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CHAPTER

4 Drug Biotransformation

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CASE STUDY

A 40-year-old woman presents to the emergency department of her local hospital somewhat disoriented, complaining of midsternal chest pain, abdominal pain, shaking, and vomiting for 2 days. She admits to having taken a "handful" of Lorcet (hydrocodone/acetaminophen, an opioid/nonopioid analgesic combination), Soma (carisoprodol, a centrally acting muscle relaxant), and Cymbalta (duloxetine HCl, an antidepressant/antifibromyalgia agent) 2 days earlier. On physical examination, the sclera of her eyes shows yellow discoloration. Laboratory analyses of blood drawn within an hour of her admission reveal abnormal liver function as indicated by the increased indices: alkaline phosphatase 302 (41–133),* alanine aminotransferase (ALT) 351 (7–56),* aspartate aminotransferase (AST) 1045 (0–35),* bilirubin 3.33 mg/dL (0.1–1.2),* and prothrombin time of 19.8 seconds (11–15).* In addition, plasma bicarbonate is reduced, and she has ~45% reduced glomerular filtration rate from the normal value at her age, elevated serum creatinine and blood urea nitrogen, markedly reduced blood glucose of 35 mg/dL, and a plasma acetaminophen concentration of 75 mcg/mL (10–20).* Her serum titer is significantly positive for hepatitis C virus (HCV). Given these data, how would you proceed with the management of this case?

*Normal values are in parentheses.

Humans are exposed daily to a wide variety of foreign compounds called **xenobiotics**—substances absorbed across the lungs or skin or, more commonly, ingested either unintentionally as compounds present in food and drink or deliberately as drugs for therapeutic or "recreational" purposes. Exposure to environmental xenobiotics may be inadvertent and accidental or—when they are present as components of air, water, and food—inescapable. Some xenobiotics are innocuous, but many can provoke biologic responses. Such biologic responses often depend on conversion of the absorbed substance into an active metabolite. The discussion that follows is applicable to xenobiotics in general (including drugs) and to some extent to endogenous compounds.

WHY IS DRUG BIOTRANSFORMATION NECESSARY?

The mammalian drug biotransformation systems are thought to have first evolved from the need to detoxify and eliminate plant and bacterial bioproducts and toxins, which later extended to drugs and other environmental xenobiotics. Renal excretion plays a pivotal role in terminating the biologic activity of some drugs, particularly those that have small molecular volumes or possess polar characteristics, such as functional groups that are fully ionized at physiologic pH. However, many drugs do not possess such physicochemical properties. Pharmacologically active organic molecules tend to be lipophilic and remain unionized or only partially ionized at physiologic pH; these are readily reabsorbed from the glomerular filtrate in the nephron. Certain lipophilic compounds are often strongly bound to plasma proteins and may not be readily filtered at the glomerulus. Consequently, most drugs would have a prolonged duration of action if termination of their action depended solely on renal excretion.

An alternative process that can lead to the termination or alteration of biologic activity is metabolism. In general, lipophilic xenobiotics are transformed to more polar and hence more readily excreted products. The role that metabolism plays in the inactivation of lipid-soluble drugs can be quite dramatic. For example, lipophilic barbiturates such as thiopental and pentobarbital would

have extremely long half-lives if it were not for their metabolic conversion to more water-soluble compounds.

Metabolic products are often less pharmacodynamically active than the parent drug and may even be inactive. However, some biotransformation products have *enhanced* activity or toxic properties. It is noteworthy that the synthesis of endogenous substrates such as steroid hormones, cholesterol, active vitamin D congeners, and bile acids involves many pathways catalyzed by enzymes associated with the metabolism of xenobiotics. Finally, drug-metabolizing enzymes have been exploited in the design of pharmacologically inactive prodrugs that are converted to active molecules in the body.

THE ROLE OF BIOTRANSFORMATION IN DRUG DISPOSITION

Most metabolic biotransformations occur at some point between absorption of the drug into the circulation and its renal elimination. A few transformations occur in the intestinal lumen or intestinal wall. In general, all of these reactions can be assigned to one of two major categories called **phase I** and **phase II reactions** (Figure 4–1).

Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (–OH, $–NH_2$, –SH). Often these metabolites are inactive, although in some instances activity is only modified or even enhanced.

If phase I metabolites are sufficiently polar, they may be readily excreted. However, many phase I products are not eliminated rapidly and undergo a subsequent reaction in which an endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid combines with the newly incorporated functional group to form a highly polar conjugate. Such conjugation or synthetic reactions are the hallmarks of phase II metabolism. A great variety of drugs undergo these sequential biotransformation reactions, although in some instances, the parent drug may already possess a functional group that may form a conjugate directly. For example, the hydrazide moiety of isoniazid is known to form an

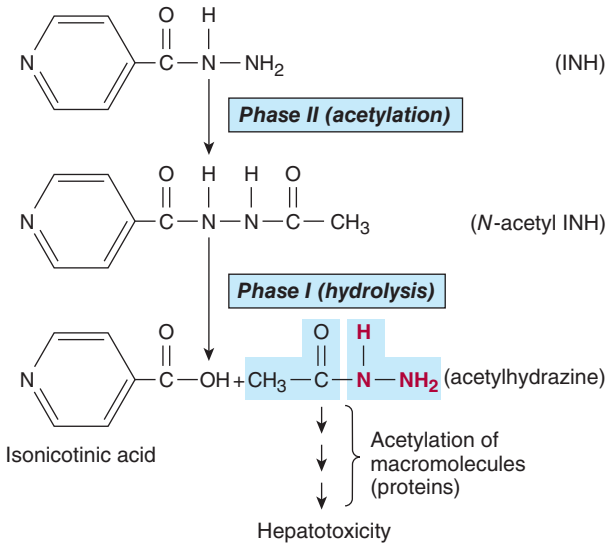


FIGURE 4–2 Phase II activation of isoniazid (INH) to a hepatotoxic metabolite.

N-acetyl conjugate in a phase II reaction. This conjugate is then a substrate for a phase I type reaction, namely, hydrolysis to isonicotinic acid (Figure 4–2). Thus, phase II reactions may actually precede phase I reactions.

WHERE DO DRUG BIOTRANSFORMATIONS OCCUR?

Although every tissue has some ability to metabolize drugs, the liver is the principal organ of drug metabolism. Other tissues that display considerable activity include the gastrointestinal tract, the lungs, the skin, the kidneys, and the brain. After oral administration, many drugs (eg, isoproterenol, meperidine, pentazocine, morphine) are absorbed intact from the small intestine and transported first

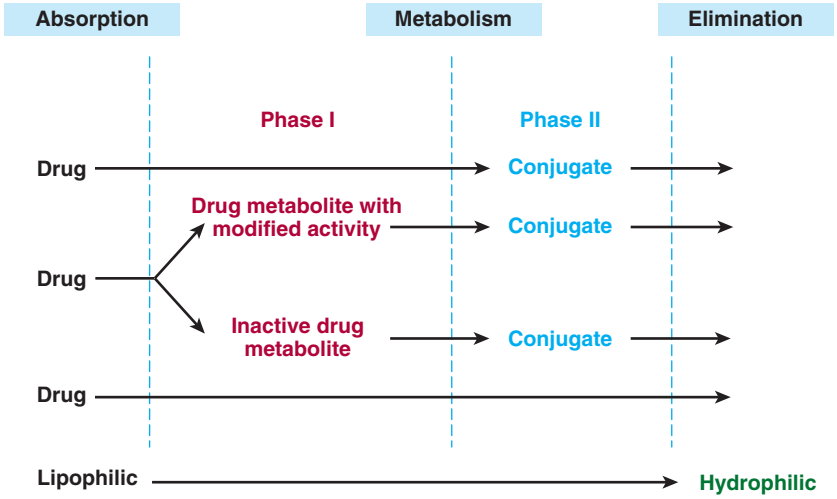


FIGURE 4–1 Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I reactions.

via the portal system to the liver, where they undergo extensive metabolism. This process is called the **first-pass effect** (see Chapter 3). Some orally administered drugs (eg, clonazepam, chlorpromazine, cyclosporine) are more extensively metabolized in the intestine than in the liver, while others (eg, midazolam) undergo significant (~50%) intestinal metabolism. Thus, intestinal metabolism can contribute to the overall first-pass effect, and individuals with compromised liver function may rely increasingly on such intestinal metabolism for drug elimination. Compromise of intestinal metabolism of certain drugs (eg, felodipine, cyclosporine A) can also result in significant elevation of their plasma levels and clinically relevant drug-drug interactions (**DDIs**, see below). First-pass effects may limit the bioavailability of orally administered drugs (eg, lidocaine) so greatly that alternative routes of administration must be used to achieve therapeutically effective blood levels. Furthermore, the lower gut harbors intestinal microorganisms that are capable of many biotransformation reactions. In addition, drugs may be metabolized by gastric acid (eg, penicillin), by digestive enzymes (eg, polypeptides such as insulin), or by enzymes in the wall of the intestine (eg, sympathomimetic catecholamines).

Although drug biotransformation in vivo can occur by spontaneous, noncatalyzed chemical reactions, most transformations are catalyzed by specific cellular enzymes. At the subcellular level, these enzymes may be located in the endoplasmic reticulum, mitochondria, cytosol, lysosomes, or even the nuclear envelope or plasma membrane.

MICROSOMAL MIXED FUNCTION OXIDASE SYSTEM & PHASE I REACTIONS

Many drug-metabolizing enzymes are located in the lipophilic endoplasmic reticulum membranes of the liver and other tissues. When these lamellar membranes are isolated by homogenization and fractionation of the cell, they re-form into vesicles called **microsomes.** Microsomes retain most of the morphologic and functional characteristics of the intact membranes, including the rough and smooth surface features of the rough (ribosome-studded) and smooth (no ribosomes) endoplasmic reticulum. Whereas the rough microsomes tend to be dedicated to protein synthesis, the smooth microsomes are relatively rich in enzymes responsible for oxidative drug metabolism. In particular, they contain the important class of enzymes known as the **mixed function oxidases** (MFOs), or **monooxygenases.** The activity of these enzymes requires both a reducing agent (nicotinamide adenine dinucleotide phosphate [**NADPH**]) and molecular oxygen; in a typical reaction, one molecule of oxygen is consumed (reduced) per substrate molecule, with one oxygen atom appearing in the product and the other in the form of water.

In this oxidation-reduction process, two microsomal enzymes play a key role. The first of these is a flavoprotein, **NADPH-cytochrome P450 oxidoreductase** (POR, or CPR). One mole of this enzyme contains 1 mol each of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The second microsomal enzyme is a hemoprotein called **cytochrome P450,** which serves as the terminal oxidase. In fact, the microsomal membrane harbors multiple forms of this hemoprotein, and this multiplicity is increased by repeated administration of or exposure to exogenous chemicals (see text that follows). The name cytochrome P450 (abbreviated as **P450** or **CYP**) is derived from the spectral properties of this hemoprotein. In its reduced (ferrous) form, it binds carbon monoxide to give a complex that absorbs light maximally at 450 nm. The relative abundance of P450s, compared with that of the reductase in the liver, contributes to making P450 heme reduction a rate-limiting step in hepatic drug oxidations.

Microsomal drug oxidations require P450, P450 reductase, NADPH, and molecular oxygen. A simplified scheme of the oxidative cycle is presented in Figure 4–3. Briefly, oxidized (Fe^{+3})

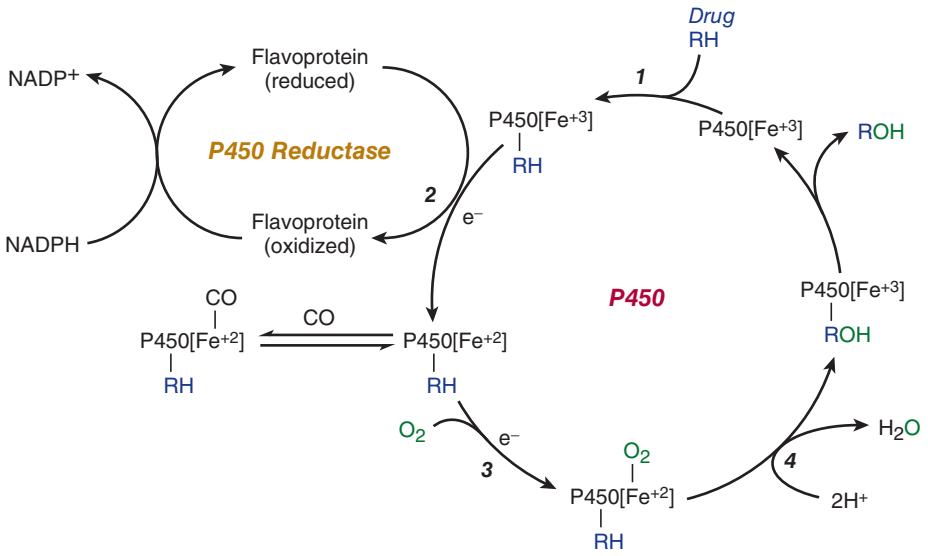


FIGURE 4–3 Cytochrome P450 cycle in drug oxidations. e^-, electron; RH, parent drug; ROH, oxidized metabolite.

P450 combines with a drug substrate to form a binary complex (step 1). NADPH donates an electron to the flavoprotein P450 reductase, which in turn reduces the oxidized P450-drug complex (step 2). A second electron is introduced from NADPH via the same P450 reductase, which serves to reduce molecular oxygen and to form an "activated oxygen"–P450–substrate complex (step 3). This complex in turn transfers activated oxygen to the drug substrate to form the oxidized product (step 4).

The potent oxidizing properties of this activated oxygen permit oxidation of a large number of substrates. Substrate specificity is very low for this enzyme complex. High lipid solubility is the only common structural feature of the wide variety of structurally unrelated drugs and chemicals that serve as substrates in this system (Table 4–1). However, compared with many other enzymes including phase II enzymes, P450s are remarkably sluggish catalysts, and their drug biotransformation reactions are slow.

HUMAN LIVER P450 ENZYMES

Gene arrays combined with immunoblotting analyses of microsomal preparations, as well as the use of relatively selective functional markers and selective P450 inhibitors, have identified numerous P450 isoforms (CYP: 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 4A11, and 7) in the human liver. Of these, **CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1,** and **CYP3A4** appear to be the most important forms, accounting for approximately 15%, 4%, 1%, 20%, 5%, 10%, and 30%, respectively, of the total human liver P450 content. Together, they are responsible for catalyzing the bulk of the hepatic drug and xenobiotic metabolism (Table 4–2, Figure 4–4).

It is noteworthy that CYP3A4 alone is responsible for the metabolism of over 50% of the prescription drugs metabolized by the liver. The involvement of individual P450s in the metabolism of a given drug may be screened in vitro by means of selective functional markers, selective chemical P450 inhibitors, and P450 antibodies. In vivo, such screening may be accomplished by means of relatively selective noninvasive markers, which include breath tests or urinary analyses of specific metabolites after administration of a P450-selective substrate probe.

Enzyme Induction

Some of the chemically dissimilar P450 substrate drugs, on repeated administration, *induce* P450 expression by enhancing the rate of its synthesis or reducing its rate of degradation (Table 4–2). Induction results in accelerated substrate metabolism and usually in a decrease in the pharmacologic action of the inducer and also of co-administered drugs. However, in the case of drugs metabolically transformed to reactive metabolites, enzyme induction may exacerbate metabolite-mediated toxicity.

Various substrates induce P450 isoforms having different molecular masses and exhibiting different substrate specificities and immunochemical and spectral characteristics.

Environmental chemicals and pollutants are also capable of inducing P450 enzymes. Exposure to benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons, which are present in tobacco smoke, charcoal-broiled meat, and other organic pyrolysis products, is known to induce CYP1A enzymes and to alter the rates of drug metabolism. Other environmental chemicals known to induce specific P450s include the polychlorinated biphenyls (PCBs), which were once used widely in industry as insulating materials and plasticizers, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin, TCDD), a trace byproduct of the chemical synthesis of the defoliant 2,4,5-T (see Chapter 56).

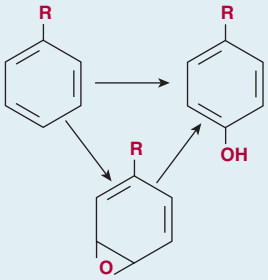
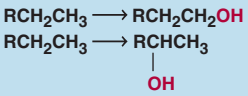
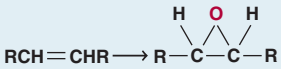
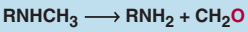
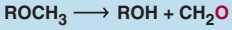
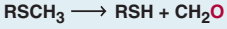
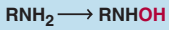
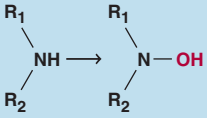
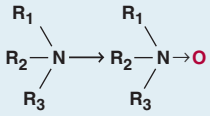
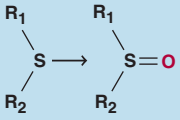
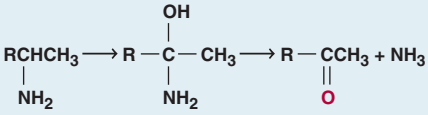
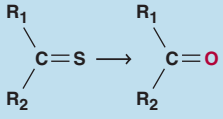
Increased P450 synthesis requires enhanced transcription and translation along with increased synthesis of heme, its prosthetic cofactor. A cytoplasmic receptor (termed AhR) for polycyclic aromatic hydrocarbons (eg, benzo[*a*]pyrene, dioxin) has been identified. The translocation of the inducer-receptor complex into the nucleus, followed by ligand-induced dimerization with Arnt, a closely related nuclear protein, leads to subsequent activation of regulatory elements of *CYP1A* genes, resulting in their induction. This is also the mechanism of CYP1A induction by cruciferous vegetables, and the proton pump inhibitor, omeprazole. A pregnane X receptor (PXR), a member of the steroid-retinoid-thyroid hormone receptor family, has recently been shown to mediate CYP3A induction by various chemicals (dexamethasone, rifampin, mifepristone, phenobarbital, atorvastatin, and hyperforin, a constituent of St. John's wort) in the liver and intestinal mucosa. A similar receptor, the constitutive androstane receptor (CAR), has been identified for the relatively large and structurally diverse phenobarbital class of inducers of CYP2B6, CYP2C9, and CYP3A4. Peroxisome proliferator receptor α (PPAR-α) is yet another nuclear receptor highly expressed in liver and kidneys, which uses lipid-lowering drugs (eg, fenofibrate and gemfibrozil) as ligands. Consistent with its major role in the regulation of fatty acid metabolism, PPAR-α mediates the induction of CYP4A enzymes, responsible for the metabolism of fatty acids such as arachidonic acid and its physiologically relevant derivatives. It is noteworthy that on binding of its particular ligand, PXR, CAR, and PPAR-α each forms heterodimers with another nuclear receptor, the retinoid X-receptor (RXR). This heterodimer in turn binds to response elements within the promoter regions of specific *P450* genes to induce gene expression.

P450 enzymes may also be induced by **substrate stabilization,** eg, decreased degradation, as is the case with troleandomycin- or clotrimazole-mediated induction of CYP3A enzymes, the ethanol-mediated induction of CYP2E1, and the isosafrole-mediated induction of CYP1A2.

Enzyme Inhibition

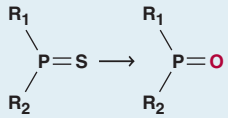
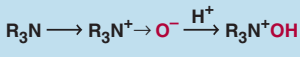
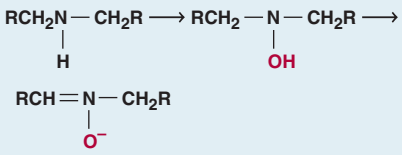
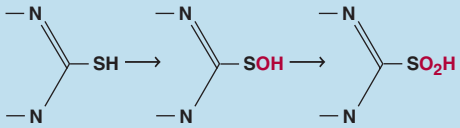
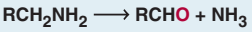
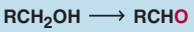
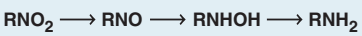
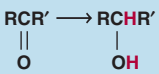
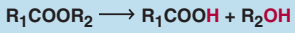
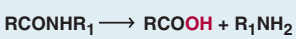
Certain drug substrates inhibit cytochrome P450 enzyme activity (Table 4–2). Imidazole-containing drugs such as cimetidine and ketoconazole bind tightly to the P450 heme iron and effectively reduce the metabolism of endogenous substrates (eg, testosterone) or other co-administered drugs through competitive inhibition. Macrolide antibiotics such as troleandomycin, erythromycin, and erythromycin derivatives are metabolized, apparently by CYP3A, to metabolites that complex the cytochrome P450 heme iron and render it catalytically inactive. Another compound that acts through this mechanism is the inhibitor proadifen (SKF-525-A, used in research), which binds tightly to the heme iron and

TABLE 4–1 Phase I reactions.

Reaction Class	Structural Change	Drug Substrates
Oxidations		
Cytochrome P450-dependent oxidations:		
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17α-ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations		Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation		Aldrin
Oxidative dealkylation		
N-Dealkylation		Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation		Codeine, *p*-nitroanisole
S-Dealkylation		6-Methylthiopurine, methitural
***N*-Oxidation**		
Primary amines		Aniline, chlorphentermine
Secondary amines		2-Acetylaminofluorene, acetaminophen
Tertiary amines		Nicotine, methaqualone
***S*-Oxidation**		Thioridazine, cimetidine, chlorpromazine
Deamination		Amphetamine, diazepam
Desulfuration		Thiopental

(*continued*)

TABLE 4–1 Phase I reactions. (Continued)

Reaction Class	Structural Change	Drug Substrates
Cytochrome P450- dependent oxidations: (continued)		
		Parathion
Dechlorination		Carbon tetrachloride
Cytochrome P450-independent oxidations:		
Flavin monooxygenase (Ziegler's enzyme)		Chlorpromazine, amitriptyline, benzphetamine
		Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases		Phenylethylamine, epinephrine
Dehydrogenations		Ethanol
Reductions		
Azo reductions		Prontosil, tartrazine
Nitro reductions		Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions		Metyrapone, methadone, naloxone
Hydrolyses		
Esters		Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides		Procainamide, lidocaine, indomethacin

quasi-irreversibly inactivates the enzyme, thereby inhibiting the metabolism of potential substrates.

Some substrates irreversibly inhibit P450s via covalent interaction of a metabolically generated reactive intermediate that may react with the P450 apoprotein or heme moiety or even cause the heme to fragment and irreversibly modify the apoprotein. The antibiotic chloramphenicol is metabolized by CYP2B1 to a species that modifies the P450 protein and thus also inactivates the enzyme. A growing list of such **suicide inhibitors**—inactivators that attack the heme or the protein moiety—includes certain steroids (ethinyl estradiol, norethindrone, and spironolactone); fluroxene; allobarbital; the analgesic sedatives allylisopropylacetylurea, diethylpentenamide, and ethchlorvynol; carbon disulfide; grapefruit furanocoumarins; selegiline; phencyclidine; ticlopidine and clopidogrel; ritonavir; and propylthiouracil. On the other hand, the barbiturate secobarbital is found to inactivate CYP2B1 by modification of *both* its heme and protein moieties. Other metabolically activated drugs whose P450 inactivation mechanism is not fully elucidated are mifepristone, troglitazone, raloxifene, and tamoxifen.

TABLE 4–2 Human liver P450s (CYPs), and some of the drugs metabolized (substrates), inducers, and selective inhibitors. Note: Some P450 substrates can be potent competitive inhibitors and/or mechanism-based inactivators.

CYP	Substrates	Inducers	Inhibitors
1A2	Acetaminophen, alosetron, antipyrine, caffeine, clomipramine, clozapine, duloxetine, flutamide, frovatriptan, melatonin, mexiletine, mirtazapine, olanzapine, phenacetin, ramelteon, rasagiline, ropinirole, tacrine, tamoxifen, theophylline, tizanidine, triamterene, warfarin, zolmitriptan	Charcoal-broiled foods, cruciferous vegetables, grilled meat, lansoprazole, omeprazole, primidone, rifampin, smoking	Artemisinin, atazanavir, cimetidine, ciprofloxacin, enoxacin, ethinyl estradiol, fluvoxamine, furafylline, galangin, mexiletene, tacrine, thiabendazole, zileuton
2A6	Coumarin, dexmedetomidine, tobacco nitrosamines, nicotine (to cotinine and 2′-hydroxynicotine)	Efavirenz, rifampin, phenobarbital	Clotrimazole, isoniazid, ketoconazole, letrozole, menthofuran, methimazole, methoxsalen, miconazole, tranylcypromine
2B6	Artemisinin, bupropion, clopidogrel, cyclophosphamide, efavirenz, ifosfamide, irinotecan, ketamine, *S*-mephobarbital, *S*-mephenytoin (*N*-demethylation to nirvanol), methadone, nevirapine, promethazine, propofol, selegiline, sertraline, ticlopidine	Carbamazepine, cyclophosphamide, fosphenytoin, nevirapine, phenobarbital, primidone, rifampin	Amiodarone, amlodipine, clopidogrel, clotrimazole, desipramine, disulfiram, doxorubicin, ethinyl estradiol, fluoxetine, fluvoxamine, isoflurane, ketoconazole, mestranol, methimazole, nefazodone, nelfinavir, orphenadrine, paroxetine, phencyclidine, sertraline, thiotepa, ticlopidine
2C8	Amiodarone, cabazitaxel, carbamazepine, chloroquine, diclofenac, ibuprofen, paclitaxel, all-*trans*-retinoic acid, repaglinide, rosiglitazone, treprostinil	Rifampin, barbiturates	Deferasirox, gemfibrozil, lapatinib, montelukast, pioglitazone, quercetin, rosiglitazone, trimethoprim
2C9	Alosetron, bosentan, celecoxib, chlorpropamide, diclofenac, dronabinol, flurbiprofen, fluvastatin, glimepiride, glipizide, glyburide, hexobarbital, ibuprofen, indomethacin, irbesartan, losartan, meloxicam, montelukast, naproxen, nateglinide, phenobarbital, phenytoin, piroxicam, rosiglitazone, rosuvastatin, sulfamethoxazole, sulfaphenazole, ticrynafen, tolbutamide, torsemide, trimethadione, valsartan, *S*-warfarin	Aminoglutethimide, barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's wort	Amiodarone, clopidogrel, delavirdine, disulfiram, doxifluridine, efavirenz, fluconazole, fluvoxamine, fluorouracil, imatinib, leflunomide, metronidazole, miconazole, phenytoin, sulfamethoxazole, sulfaphenazole, sulfinpyrazone, tienilic acid, valproic acid, voriconazole
2C18	Tolbutamide, phenytoin	Phenobarbital	
2C19	Aripiprazole, carisoprodol, citalopram, clomipramine, clopidogrel, clozapine, desipramine, diazepam, diphenhydramine, doxepin, escitalopram, fluoxetine, imipramine, lansoprazole, *S*-mephenytoin, methadone, moclobemide, naproxen, nelfinavir, nirvanol, olanzapine, omeprazole, pantoprazole, phenobarbital, phenytoin, proguanil, propranolol, rabeprazole, sertraline, thalidomide, voriconazole, *R*-warfarin	Aminoglutethimide, artemisinin, barbiturates, carbamazepine, phenytoin, primidone, rifampin, rifapentine, St. John's wort	*N*3-Benzylnirvanol, *N*3-benzylphenobarbital, chloramphenicol, cimetidine, clopidogrel, delavirdine, efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, isoniazid, moclobemide, modafinil, nootkatone, omeprazole, ticlopidine, voriconazole
2D6	Amitriptyline, atomoxetine, bufuralol, bupranolol, carvedilol, chlorpheniramine, chlorpromazine, clomipramine, clozapine, codeine, debrisoquine, desipramine, dextromethorphan, dihydrocodeine, encainide, flecainide, fluoxetine, fluvoxamine, guanoxan, haloperidol, hydrocodone, imipramine, maprotiline, 4–methoxy-amphetamine, metoclopramide, metoprolol, mexiletine, nebivolol, nortriptyline, oxycodone, palonosetron, paroxetine, perhexiline, perphenazine, phenformin, propafenone, propoxyphene, propranolol, risperidone, selegiline (deprenyl), sparteine, tamoxifen, thioridazine, timolol, tolterodine, tricyclic antidepressants, tramadol, trazodone, venlafaxine	Unknown	Bupropion, cinacalcet, chloroquine, diphenhydramine, fluoxetine, haloperidol, imatinib, paroxetine, propafenone, propoxyphene, quinidine, terbinafine, thioridazine
2E1	Acetaminophen, chlorzoxazone, dacarbazine, enflurane, ethanol (a minor pathway), halothane, isoflurane, isoniazid, sevoflurane, theophylline, trimethadione	Ethanol, isoniazid	Amitriptyline, chlorpromazine, cimetidine, clomethiazole, clotrimazole, clozapine, disulfiram, diethylthiocarbamate, diallyl sulfide, econazole, methimazole, methoxsalen, 4-methylpyrazole, miconazole, modafinil, ritonavir, selegiline, sildenafil, sulconazole, ticlopidine, tioconazole

(*continued*)

TABLE 4–2 Human liver P450s (CYPs), and some of the drugs metabolized (substrates), inducers, and selective inhibitors. Note: Some P450 substrates can be potent competitive inhibitors and/or mechanism-based inactivators. (Continued)

CYP	Substrates	Inducers	Inhibitors
3A4[1]	Acetaminophen, alfentanil, alfuzosin, almotriptan, alprazolam, amiodarone, amlodipine, aprepitant, astemizole, atazanavir, atorvastatin, bepridil, bexarotene, bosentan, bromocriptine, budesonide, buspirone, carbamazepine, cisapride, clarithromycin, clonazepam, clopidogrel, cocaine, colchicine, conivaptan, cortisol, cyclosporine, dapsone, darunavir, dasatinib, delavirdine, dexamethasone, diazepam, dihydroergotamine, dihydropyridines, diltiazem, disopyramide, doxorubicin, droperidol, dutasteride, ebastine, efavirenz, eletriptan, eplerenone, ergotamine, erlotinib, erythromycin, estazolam, eszopiclone, ethinyl estradiol, ethosuximide, etoposide, everolimus, exemestane, felodipine, fentanyl, finasteride, flurazepam, fluticasone, fosamprenavir, galantamine, gefitinib, gestodene, granisetron, halofantrine, ifosfamide, imatinib, indinavir, irinotecan, isradipine, itraconazole, ixabepilone, lapatinib, lidocaine, loperamide, lopinavir, loratadine, lovastatin, macrolides, maraviroc, mefloquine, methadone, methylprednisolone, miconazole, midazolam, mifepristone, modafinil, nefazodone, nevirapine, nicardipine, nifedipine, nimodipine, nisoldipine, paclitaxel, paricalcitol, pimozide, pioglitazone, praziquantel, prednisolone, prednisone, progesterone, quetiapine, quinacrine, quinidine, quinine, ranolazine, rapamycin, repaglinide, rifabutin, ritonavir, saquinavir, sibutramine, sildenafil, simvastatin, sirolimus, solifenacin, spironolactone, sufentanil, sulfamethoxazole, sunitinib, tacrolimus, tadalafil, tamoxifen, tamsulosin, teniposide, terfenadine, testosterone, tetrahydrocannabinol, tiagabine, tinidazole, tipranavir, tolvaptan, topiramate, triazolam, troleandomycin, vardenafil, verapamil, vinblastine, vincristine, ziprasidone, zolpidem, zonisamide, zopiclone	Aminoglutethimide, avasimibe, barbiturates, carbamazepine, efavirenz, glucocorticoids, nevirapine, pioglitazone, phenytoin, primidone, rifampin, rifapentine, St. John's wort	Amprenavir, azamulin, boceprevir, clarithromycin, conivaptan, diltiazem, erythromycin, fluconazole, grapefruit juice (furanocoumarins), indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, verapamil, voriconazole

[1]CYP3A5 has similar substrate and inhibitor profiles but, except for a few drugs, is generally less active than CYP3A4.

PHASE II REACTIONS

Parent drugs or their phase I metabolites that contain suitable chemical groups often undergo coupling or conjugation reactions with an endogenous substance to yield **drug conjugates** (Table 4–3). In general, conjugates are polar molecules that are readily excreted and often inactive. Conjugate formation involves high-energy intermediates and specific transfer enzymes. Such enzymes **(transferases)** may be located in microsomes or in the cytosol. Of these, uridine 5′-diphosphate (UDP)-glucuronosyl transferases **(UGTs)** are the most dominant enzymes (Figure 4–4). These microsomal enzymes catalyze the coupling of an activated endogenous substance (such as the UDP derivative of glucuronic acid) with a drug (or endogenous compound such as bilirubin, the end product of heme metabolism). Nineteen *UGT* genes (*UGTA1* and *UGT2*) encode UGT proteins involved in the metabolism of drugs and xenobiotics. Similarly, 11 human sulfotransferases **(SULTs)** catalyze the sulfation of substrates using 3′-phosphoadenosine 5′-phosphosulfate **(PAPS)** as the endogenous sulfate donor. Cytosolic and microsomal glutathione **(GSH)** transferases **(GSTs)** are also engaged in the metabolism of drugs and xenobiotics, and in that of leukotrienes and prostaglandins, respectively. Chemicals containing an aromatic amine or a hydrazine moiety (eg, isoniazid) are substrates of cytosolic *N*-acetyltransferases **(NATs),** encoded by *NAT1* and *NAT2* genes, which utilize **acetyl-CoA** as the endogenous cofactor.

S-Adenosyl-L-methionine (**SAMe**; AdoMet)-mediated *O*-, *N*-, and *S*-methylation of drugs and xenobiotics by methyltransferases **(MTs)** also occurs. Finally, endobiotic, drug, and xenobiotic epoxides generated via P450-catalyzed oxidations can also be hydrolyzed by microsomal or cytosolic epoxide hydrolases **(EHs).** Conjugation of an activated drug such as the *S*-CoA derivative of benzoic acid, with an endogenous substrate, such as glycine, also occurs. Because the endogenous substrates originate in the diet, nutrition plays a critical role in the regulation of drug conjugations.

Phase II reactions are relatively faster than P450-catalyzed reactions, thus effectively accelerating drug biotransformation.

Drug conjugations were once believed to represent terminal inactivation events and as such have been viewed as "true detoxification" reactions. However, this concept must be modified, because it is now known that certain conjugation reactions (acyl glucuronidation of nonsteroidal anti-inflammatory drugs, *O*-sulfation of *N*-hydroxyacetylaminofluorene, and *N*-acetylation of isoniazid) may lead to the formation of reactive species responsible for the toxicity of the drugs. Furthermore, sulfation is known to activate the orally active prodrug minoxidil into a very efficacious vasodilator, and morphine-6-glucuronide is more potent than morphine itself.

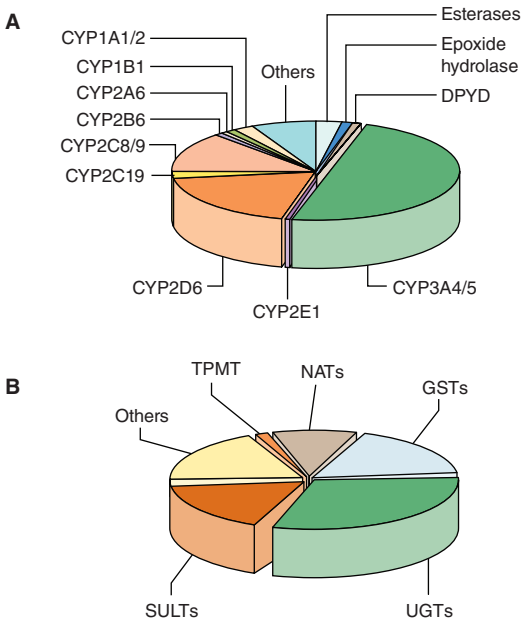


FIGURE 4–4 Relative contributions of various cytochrome P450 isoforms (**A**) and different phase II pathways (**B**) to metabolism of drugs in clinical use. Many drugs are metabolized by two or more of these pathways. Note that two pathways, CYP3A4/5 and UGT, are involved in the metabolism of more than 75% of drugs in use. DPYD, dihydropyrimidine dehydrogenase; GST, glutathione-*S*-transferase; NAT, *N*-acetyltransferase; SULT, sulfotransferase; TPMT, thiopurine methyltransferase; UGT, UDP-glucuronosyltransferase. (Reproduced, with permission, from Brunton LL, Chabner BA, Knollman BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th ed. McGraw-Hill, 2011. Copyright © The McGraw-Hill Companies, Inc.)

METABOLISM OF DRUGS TO TOXIC PRODUCTS

Metabolism of drugs and other foreign chemicals may not always be an innocuous biochemical event leading to detoxification and elimination of the compound. Indeed, as previously noted, several compounds have been shown to be metabolically transformed to reactive intermediates that are toxic to various organs. Such toxic reactions may not be apparent at low levels of exposure to parent compounds when alternative detoxification mechanisms are not yet overwhelmed or compromised and when the availability of endogenous detoxifying cosubstrates (GSH, glucuronic acid, sulfate) is not limited. However, when these resources are exhausted, the toxic pathway may prevail, resulting in overt organ toxicity or carcinogenesis. The number of specific examples of such drug-induced toxicity is expanding rapidly. An example is acetaminophen (APAP; paracetamol)-induced hepatotoxicity (Figure 4–5). Acetaminophen, an analgesic antipyretic drug, is quite safe in therapeutic doses (1.2 g/d for an adult). It normally undergoes glucuronidation and sulfation to the corresponding conjugates, which together make up 95% of the total excreted metabolites. The alternative P450-dependent GSH conjugation pathway accounts for the remaining 5%. When acetaminophen intake far exceeds therapeutic doses, the glucuronidation and sulfation pathways are saturated, and the P450-dependent pathway becomes increasingly important. Little or no hepatotoxicity results as long as hepatic GSH is available for conjugation. However, with time, hepatic GSH is depleted faster than it can be regenerated, and a reactive, toxic metabolite accumulates. In the absence of intracellular nucleophiles such as GSH, this

TABLE 4–3 Phase II reactions.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid (UDPGA)	UDP glucuronosyltransferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*-Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate (PAPS)	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3- hydroxycoumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine (SAM)	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, *cis*-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

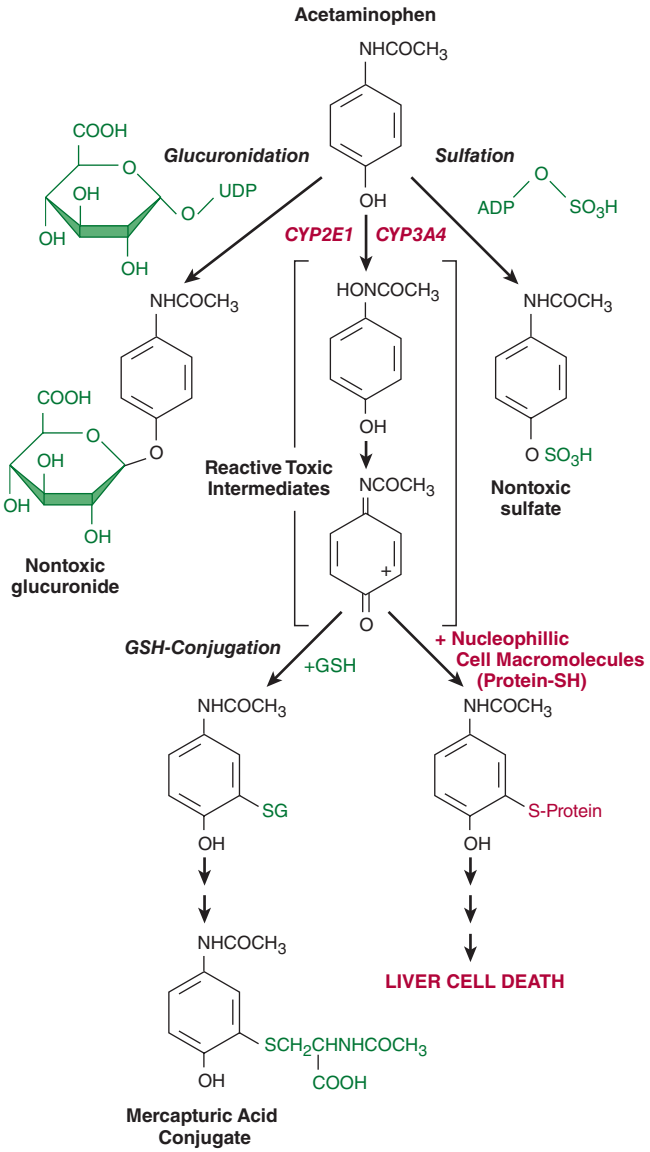


FIGURE 4–5 Metabolism of acetaminophen (top center) to hepatotoxic metabolites. GSH, glutathione; SG, glutathione moiety.

reactive metabolite (*N*-acetylbenzoiminoquinone) not only reacts with nucleophilic groups of cellular proteins resulting in direct hepatocellular damage, but also participates in redox cycling, thereby generating reactive O_2 species (**ROS**) and consequent oxidative stress that greatly enhance acetaminophen-induced hepatotoxicity.

The chemical and toxicologic characterization of the electrophilic nature of the reactive acetaminophen metabolite has led to the development of effective antidotes—cysteamine and *N*-acetylcysteine (NAC; Acetadote; Mucomyst). Administration of *N*-acetylcysteine (the safer of the two) within 8–16 hours after acetaminophen overdosage has been shown to protect victims from fulminant hepatotoxicity and death (see Chapter 58). Administration of GSH is not effective because it does not cross cell membranes readily.

CLINICAL RELEVANCE OF DRUG METABOLISM

The dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients because of individual differences in drug distribution and rates of drug metabolism and elimination. These differences are determined by genetic factors as well as nongenetic variables, such as commensal gut microbiota, age, sex, liver size, liver function, circadian rhythm, body temperature, and nutritional and environmental factors such as concomitant exposure to inducers or inhibitors of drug metabolism. The discussion that follows summarizes the most important of these variables.

Individual Differences

Individual differences in metabolic rate depend on the nature of the drug itself. Thus, within the same population, steady-state plasma levels may reflect a 30-fold variation in the metabolism of one drug and only a twofold variation in the metabolism of another.

Genetic Factors

Genetic factors that influence enzyme levels account for some of these differences, giving rise to "genetic polymorphisms" in drug metabolism (see also Chapter 5). The first examples of drugs found to be subject to genetic polymorphisms were the muscle relaxant succinylcholine, the antituberculosis drug isoniazid, and the anticoagulant warfarin. A true genetic polymorphism is defined as the occurrence of a variant allele of a gene at a population frequency of ≥ 1%, resulting in altered expression or functional activity of the gene product, or both. Well-defined and clinically relevant genetic polymorphisms in both phase I and phase II drug-metabolizing enzymes exist that result in altered efficacy of drug therapy or adverse drug reactions **(ADRs).** The latter frequently necessitate dose adjustment (Table 4–4), a consideration particularly crucial for drugs with low therapeutic indices.

A. Phase I Enzyme Polymorphisms

Genetically determined defects in the phase I oxidative metabolism of several drugs have been reported (Table 4–4; see also Chapter 5). These defects are often transmitted as autosomal recessive traits and may be expressed at any one of the multiple metabolic transformations that a chemical might undergo. Human liver P450s 3A4, 2C9, 2D6, 2C19, 1A2, and 2B6 are responsible for about 75% of all clinically relevant phase I drug metabolism (Figure 4–4), and thus for about 60% of all physiologic drug biotransformation and elimination. Thus, genetic polymorphisms of these enzymes, by significantly influencing phase I drug metabolism, can alter their pharmacokinetics and the magnitude or the duration of drug response and associated events.

Three P450 genetic polymorphisms have been particularly well characterized, affording some insight into possible underlying molecular mechanisms, and are clinically noteworthy, as they require therapeutic dosage adjustment. The first is the **debrisoquin-sparteine oxidation** type of polymorphism, which

TABLE 4–4 Some examples of genetic polymorphisms in phase I and phase II drug metabolism.

Enzyme Involved	Defect	Genotype	Drug and Therapeutic Use	Clinical Consequences[1]
CYP1A2	*N*-Demethylation	**EM**	Caffeine (CNS stimulant)	Reduced CNS stimulation due to increased gene inducibility and thus increased metabolism/clearance in cigarette smokers and frequent ingesters of omeprazole.
	N-Demethylation	**PM**	Caffeine (CNS stimulant)	Enhanced CNS stimulation.
CYP2A6	Oxidation	**PM**	Nicotine (cholinoceptorstimulant)	Nicotine toxicity. Lesser craving for frequent cigarette smoking.
	Oxidation	**EM**	Nicotine (cholinoceptorstimulant)	Increased nicotine metabolism. Greater craving for frequent cigarette smoking.
	Oxidation	**PM**	Coumarin (anticoagulant)	Increased risk of bleeding.
	Oxidation	**EM**	Coumarin (anticoagulant)	Increased clearance. Greater risk of thrombosis.
CYP2B6	Oxidation, *N*-Dechloroethylation	**PM**	Cyclophosphamide, ifosfamide (anti-cancer)	Reduced clearance. Increased risk of ADRs.
	Oxidation	**PM**	Efavirenz, nevirapine (anti-HIV)	Reduced clearance. Increased risk of ADRs.
CYP2C8	Hydroxylation	**PM**	Repaglinide, rosiglitazone, pioglitazone (antidiabetic)	Reduced clearance. Increased risk of ADRs.
	Hydroxylation	**PM**	Paclitaxel (anti-cancer)	Reduced clearance. Increased risk of ADRs (myelosuppression).
	N-Deethylation/ *N*-Dealkylation	**PM**	Amodiaquine, chloroquine (antimalarial)	Reduced clearance. Increased risk of ADRs.
	N-Deethylation	**PM**	Amiodarone (antiarrhythmic)	Reduced clearance. Increased risk of ADRs.
CYP2C9	Hydroxylation	**PM**	Celecoxib, diclofenac, flurbiprofen, *S*-ibuprofen (NSAIDs)	Reduced clearance. Increased risk of ADRs.
	Hydroxylation	**PM**	*S*-Warfarin, *S*-acenocoumarol (anticoagulants)	Enhanced bleeding risk. Clinically highly relevant. Dose adjustment required.
	Hydroxylation	**PM**	Tolbutamide (antidiabetic)	Cardiotoxicity.
	Hydroxylation	**PM**	Phenytoin (antiepileptic)	Nystagmus, diplopia, and ataxia.
CYP2C19	*N*-Demethylation	**PM**	Amitriptyline, clomipramine (antidepressants)	Reduced clearance. Increased risk of ADRs. Dose adjustment required.
	Oxidation	**PM**	Moclobemide (MAOI)	
	N-Demethylation	**PM**	Citalopram (SSRI)	Increased risk of gastrointestinal side effects.
	O-Demethylation	**PM**	Omeprazole (PPI)	Increased therapeutic efficacy.
	Hydroxylation	**PM**	Mephenytoin (antiepileptic)	Overdose toxicity.
	N-Demethylation	**EM**	Escitalopram (antidepressants)	Increased gene transcription resulting in increased activity and thus reduced therapeutic efficacy.
	O-Demethylation	**EM**	Omeprazole (PPI)	Reduced therapeutic efficacy.
	Hydroxylation	**EM**	Tamoxifen (anti-cancer)	Increased metabolic activation, increased therapeutic efficacy; reduced risk of relapse. Dose adjustment required.
	Oxidative cyclization	**EM**	Chlorproguanil (antimalarial)	Increased metabolic activation, increased therapeutic efficacy. Dose adjustment required.
	Oxidation	**EM**	Clopidogrel (antiplatelet)	Increased metabolic activation, increased therapeutic efficacy. Dose adjustment required.
CYP2D6	Oxidation	**PM**	Bufuralol (β-adrenoceptor blocker)	Exacerbation of β blockade, nausea.
	O-Demethylation	**PM**	Codeine (analgesic)	Reduced metabolic activation to morphine and thus reduced analgesia.
	Oxidation	**PM**	Debrisoquin (antihypertensive)	Orthostatic hypotension.

(*continued*)

TABLE 4–4 Some examples of genetic polymorphisms in phase I and phase II drug metabolism. (Continued)

Enzyme Involved	Defect	Genotype	Drug and Therapeutic Use	Clinical Consequences[1]
	N-Demethylation	**PM**	Nortriptyline (antidepressant)	Reduced clearance. Increased risk of ADRs.
	Oxidation	**PM**	Sparteine	Oxytocic symptoms.
	O-Demethylation	**PM**	Dextromethorphan (antitussive)	Reduced clearance. Increased risk of ADRs.
	O-Demethylation	**PM**	Tramadol (analgesic)	Increased risk of seizures.
	Hydroxylation	**PM**	Tamoxifen (anti-cancer)	Reduced metabolic activation to the therapeutically active endoxifen and thus reduced therapeutic efficacy.
	O-Demethylation	**UM**	Codeine (analgesic)	Increased metabolic activation to morphine and thus increased risk of respiratory depression.
	N-Demethylation	**UM**	Nortriptyline (antidepressant)	Reduced therapeutic efficacy due to increased clearance.
	O-Demethylation	**UM**	Tramadol (analgesic)	Reduced therapeutic efficacy due to increased clearance.
CYP3A4		**PM?**	All drugs metabolized by this enzyme would be potentially affected	Reduced clearance. Dose adjustment may be required to avoid drug-drug interactions.
CYP3A5		**PM?**	Saquinavir, and other CYP3A substrates	Usually less catalytically active than CYP3A4. A higher frequency of a functional CYP3A5∗1 allele is seen in Africans than in Caucasians; the latter most often carry the defective CYP3A5∗3 allele. This may significantly affect therapeutics of CYP3A substrates in CYP3A5∗1 or CYP3A5∗3 homozygous individuals.
ALDH	Aldehyde dehydrogenation	**PM**	Ethanol (recreational drug)	Facial flushing, hypotension, tachycardia, nausea, vomiting.
BCHE	Ester hydrolysis	**PM**	Succinylcholine (muscle relaxant)	Prolonged apnea.
			Mivacurium (neuromuscular blocker)	Prolonged muscle paralysis.
			Cocaine (CNS stimulant)	Increased blood pressure, tachycardia, ventricular arrhythmias.
GST	GSH-conjugation	**PM**	Acetaminophen (analgesic), Busulfan (anti-cancer)	Impaired GSH conjugation due to gene deletion.
NAT2	*N*-Acetylation	**PM**	Hydralazine (antihypertensive)	Lupus erythematosus-like syndrome.
	N-Acetylation	**PM**	Isoniazid (antitubercular)	Peripheral neuropathy.
TPMT	*S*-Methylation	**PM**	6-Thiopurines (anti-cancer)	Myelotoxicity.
UGT1A1	Glucuronidation	**PM**	Bilirubin (heme metabolite)	Hyperbilirubinemia.
			Irinotecan (anti-cancer)	Reduced clearance. Dose adjustment may be required to avoid toxicity (GI dysfunction, immunosuppression).

[1]Observed or predictable.

ADR, adverse drug reaction; EM, extensive metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

apparently occurs in 3–10% of Caucasians and is inherited as an autosomal recessive trait. In affected individuals, the **CYP2D6**-dependent oxidations of debrisoquin and other drugs (Table 4–2; Figure 4–6) are impaired. These defects in oxidative drug metabolism are probably co-inherited. The precise molecular basis for the defect appears to be faulty expression of the P450 protein due to either defective mRNA splicing or protein folding, resulting in little or no isoform-catalyzed drug metabolism and thereby conferring a **poor metabolizer (PM)** phenotype. This PM phenotype correlates with a higher risk of relapse in patients with breast cancer treated with tamoxifen, an anticancer drug that relies on its CYP2D6-dependent metabolic activation to endoxifen for its efficacy. More recently, however, another polymorphic genotype has been reported that results in **ultrarapid metabolism** of relevant drugs due to the presence of CYP2D6 allelic variants with up to 13 gene copies in tandem. This ultrarapid metabolizer **(UM)** genotype is most common in Ethiopians and Saudi Arabians, populations that display it in up to one third of individuals. As a result,

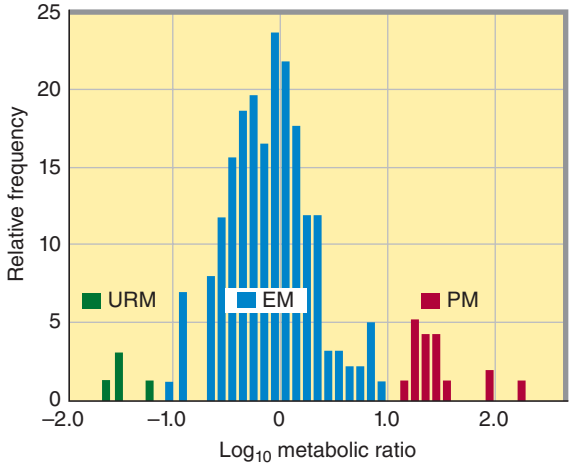


FIGURE 4–6 Genetic polymorphism in debrisoquin 4-hydroxylation by CYP2D6 in a Caucasian population. The semilog frequency distribution histogram of the metabolic ratio (MR; defined as percent of dose excreted as unchanged debrisoquin divided by the percent of dose excreted as 4-hydroxydebrisoquin metabolite) in the 8-hour urine collected after oral ingestion of 12.8 mg debrisoquin sulfate (equivalent to 10 mg free debrisoquin base). Individuals with MR values >12.6 were phenotyped as poor metabolizers (PM, *red bars*), and those with MR values <12.6 but >0.2 were designated as extensive metabolizers (EM, *blue bars*). Those with MR values <0.2 were designated as ultrarapid metabolizers (URM, *green bars*) based on the MR values (0.01–0.1) of individuals with documented multiple copies of CYP2D6 allelic variants resulting from inherited amplification of this gene. (Data from Woolhouse et al: Debrisoquin hydroxylation polymorphism among Ghanians and Caucasians. Clin Pharmacol Ther 1979;26:584.)

these subjects require twofold to threefold higher daily doses of nortriptyline (an antidepressant and a CYP2D6 substrate) to achieve therapeutic plasma levels. The poor responsiveness to antidepressant therapy of the UM phenotype also clinically correlates with a higher incidence of suicides relative to that of deaths due to natural causes in this patient population. Conversely, in these UM populations, the prodrug codeine (another CYP2D6 substrate) is metabolized much faster to morphine, often resulting in undesirable adverse effects of morphine, such as abdominal pain. Indeed, intake of high doses of codeine by a mother of the ultrarapid metabolizer type was held responsible for the morphine-induced death of her breast-fed infant.

The second well-studied genetic drug polymorphism involves the stereoselective **aromatic (4)-hydroxylation** of the anticonvulsant mephenytoin, catalyzed by **CYP2C19.** This polymorphism, which is also inherited as an autosomal recessive trait, occurs in 3–5% of Caucasians and 18–23% of Japanese populations. It is genetically independent of the debrisoquin-sparteine polymorphism. In normal "**extensive metabolizers**" (EMs) (*S*)-mephenytoin is extensively hydroxylated by CYP2C19 at the 4 position of the phenyl ring before its glucuronidation and rapid excretion in the urine, whereas (*R*)-mephenytoin is slowly *N*-demethylated to nirvanol, an active metabolite. PMs, however, appear to totally lack the stereospecific (*S*)-mephenytoin hydroxylase activity, so both (*S*)- and (*R*)-mephenytoin enantiomers are *N*-demethylated to nirvanol, which accumulates in much higher concentrations. Thus, PMs of mephenytoin show signs of profound sedation and ataxia after doses of the drug that are well tolerated by normal metabolizers. Two defective CYP2C19 variant alleles (*CYP2C19*2* and *CYP2C19*3*), the latter predominant in Asians, are largely responsible for the PM genotype. The molecular bases include splicing defects resulting in a truncated, nonfunctional protein. CYP2C19 is responsible for the metabolism of various clinically relevant drugs (Table 4–4). Thus, it is clinically important to recognize that the safety of each of these drugs may be severely reduced in persons with the PM phenotype. On the other hand, the PM phenotype can notably increase the therapeutic efficacy of omeprazole, a proton-pump inhibitor, in gastric ulcer and gastroesophageal reflux diseases (see Chapter 5 for additional discussion of the CYP2C19 polymorphism).

Another CYP2C19 variant allele (*CYP2C19*17*) exists that is associated with increased transcription and thus higher CYP2C19 expression and even higher functional activity than that of the wild type CYP2C19-carrying EMs. Individuals carrying this *CYP2C19*17* allele exhibit higher metabolic activation of prodrugs such as the breast cancer drug tamoxifen, the antimalarial chlorproguanil, and the antiplatelet drug clopidogrel. The former event is associated with a lower risk of breast cancer relapse, and the latter event with an increased risk of bleeding. Carriers of the *CYP2C19*17* allele are also known to enhance the metabolism and thus the elimination of drugs such as the antidepressants escitalopram and imipramine, as well as the antifungal voriconazole. This consequently impairs the therapeutic efficacy of these drugs, thus requiring clinical dosage adjustments.

The third relatively well-characterized genetic polymorphism is that of **CYP2C9.** Two well-characterized variants of this enzyme exist, each with amino acid mutations that result in altered metabolism. The *CYP2C9*2* allele encodes an Arg144Cys mutation, exhibiting impaired functional interactions with **POR**. The other allelic variant, *CYP2C9*3*, encodes an enzyme with an Ile359Leu mutation that has lowered affinity for many substrates. For example, individuals displaying the *CYP2C9*3* phenotype have greatly reduced tolerance for the anticoagulant warfarin. The warfarin clearance in *CYP2C9*3*-homozygous individuals is about 10% of normal values, and these people have a much lower tolerance for the drug than those who are homozygous for the normal wild type allele. These individuals also have a much higher risk of adverse effects with warfarin (eg, bleeding) and with other CYP2C9 substrates such as phenytoin, losartan, tolbutamide, and some nonsteroidal anti-inflammatory drugs (Table 4–4). Note, however, that despite the predominant role of CYP2C9 in warfarin clearance (particularly that of its pharmacologically more potent *S*-isomer), warfarin maintenance doses are largely dictated by polymorphisms in the *VKORC1* gene responsible for the expression of vitamin K epoxide reductase, the specific cellular target of warfarin, rather than by *CYP2C9*2/*3* polymorphisms alone (see Chapter 5).

Allelic variants of CYP3A4 have also been reported, but their contribution to the well-known interindividual variability in drug metabolism apparently is limited. On the other hand, the expression of **CYP3A5,** another human liver isoform, is markedly polymorphic, ranging from 0% to 100% of the total hepatic CYP3A content. This CYP3A5 protein polymorphism is now known to result from

a single nucleotide polymorphism **(SNP)** within intron 3, which enables normally spliced CYP3A5 transcripts in 5% of Caucasians, 29% of Japanese, 27% of Chinese, 30% of Koreans, and 73% of African Americans. Thus, it can significantly contribute to interindividual differences in the metabolism of preferential CYP3A5 substrates such as midazolam. Two other CYP3A5 allelic variants that result in a PM phenotype are also known.

Polymorphisms in the *CYP2A6* gene have also been recently characterized, and their prevalence is apparently racially linked. CYP2A6 is responsible for nicotine oxidation, and tobacco smokers with low CYP2A6 activity consume less and have a lower incidence of lung cancer. CYP2A6 1B allelic variants associated with faster rates of nicotine metabolism have been recently discovered. It remains to be determined whether patients with these faster variants will fall into the converse paradigm of increased smoking behavior and lung cancer incidence.

Additional genetic polymorphisms in drug metabolism are being discovered. Of these, the gene for **CYP2B6** has become noteworthy as one of the most polymorphic P450 genes, with a 20- to 250-fold variation in interindividual CYP2B6 expression. Despite its low (1–5%) contribution to the total liver P450 content, these CYP2B6 polymorphisms may have a significant impact on the CYP2B6-dependent metabolism of several clinically relevant drugs such as cyclophosphamide, *S*-methadone, efavirenz, nevirapine, bupropion, selegiline, and propofol. Of clinical relevance, women (particularly Hispanic-American women) express considerably higher hepatic levels of CYP2B6 protein than men.

Studies of theophylline metabolism in monozygotic and dizygotic twins that included pedigree analysis of various families have revealed that a distinct polymorphism may exist for this drug and may be inherited as a recessive genetic trait. Genetic drug metabolism polymorphisms also appear to occur for aminopyrine and carbocysteine oxidations. Regularly updated information on human P450 polymorphisms is available at http://www.cypalleles.ki.se/.

Although genetic polymorphisms in drug oxidations often involve specific P450 enzymes, such genetic variations can also occur in other enzymes. Recently, genetic polymorphisms in POR, the essential P450 electron donor, have been reported. In particular, an allelic variant (at a 28% frequency) encoding a POR A503V mutation has been reported to result in impaired CYP17-dependent sex steroid synthesis and impaired CYP3A4- and CYP2D6-dependent drug metabolism in vitro. Its involvement in clinically relevant drug metabolism, while predictable, remains to be established. Descriptions of a polymorphism in the oxidation of trimethylamine, believed to be metabolized largely by the **flavin monooxygenase (Ziegler's enzyme),** result in the "fish-odor syndrome" in slow metabolizers, thus suggesting that genetic variants of other non-P450-dependent oxidative enzymes may also contribute to such polymorphisms.

B. Phase II Enzyme Polymorphisms

Succinylcholine is metabolized only half as rapidly in persons with genetically determined deficiency in pseudocholinesterase (now generally referred to as butyrylcholinesterase [**BCHE**]) as in persons with normally functioning enzyme. Different mutations, inherited as autosomal recessive traits, account for the enzyme deficiency. Deficient individuals treated with succinylcholine as a surgical muscle relaxant may become susceptible to prolonged respiratory paralysis (succinylcholine apnea). Similar pharmacogenetic differences are seen in the acetylation of isoniazid. The defect in slow acetylators (of isoniazid and similar amines) appears to be caused by the synthesis of less of the NAT2 enzyme rather than of an abnormal form of it. Inherited as an autosomal recessive trait, the **slow acetylator phenotype** occurs in about 50% of blacks and whites in the USA, more frequently in Europeans living in high northern latitudes, and much less commonly in Asians and Inuit (Eskimos). The slow acetylator phenotype is also associated with a higher incidence of isoniazid-induced peripheral neuritis, drug-induced autoimmune disorders, and bicyclic aromatic amine-induced bladder cancer.

A clinically important polymorphism of the *TPMT* (thiopurine *S*-methyltransferase) gene is encountered in Europeans (frequency, 1:300), resulting in a rapidly degraded mutant enzyme and consequently deficient *S*-methylation of aromatic and heterocyclic sulfhydryl compounds including the anti-cancer thiopurine drugs 6-mercaptopurine, thioguanine, and azathioprine, required for their detoxification. Patients inheriting this polymorphism as an autosomal recessive trait are at high risk of thiopurine drug-induced fatal hematopoietic toxicity.

Genetic polymorphisms in the expression of other phase II enzymes (UGTs and GSTs) also occur. Thus, UGT polymorphisms (*UGT1A1*28*) are associated with hyperbilirubinemic diseases (Gilbert's syndrome) as well as toxic effects due to impaired drug conjugation and/or elimination (eg, the anticancer drug irinotecan). Similarly, genetic polymorphisms (*GSTM1*) in GST (mu1 isoform) expression can lead to significant adverse effects and toxicities of drugs dependent on its GSH conjugation for elimination.

C. Role of Pharmacogenomic Testing in Clinically Safe & Effective Drug Therapy

Despite our improved understanding of the molecular basis of pharmacogenetic defects in drug-metabolizing enzymes, their impact on drug therapy and ADRs, and the availability of validated pharmacogenetic biomarkers to identify patients at risk, this clinically relevant information has not been effectively translated to patient care. Thus, the much-heralded potential for personalized medicine, except in a few instances of drugs with a relatively low therapeutic index (eg, warfarin), has remained largely unrealized. This is so even though 98% of US physicians are apparently aware that such genetic information may significantly influence therapy. This is partly due to the lack of adequate training in translating this knowledge to medical practice, and partly due to the logistics of genetic testing and the issue of cost-effectiveness. Severe ADRs are known to contribute to 100,000 annual US deaths, about 7% of all hospital admissions, and an increased average length of hospital stay. Genotype information could greatly enhance safe and efficacious clinical therapy through dose adjustment or alternative drug therapy, thereby curbing much of the rising ADR incidence and its associated costs. (See Chapter 5 for further discussion.)

Commensal Gut Microbiota

It is increasingly recognized that the human gut microbiome can also significantly influence drug responses. It thus serves as another relevant source of therapeutic misadventures and adverse

drug-drug interactions. More than 1000 species of intestinal microorganisms have been identified, including obligate anaerobic bacteria and various yeasts that coexist in a dynamic, often symbiotic, ecological equilibrium. Their biotransformation repertoire is nonoxidative, albeit highly versatile, extending from predominantly reductive and hydrolytic reactions to decarboxylation, dehydroxylation, dealkylation, dehalogenation, and deamination. Notably, such bacterially mediated reduction of the cardiac drug digoxin significantly contributes to its metabolism and elimination. Co-treatment with antibiotics such as erythromycin or tetracycline increases digoxin serum levels twofold, increasing the risk of cardiotoxicity. Similarly, drugs that are primarily glucuronidated in the liver are excreted into the gut via the bile, whereupon they are subjected to de-glucuronidation by gut microbial β-glucuronidases (hydrolases). The pharmacologically active parent aglycone is subsequently reabsorbed into the portal circulation with consequent extension of its pharmacologic action and hepatic phase II reconjugation and subsequent enterohepatic recycling. Thus, if the parent drug is dosage limited or has a low therapeutic index, this may mean increased toxicity. For example, under normal dosage, the analgesic acetaminophen is largely metabolized via glucuronidation and sulfation, as discussed earlier, and eliminated into the hepatic sinusoidal plasma. However, upon overdosage, the increased production of these metabolites is quite likely to saturate their normal excretory transport process. Their consequently enhanced biliary excretion would subject a greater fraction of the acetaminophen-glucuronide to de-glucuronidation by intestinal microbial β-glucuronidases, which may further contribute to the toxic acetaminophen burden. This possibility is even more relevant for glucuronides of parent drugs of noted gastrointestinal toxicity. Accordingly, selective inhibition of microbial β-glucuronidases has been documented to alleviate the gastrointestinal toxicity of anticancer drugs such as irinotecan, as well as the enteropathies induced by nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, ketoprofen or diclofenac, that incur substantial enterohepatic circulation. This possibility has fueled the pharmaceutical design and development of even more selective inhibitors targeted against microbial β-glucuronidases.

Diet & Environmental Factors

Diet and environmental factors contribute to individual variations in drug metabolism. Charcoal-broiled foods and cruciferous vegetables are known to induce CYP1A enzymes, whereas grapefruit juice is known to inhibit the CYP3A metabolism of co-administered drug substrates (Table 4–2; also see below). Cigarette smokers metabolize some drugs more rapidly than nonsmokers because of enzyme induction (see previous section). Industrial workers exposed to some pesticides metabolize certain drugs more rapidly than unexposed individuals. Such differences make it difficult to determine effective and safe doses of drugs that have narrow therapeutic indices.

Age & Sex

Increased susceptibility to the pharmacologic or toxic activity of drugs has been reported in very young and very old patients compared with young adults (see Chapters 59 and 60). Although this may reflect differences in absorption, distribution, and excretion, differences in drug metabolism also play a role. Slower metabolism could be due to reduced activity of metabolic enzymes or reduced availability of essential endogenous cofactors.

Sex-dependent variations in drug metabolism have been well documented in rats but not in other rodents. Young adult male rats metabolize drugs much faster than mature female rats or prepubertal male rats. These differences in drug metabolism have been clearly associated with androgenic hormones. Clinical reports suggest that similar sex-dependent differences in drug metabolism also exist in humans for ethanol, propranolol, some benzodiazepines, estrogens, and salicylates.

Drug-Drug Interactions (DDIs) During Metabolism

Many substrates, by virtue of their relatively high lipophilicity, are not only retained at the active site of the enzyme but remain nonspecifically bound to the lipid endoplasmic reticulum membrane. In this state, they may induce microsomal enzymes, particularly after repeated use. Acutely, depending on the residual drug levels at the active site, they also may competitively inhibit metabolism of a simultaneously administered drug.

Enzyme-inducing drugs include various sedative-hypnotics, antipsychotics, anticonvulsants, the antitubercular drug rifampin, and insecticides (Table 4–5). Patients who routinely ingest barbiturates, other sedative-hypnotics, or certain antipsychotic drugs may require considerably higher doses of warfarin to maintain a therapeutic effect. On the other hand, discontinuance of the sedative inducer may result in reduced metabolism of the anticoagulant and bleeding—a toxic effect of the ensuing enhanced plasma levels of the anticoagulant. Similar interactions have been observed in individuals receiving various combinations of drug regimens such as rifampin, antipsychotics, or sedatives with contraceptive agents, sedatives with anticonvulsant drugs, and even alcohol with hypoglycemic drugs (tolbutamide). One inducer of note is St. John's wort, a popular over-the-counter herbal medicine ingested as treatment for mild to severe depression. Because of its marked induction of hepatic CYP3A4 and, to a lesser extent, CYP2C9 and CYP2C19, St. John's wort has been linked to a large number of DDIs. Most of such DDIs stem from P450 induction by St. John's wort and entail accelerated P450-dependent metabolism of the co-ingested drug (eg, alprazolam, contraceptive estrogens, warfarin, lovastatin, delavirdine, ritonavir). In contrast, St. John's wort-mediated CYP2C19 induction may enhance the activation of the antiplatelet prodrug clopidogrel by accelerating its conversion to the active metabolite. Finally, some St. John's wort-elicited DDIs may entail decreased P450-dependent metabolism due to competitive inhibition and consequently increased plasma levels and clinical effect (eg, meperidine, hydrocodone, morphine, oxycodone). Other DDIs entail synergistic increases in serotonin levels (due to monoamine oxidase inhibition) and correspondingly increased serotonergic tone and adverse effects (eg, paroxetine, sertraline, fluoxetine, fenfluramine).

It must also be noted that an inducer may enhance not only the metabolism of other drugs but also its own metabolism.

TABLE 4–5 Partial list of drugs that enhance drug metabolism in humans.

Inducer	Drugs Whose Metabolism Is Enhanced
Benzo[*a*]pyrene	Theophylline
Carbamazepine	Carbamazepine, clonazepam, itraconazole
Chlorcyclizine	Steroid hormones
Ethchlorvynol	Warfarin
Glutethimide	Antipyrine, glutethimide, warfarin
Griseofulvin	Warfarin
Phenobarbital and other barbiturates[1]	Barbiturates, chloramphenicol, chlorpromazine, cortisol, coumarin anticoagulants, desmethyl imipramine, digitoxin, doxorubicin, estradiol, itraconazole, phenylbutazone, phenytoin, quinine, testosterone
Phenylbutazone	Aminopyrine, cortisol, digitoxin
Phenytoin	Cortisol, dexamethasone, digitoxin, itraconazole, theophylline
Rifampin	Coumarin anticoagulants, digitoxin, glucocorticoids, itraconazole, methadone, metoprolol, oral contraceptives, prednisone, propranolol, quinidine, saquinavir
Ritonavir[2]	Midazolam
St. John's wort[3]	Alprazolam, cyclosporine, digoxin, indinavir, oral contraceptives, ritonavir, simvastatin, tacrolimus, warfarin

[1]Secobarbital is an exception. See Table 4–6 and text.

[2]With chronic (repeated) administration; acutely, ritonavir is a potent CYP3A4 inhibitor/inactivator.

[3]For a more comprehensive list of drugs whose metabolism is enhanced by St. John's wort, see Rahimi and Abdollahi, 2012; Russo et al, 2014; and Tsai et al, 2012.

TABLE 4–6 Partial list of drugs that inhibit drug metabolism in humans.

Inhibitor[1]	Drug Whose Metabolism Is Inhibited
Allopurinol, chloramphenicol, isoniazid	Antipyrine, dicumarol, probenecid, tolbutamide
Chlorpromazine	Propranolol
Cimetidine	Chlordiazepoxide, diazepam, warfarin, others
Dicumarol	Phenytoin
Diethylpentenamide	Diethylpentenamide
Disulfiram	Antipyrine, ethanol, phenytoin, warfarin
Ethanol	Chlordiazepoxide (?), diazepam (?), methanol
Grapefruit juice[2]	Alprazolam, atorvastatin, cisapride, cyclosporine, midazolam, triazolam
Itraconazole	Alfentanil, alprazolam, astemizole, atorvastatin, buspirone, cisapride, cyclosporine, delavirdine, diazepam, digoxin, felodipine, indinavir, loratadine, lovastatin, midazolam, nisoldipine, phenytoin, quinidine, ritonavir, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, triazolam, verapamil, warfarin
Ketoconazole	Astemizole, cyclosporine, terfenadine
Nortriptyline	Antipyrine
Oral contraceptives	Antipyrine
Phenylbutazone	Phenytoin, tolbutamide
Ritonavir	Amiodarone, cisapride, itraconazole, midazolam, triazolam
Saquinavir	Cisapride, ergot derivatives, midazolam, triazolam
Secobarbital	Secobarbital
Spironolactone	Digoxin
Troleandomycin	Theophylline, methylprednisolone

[1]While some inhibitors are selective for a given P450 enzyme, others are more general and can inhibit several P450s concurrently.

[2]Active components in grapefruit juice include furanocoumarins such as 6′, 7′-dihydroxybergamottin (which inactivates both intestinal and liver CYP3A4) as well as other unknown components that inhibit P-glycoprotein-mediated intestinal drug efflux and consequently further enhance the bioavailability of certain drugs such as cyclosporine. For a more comprehensive list of drugs whose metabolism is inhibited by grapefruit juice furanocoumarins, see Bailey et al, 2013.

Thus, continued use of some drugs may result in a pharmacokinetic type of **tolerance**—progressively reduced therapeutic effectiveness due to enhancement of their own metabolism.

Conversely, simultaneous administration of two or more drugs may result in impaired elimination of the more slowly metabolized drug and prolongation or potentiation of its pharmacologic effects (Table 4–6). Both competitive substrate inhibition and irreversible substrate-mediated enzyme inactivation may augment plasma drug levels and lead to toxic effects from drugs with narrow therapeutic indices. Indeed, such acute interactions of terfenadine (a second-generation antihistamine) with a CYP3A4 substrate-inhibitor (ketoconazole, erythromycin, or grapefruit juice) resulted in fatal cardiac arrhythmias (torsades de pointes) requiring its withdrawal from the market. Similar DDIs with CYP3A4 substrate-inhibitors (such as the antibiotics erythromycin and clarithromycin, the antidepressant nefazodone, the antifungals itraconazole and ketoconazole, and the HIV protease inhibitors indinavir and ritonavir) and consequent cardiotoxicity led to withdrawal or restricted use of the 5-HT_4 agonist cisapride. Similarly, allopurinol both prolongs the duration and enhances the chemotherapeutic and toxic actions of mercaptopurine by competitive inhibition of xanthine oxidase. Consequently, to avoid bone marrow toxicity, the dose of mercaptopurine must be reduced in patients receiving allopurinol. Cimetidine, a drug used in the treatment of peptic ulcer, has been shown to potentiate

the pharmacologic actions of anticoagulants and sedatives. The metabolism of the sedative chlordiazepoxide has been shown to be inhibited by 63% after a single dose of cimetidine; such effects are reversed within 48 hours after withdrawal of cimetidine.

Impaired metabolism may also result if a simultaneously administered drug irreversibly inactivates a common metabolizing enzyme. These inhibitors, in the course of their metabolism by cytochrome P450, inactivate the enzyme and result in impairment of their own metabolism and that of other cosubstrates. This is the case of the furanocoumarins in grapefruit juice, eg, 6′,7′-dihydroxybergamottin and bergamottin, which inactivate CYP3A4 in the intestinal mucosa and consequently enhance its proteolytic degradation. This impairment of intestinal first-pass CYP3A4-dependent metabolism significantly enhances the bioavailability of drugs such as ergotamine, felodipine, nifedipine, terfenadine, verapamil, ethinylestradiol, lovastatin, saquinavir, and cyclosporine A and is associated with clinically relevant DDIs and food-drug interactions. The list of drugs subject to DDIs involving grapefruit juice is extensive and includes many drugs with a very narrow therapeutic index and a high potential for lethal adverse reactions. However, it must be borne in mind that not all commercially available grapefruit juices are equally potent, as the CYP3A4 inactivation potency is totally dependent on the amount of furanocoumarins extracted into the juice from the zest (highest), pith, and pulp of the grapefruit. Furthermore, recovery from these interactions is dependent on CYP3A4 resynthesis and thus may be slow.

Interactions between Drugs & Endogenous Compounds

Some drugs require conjugation with endogenous substrates such as GSH, glucuronic acid, or sulfate for their inactivation. Consequently, different drugs may compete for the same endogenous substrates, and the faster-reacting drug may effectively deplete endogenous substrate levels and impair the metabolism of the slower-reacting drug. If the latter has a steep dose-response curve or a narrow margin of safety, potentiation of its therapeutic and toxic effects may result.

Diseases Affecting Drug Metabolism

Acute or chronic diseases that affect liver architecture or function markedly affect hepatic metabolism of some drugs. Such conditions include alcoholic hepatitis, active or inactive alcoholic cirrhosis, hemochromatosis, chronic active hepatitis, biliary cirrhosis, and acute viral or drug-induced hepatitis. Depending on their severity, these conditions may significantly impair hepatic drug-metabolizing enzymes, particularly microsomal oxidases, and thereby markedly affect drug elimination. For example, the half-lives of chlordiazepoxide and diazepam in patients with liver cirrhosis or acute viral hepatitis are greatly increased, with a corresponding increase in their effects. Consequently, these drugs may cause coma in patients with liver disease when given in ordinary doses.

Some drugs are metabolized so readily that even marked reduction in liver function does not significantly prolong their action. However, cardiac disease, by limiting blood flow to the liver, may impair disposition of those drugs whose metabolism is flow-limited (Table 4–7). These drugs are so readily metabolized by the liver that hepatic clearance is essentially equal to liver blood flow. The impaired enzyme activity or defective formation of enzymes associated with heavy metal poisoning or porphyria also results in reduced hepatic drug metabolism. Pulmonary disease may also affect drug metabolism, as indicated by the impaired hydrolysis of procainamide and procaine in patients with chronic respiratory insufficiency and the increased half-life of antipyrine (a P450 functional probe) in patients with lung cancer.

TABLE 4–7 Rapidly metabolized drugs whose hepatic clearance is blood flow-limited.

Alprenolol	Lidocaine
Amitriptyline	Meperidine
Clomethiazole	Morphine
Desipramine	Pentazocine
Imipramine	Propoxyphene
Isoniazid	Propranolol
Labetalol	Verapamil

Although the effects of endocrine dysfunction on drug metabolism have been well explored in experimental animal models, corresponding data for humans with endocrine disorders are scanty. Thyroid dysfunction has been associated with altered metabolism of some drugs and of some endogenous compounds as well. Hypothyroidism increases the half-life of antipyrine, digoxin, methimazole, and some β blockers, whereas hyperthyroidism has the opposite effect. A few clinical studies in diabetic patients indicate no apparent impairment of drug metabolism, although impairment has been noted in diabetic rats. Malfunctions of the pituitary, adrenal cortex, and gonads markedly reduce hepatic drug metabolism in rats. On the basis of these findings, it may be supposed that such disorders could significantly affect drug metabolism in humans. However, until sufficient evidence is obtained from clinical studies in patients, such extrapolations must be considered tentative.

Finally, the release of inflammatory mediators, cytokines, and nitric oxide associated with bacterial or viral infections, cancer, or inflammation are known to impair drug metabolism by inactivating P450s and enhancing their degradation.

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CASE STUDY ANSWER

Acetaminophen (APAP) is a relatively safe drug, provided it is taken at the recommended therapeutic doses. As discussed in the text, at normally ingested dosages, 95% of APAP is converted by phase II enzymes into much less toxic and more water-soluble APAP-glucuronide and APAP-sulfate, both of which are eliminated in the urine (Figure 4–5). Five percent of parent APAP is converted by phase I P450 enzymes into a reactive toxic product that is conjugated by GSH, excreted in the urine, and thus detoxified. However, APAP's safety may be greatly compromised in mixed drug overdoses, ie, when ingested with other drugs such as hydrocodone, duloxetine, and carisoprodol, which compete with APAP for phase II-dependent elimination or for cellular cofactors (GSH, UDPGA, PAPS) involved in these processes. Accordingly, more APAP is diverted into its hepatotoxic reactive metabolite pathway, resulting in liver cell damage. Moreover, HCV infection could indeed have further compromised liver function including drug metabolism. APAP's half-life is 2 hours, and therapeutic and toxic blood levels are 15 mcg/mL and > 300 mcg/mL, respectively (Chapter 3). Given that at 48 hours after ingestion (ie, 24 half-lives later), the patient's APAP blood level is 75 mcg/mL, it is obvious that her initial APAP levels were dangerously above the toxic range, and thus upon ED admission, her liver function tests are consistent with ongoing liver failure. She should be given *N*-acetylcysteine, the APAP-specific antidote (Acetadote, Mucomyst; see Chapter 58) and continuous intravenous glucose infusion to provide the precursor (glucose) for generating the UDPGA cofactor required for APAP glucuronidation, as well as the fluid to induce urine output and accelerate APAP-metabolite elimination.