takes St. John's wort, therapeutic failure may occur.[13-16] Characteristically, the consequences of CYP3A induction are not immediate, since new protein must be synthesized. Steady-state levels generally are reached in two to three weeks. Similarly, "washing out" the induction effect after discontinuing the inducing agent also takes several weeks. During and after these periods, adequate drug therapy is still achievable by instituting appropriate stepwise increases or decreases in the medication dose, along with monitoring plasma levels, when available.

The mechanism by which CYP3A4 is up-regulated involves intracellular binding of the inducer to the nuclear receptor, NR1I2, also called the pregnane X receptor (PXR) or the steroid X receptor. Subsequently, this receptor forms a heterodimer with the retinoid X receptor (RXR). The heterodimer then functions as a transcription factor by interacting with cognate response elements located in the 5′ regulatory region of the *CYP3A4* gene but not the *CYP3A5* gene.[17] The net result is increased synthesis of new CYP3A4 protein (Fig. 3A).

This mechanism is not unique to *CYP3A4*, since many other genes also have PXR–RXR response elements in their 5′ regulatory regions. Therefore, inducing agents such as rifampin up-regulate a battery of other proteins, including CYP2C9, phase II enzymes, and membrane transporters that limit oral absorption and distribution and enhance excretion of drugs.[18] Furthermore, nuclear receptors such as the constitutive androstane receptor also seem to

play a role in the induction of CYP3A4 and other cytochrome P-450 enzymes. The notion that PXR and the constitutive androstane receptor function as "chemo-sensors" to facilitate an adaptive response in hepatic tissue also appears to extend to other nuclear receptors and ligands involved in the regulation of fatty acids (peroxisome-proliferator–activated receptors), oxysterols (liver X receptor), and bile acids (farnesoid X receptor).[18,19]

GENETIC POLYMORPHISMS IN DRUG METABOLISM

In contrast to CYP3A, the distribution of the activity of other cytochrome P-450 enzymes among the population is polymodal; people are often classified as having either an extensive or a poor ability to metabolize. This distribution is determined by genetic polymorphisms and variant alleles — present in more than 1 percent of a given human population — that confer increased, decreased, or no activity (null). As a result, variability among people can be extremely large.[20,21] If the elimination of a drug is predominantly determined by metabolism, and a single cytochrome P-450 enzyme is primarily responsible, a functional polymorphism may have important clinical consequences. The frequency of variant alleles and their encoded proteins varies among populations according to race and ethnic background.[22] However, for a patient, the critical determinant is the genotype of the particular enzyme and not race or ethnic group, which is assigned by subjective criteria.[22,23]

DRUG METABOLISM BY CYP2D6

In the superfamily of cytochrome P-450 enzymes, CYP2D6 was the first example of genetic polymorphism identified.[4] Some 78 variants of CYP2D6 have been identified; many result in inactive enzyme, whereas some reduce the catalytic activity of the enzyme. Gene duplication — ranging from 3 to 13 copies — resulting in increased CYP2D6 activity also occurs.[22] Gene duplication is relatively rare in northern Europeans but may occur in up to 29 percent of persons with a northeastern African background. The following four phenotypic subpopulations exist that define the rate of drug metabolism by CYP2D6: persons with a poor, an intermediate, an extensive, or an ultrarapid ability to metabolize. Five to 10 percent of whites have a poor ability to metabolize (homozygous for null variants), as do 1 to 2 percent of Southeast Asians. Some variants are more common in certain populations. For example, CYP2D6*17, which has reduced activity, is found predominantly in blacks, whereas CYP2D6*10 (which also confers reduced activity) is common among Southeast Asians but not among other populations.[22] More than 65 commonly used drugs are metabolized by CYP2D6, some of which are listed in Table 3.

CYP2D6 polymorphisms are clinically important mainly because of the greater likelihood of adverse reactions among persons with poor metabolism, because of the high plasma concentration of the affected drug, and lack of efficacy among persons with ultrarapid metabolism, owing to the consequently low plasma concentration of the affected drug. Because genotyping has not been performed in most people, the response to particular drugs is usually unanticipated. For example, increased cardiovascular toxicity is more likely after usual doses of venlafaxine, a selective serotonin-reuptake in-

Table 2. Common Drug Substrates, Inhibitors, and Inducers of CYP3A, According to Drug Class.*

CYP3A Substrates	CYP3A Inhibitors	CYP3A Inducers
Calcium-channel blockers	Calcium-channel blockers	Rifamycins
Diltiazem	Diltiazem	Rifabutin
Felodipine	Verapamil	Rifampin
Nifedipine	Azole antifungal agents	Rifapentine
Verapamil	Itraconazole	Anticonvulsant agents
Immunosuppressant agents	Ketoconazole	Carbamazepine
Cyclosporine	Macrolide antibiotics	Phenobarbital
Tacrolimus	Clarithromycin	Phenytoin
Benzodiazepines	Erythromycin	Anti-HIV agents
Alprazolam	Troleandomycin	Efavirenz
Midazolam	(Not azithromycin)	Nevirapine
Triazolam	Anti-HIV agents	Others
Statins	Delavirdine	St. John's wort
Atorvastatin	Indinavir	
Lovastatin	Ritonavir	
(Not pravastatin)	Saquinavir	
Macrolide antibiotics	Others	
Clarithromycin	Grapefruit juice	
Erythromycin	Mifepristone	
Anti-HIV agents	Nefazodone	
Indinavir		
Nelfinavir		
Ritonavir		
Saquinavir		
Others		
Losartan		
Sildenafil		

* These inhibitors and inducers can interact with any CYP3A substrate and may have important clinical consequences. HIV denotes human immunodeficiency virus.

Table 3. Common Drug Substrates and Clinically Important Inhibitors of CYP2D6.

CYP2D6 Substrates	CYP2D6 Inhibitors
Beta-blockers	
Alprenolol	
Bufuralol	
Carvedilol	
Metoprolol	
Propranolol	
Timolol	
Tricyclic antidepressants	
Amitriptyline (in part)	Clomipramine
Clomipramine (in part)	
Desipramine	
Imipramine (in part)	
Nortriptyline	
Antiarrhythmic agents	
Flecainide	Quinidine
Mexiletine	
Propafenone	
Antipsychotic agents and SSRIs*	
Fluoxetine	Fluoxetine
Haloperidol	Haloperidol
Paroxetine	Paroxetine
Perphenazine	
Venlafaxine	
Opioids	
Codeine	
Dextromethorphan	

* SSRIs denotes selective serotonin-reuptake inhibitors.

hibitor (SSRI),[24] and adverse effects of tricyclic antidepressants are more frequent in persons with poor metabolism than in those with extensive metabolism.[25] Similarly, persons with poor metabolism have a greater risk of adverse effects when taking metoprolol than do persons with other types of metabolism.[26] CYP2D6 is responsible for the conversion of codeine to morphine, an active metabolite; adequate experimental or clinical pain relief is more difficult to achieve in persons with poor metabolism.[27] In contrast, several case reports have noted morphine-like adverse effects among persons with the phenotype of ultrarapid metabolism.[28,29]

A disposition to impaired CYP2D6 metabolism is generally inherited; in addition, certain drug interactions can result in such a phenotype. Quinidine, fluoxetine, and paroxetine are potent inhibitors of CYP2D6, and each of those drugs is able to convert extensive metabolism in a person into poor metabolism — a phenomenon termed phenocopying. This has clinical relevance when SSRIs are used in combination with tricyclic antidepressants. In this situation, plasma levels of tricyclic agents may be increased by a factor of two to four after coadministration of SSRIs.[30] Moreover, inhibition may last for several weeks after the discontinuation of fluoxetine, because of persistent inhibitory metabolites. In the case of codeine, inhibition of CYP2D6 may result in a loss of analgesic efficacy.

Inhibitory interactions do not occur in persons with poor metabolism who lack active enzyme, so genotype should be considered. Coadministration of inhibitors of CYP2D6, such as SSRIs, may also result in the inhibition of other drug-metabolizing enzymes, including CYP2C9, CYP2C19, and the CYP3A enzymes.[31]

DRUG METABOLISM BY CYP2C19

CYP2C19 is important in the metabolism of proton-pump inhibitors (omeprazole, lansoprazole, rabeprazole, and pantoprazole), fluoxetine, sertraline, and nelfinavir. Several inactive genetic variants exist, though two (CYP2C19*2 and CYP2C19*3) account for more than 95 percent of cases of poor metabolism of the relevant medications. Population heterogeneities in alleles and phenotypes are present. Two to three percent of whites and 4 percent of blacks have poor metabolism, whereas 10 to 25 percent of Southeast Asians have poor metabolism.[32]

Marked differences in the plasma levels of proton-pump inhibitors occur between genotypes and phenotypes and are reflected in drug-induced changes in gastric pH.[33] Accordingly, the healing rate for both gastric and duodenal ulcers shows a *CYP2C19* gene dose effect.[34] Furthermore, the cure rate for *Helicobacter pylori* infection when a proton-pump inhibitor and amoxicillin are used depends on the *CYP2C19* genotype.[34,35] For example, the cure rate with omeprazole is 28.6 percent in persons homozygous for extensive metabolism, 60 percent in those heterozygous for extensive metabolism, and 100 percent in those homozygous for poor metabolism (overall rate, 51.6 percent). The differences in efficacy are smaller when triple therapy is used (a proton-pump inhibitor, amoxicillin, and clarithromycin or metronidazole); nevertheless, patients not cured by this standard regimen are usually homozygous for extensive metabolism, and eradication can, generally, be achieved by retreatment with a higher-dose regimen.[36] The relevance of the *CYP2C19* genotype in the use of proton-pump inhibitors for the treatment of gastroesophageal reflux disease is less clear.

DRUG METABOLISM BY CYP2C9

Rarely, patients requiring unusually small doses of phenytoin to achieve therapeutic levels have been reported, and this is now known to reflect genetic polymorphism in CYP2C9.[37] Two common allelic variants of the enzyme have markedly reduced catalytic activity (about 20 percent for CYP2C9*2 and less than 10 percent for CYP2C9*3) as compared with the wild-type enzyme (CYP2C9*1).[38] Accordingly, homozygous carriers of these variant alleles, although uncommon (0.2 to 1.0 percent of persons of European descent but essentially 0 percent of persons of Southeast Asian descent), have profoundly impaired metabolism not only of phenytoin but also of other drugs such as tolbutamide, glipizide, and warfarin.

Because warfarin is widely used and has a narrow therapeutic index, its concentration-related adverse effects (e.g., the risk of bleeding) are serious. Genetic variability in the CYP2C9-mediated metabolism of warfarin is a major factor in the efficacy and toxicity of the drug. This is because warfarin is administered as a racemate (equal proportions of S- and R-enantiomers), and most of the anticoagulant effect is associated with the S-enantiomer, which in turn is predominantly metabolized by CYP2C9.

A review of several retrospective studies among outpatients receiving long-term warfarin therapy indicates that the mean maintenance dose of warfarin depends on the *CYP2C9* genotype.[39] Thus, the maintenance dose of warfarin in persons heterozygous for CYP2C9*2/*3 is lower than the dose in patients who are homozygous for the normal enzyme or who are compound heterozygotes. For the small group of patients who carry the homozygous CYP2C9*3 genotype, even smaller doses of warfarin are necessary to achieve target anticoagulation (1 to 1.5 mg a day vs. 4 to 6 mg a day for patients with the wild-type genotype).

Patients with a variant allele have a greater risk of both minor and major bleeding complications not only during initiation of anticoagulation but also during the maintenance phase. *CYP2C9* polymorphisms appear to play a smaller role in the dosage requirements and adverse events when other anticoagulants such as acenocoumarol and phenprocoumon are used, presumably because additional enzymes are involved in the metabolism of those medications.[40]

Administration of other drugs together with warfarin also may contribute to interindividual differences in the response to anticoagulation therapy through a variety of mechanisms.[41] Although some interactions were previously thought to result from perturbation in the binding of warfarin to plasma proteins, this is no longer considered to be the case. Instead, modulation of the hepatic metabolism of warfarin, especially that of the S-enantiomer, is frequently involved in clinically important interactions. Thus, potent inhibitors of CYP2C9 such as phenylbutazone, sulfinpyrazone, amiodarone, miconazole, and fluconazole all predictably and markedly produce an almost immediate increase in the anticoagulant effect, increasing the risk of bleeding when administered along with warfarin, because these agents increase the plasma concentration of the active enantiomer. In contrast, drugs that impair the metabolism of R-warfarin, such as cimetidine and omeprazole, have only moderate potentiating effects on anticoagulation; thus, reducing the dose of warfarin is generally not required.

The 5′ regulatory region of the *CYP2C9* gene contains a PXR–RXR element; therefore, as with the CYP3A4 enzyme, agents such as rifampin, barbiturates, carbamazepine, and St. John's wort will increase warfarin metabolism and the likelihood of nonefficacious therapy.[41,42] In these cases, a dose of warfarin increased by a factor of two to four is required to maintain effective anticoagulation. The dose must be appropriately reduced once the inducing agent is no longer administered, since the level of CYP2C9 activity will return to its lower constitutive level over a period of several weeks. Given these considerations and the large number of drugs that potentially interact with warfarin, it is reasonable and prudent to monitor the level of anticoagulation more frequently when interacting drugs are prescribed.

FUTURE PERSPECTIVES

Interindividual differences in drug response are important and can cause problems when a person is prescribed a drug with a narrow therapeutic index. Pharmacodynamics related to drug-target "sensitivity," determined by genetics and other factors, may contribute,[21] but pharmacokinetic considerations related to drug disposition and metabolism are also important.

The clinical consequence of drug interactions that involve drug metabolism is well recognized and is emphasized by black-box and other warnings on

drug labels. Indeed, several approved and widely used drugs (e.g., terfenadine, astemizole, and mibefradil) have been removed from the market because of the serious adverse effects that followed concomitant administration with other commonly prescribed drugs metabolized by CYP3A. Elucidation of the mechanisms of specific interactions, especially those related to the enzymes involved in drug metabolism, can and should alert physicians to potential problems if certain drugs are coadministered. The Food and Drug Administration (FDA) has a self-teaching tutorial on this topic at its Web site (available at www.fda.gov/cder/drug/drugReactions/default.htm).

For many years, there has been strong scientific evidence that the presence of variant cytochrome P-450 alleles has important clinical consequences; nevertheless, a patient's particular genotype is rarely determined in clinical practice. The incorporation of new scientific information into the clinical arena is generally slow — there is, on average, a 17-year lag.[43]

However, other factors may contribute. In the case of CYP2D6, adverse events occurring in the poor-metabolism phenotype are undesirable but rarely life-threatening. Furthermore, these affect only a small percentage of the population, and alternative treatments are usually available. Thus, the medical need for genotyping is not critical.

When warfarin and hypoglycemic agents, both metabolized by CYP2C9, are used, surrogate markers of drug effect (i.e., international normalized ratio and blood glucose levels, respectively) generally provide adequate means for monitoring the responses of individual patients. Such established clinical markers monitor the overall effect, so that if genes other than those associated with drug metabolism are involved, the desired response itself is what is followed. In fact, single-gene effects are likely to be less common than effects involving multiple genes, each of which partially contributes to the overall genetic variability in drug response. For example, a variant of the vitamin K epoxide reductase complex, subunit 1 — the molecular target of warfarin — has recently been shown to contribute along with the CYP2C9 polymorphism to interpatient variability in dosage requirements for the anticoagulant.[44]

There have not yet been prospective clinical trials showing that knowledge of a patient's genotypic profile before prescribing drugs either increases drug efficacy, prevents or reduces adverse drug reactions, or lowers the overall costs of therapy and associated sequelae.[45,46] In December 2004, the FDA approved a microarray chip designed to routinely identify polymorphisms of drug-metabolizing enzymes related to cytochrome P-450 drug metabolism.[47] This may lead to changes in how we test patients for cytochrome P-450–mediated drug-metabolizing capabilities in clinical practice. For now, however, the individual patient is probably best served by an alert physician aware of the possibility that a genetic polymorphism in drug metabolism may be a potential factor in an unexpected drug response.

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