

Get to Know an Enzyme: CYP3A4

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In previous issues of *Pharmacy Times*, we have discussed the cytochrome P450 (CYP450) enzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6 (see www.PharmacyTimes.com/DrugInteractions). In the spirit of saving the best for last, in this issue, we will discuss the most important of all CYP450 enzymes: CYP3A4. It has been estimated that CYP3A4 metabolizes about half of all drugs on the market. Because many other commonly used drugs are moderate-to-potent *inhibitors* of CYP3A4, it is not surprising that drug toxicity of CYP3A4 substrates due to inhibition of CYP3A4 is relatively common.

CYP3A4 also is sensitive to enzyme induction, and a number of drugs are known to be CYP3A4 inducers. CYP3A4 inducers tend to lower plasma concentrations of CYP3A4 substrates, resulting in reduced efficacy of the substrate. This type of drug interaction is probably more frequent than commonly realized, because *reduced* drug effect may simply be attributed to lack of patient response.

Many drugs that are CYP3A4 substrates, inhibitors, and inducers are also substrates, inhibitors, or inducers of the ABC transport protein known as P-glycoprotein. Many drug interactions, therefore, involve additive effects of both CYP3A4 and P-glycoprotein.

CYP3A4 Substrates

Drugs metabolized by CYP3A4 are called *CYP3A4 substrates*. Keep in mind that many drugs are metabolized by more than one CYP450 enzyme, and CYP3A4 may represent only one path-

Table

CYP3A4 Substrates Producing Potentially Serious Toxicity When Combined with CYP3A4 Inhibitors	
Drug	Potential Toxicity
Alfuzosin (Uroxatral)	Severe hypotension
Alprazolam (Xanax)	Excessive CNS depression
Budesonide	Cushing's syndrome
Carbamazepine (Tegretol)	Vomiting, headache, dizziness, drowsiness, etc
Colchicine	Fever, diarrhea, muscle pain, paresthesias (may be fatal)
Cyclosporine (eg, Neoral)	Cyclosporine toxicity
Dexamethasone	Cushing's syndrome
Disopyramide (Norpace)	Cardiac arrhythmias
Ergotamine (and other ergot alkaloids)	Ergotism (peripheral ischemia, cyanosis, hypertension)
Fluticasone (Flovent)	Cushing's syndrome
Lovastatin (Mevacor)	Rhabdomyolysis
Methylprednisolone	Cushing's syndrome
Midazolam (oral)	Excessive CNS depression
Pimozide (Orap)	Torsades de pointes
Quinidine	Cardiac arrhythmias
Repaglinide (Prandin)	Hypoglycemia
Rifabutin (Mycobutin)	Uveitis, bone marrow suppression, rash
Sildenafil (Viagra)	Hypotension, syncope
Simvastatin (Zocor)	Rhabdomyolysis
Tadalafil (Cialis)	Hypotension, syncope
Triazolam (Halcion)	Excessive CNS depression
Vardenafil (Levitra)	Hypotension, syncope
Vinblastine (Velban)	Bone marrow suppression
Vincristine (Oncovin)	Peripheral neuropathy, paralytic ileus

CNS = central nervous system.

way. Unfortunately, many CYP3A4 substrates have substantial toxicity, and some patients may develop severe toxicity when CYP3A4 inhibitors are taken concurrently. A selected list of such interactions appears in the Table.

CYP3A4 Inhibitors

Drugs that inhibit CYP3A4 activity will almost always increase the plasma concentrations of the CYP3A4 substrate medications. Some drugs, such as clarithromycin, itraconazole, and ketoconazole, are


particularly potent inhibitors of CYP3A4; patients on these drugs may have markedly reduced CYP3A4 activity.

CYP3A4 Inducers

CYP3A4 inducers are drugs that increase the activity of CYP3A4. Note that the CYP3A4 enzyme is particularly susceptible to enzyme inducers, and marked reductions in the plasma concentrations of CYP3A4 substrates may occur. For example, a patient taking the potent CYP3A4 inducer rifampin may have a roughly 90% reduction in serum concentrations of CYP3A4 substrates, such as buspirone, triazolam, and verapamil. ■

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For tables listing examples of CYP3A4 substrates, inhibitors, and inducers, please visit www.PharmacyTimes.com/CYP3A4.

 For a list of references, go to www.PharmacyTimes.com.

CYP3A4 Substrates

Alfentanil (Alfenta)	Erythromycin	Paclitaxel (Taxol)
Alfuzosin (Uroxatral)	Estazolam (ProSom)	Paricalcitol (Zemplantar)
Almotriptan (Axert)	Eszopiclone (Lunesta)	Pimozide (Orap)
Alprazolam (Xanax)	Ethinyl Estradiol	Pioglitazone
Amiodarone (Cordarone)	Ethosuximide (Zarontin)	Praziquantel (Biltricide)
Amlodipine (Norvasc)	Etoposide (Vepesid)	Prednisolone
Aprepitant (Emend)	Exemestane (Aromasin)	Prednisone
Atazanavir (Reyataz)	Felodipine (Plendil)	Propoxyphene (Darvon)
Atorvastatin (Lipitor)	Fentanyl (Sublimaze)	Quazepam (Doral)
Bepridil (Vascor)	Finasteride (Proscar)	Quetiapine (Seroquel)
Bexarotene (Targretin)	Flurazepam (Dalmane)	Quinacrine
Bosentan (Tracleer)	Fosamprenavir (Lexiva)	Quinidine
Bromocriptine (Parlodel)	Galantamine (Reminyl)	Quinine
Budesonide (Entocort)	Gefitinib (Iressa)	Ranolazine (Ranexa)
Buprenorphine (Subutex)	Granisetron (Kytril)	Repaglinide (Prandin)
Bupropion (Buspar)	Halofantrine (Halfan)	Rifabutin (Rimactane)
Carbamazepine (eg, Tegretol)	Ifosfamide (Ifex)	Ritonavir (Norvir)
Cevimeline (Evoxac)	Imatinib (Gleevec)	Saquinavir (Invirase)
Cilostazol (Pletal)	Indinavir (Crixivan)	Sibutramine (Meridia)
Cisapride (Propulsid)	Irinotecan (Camptosar)	Sildenafil (Viagra)
Clarithromycin (Biaxin)	Isradipine (DynaCirc)	Simvastatin (Zocor)
Clonazepam (Klonopin)	Itraconazole (Sporanox)	Sirolimus (Rapamune)
Clopidogrel (Plavix)	Ixabepilone (Ixempra)	Solifenacin (Vesicare)
Colchicine	Ketoconazole (Nizoral)	Sufentanil (Sufenta)
Cyclophosphamide (Cytoxan)	Lapatinib (Tykerb)	Sunitinib (Sutent)
Cyclosporine (Neoral)	Levomethadyl (Orlaam)	Tacrolimus (Prograf)
Dapsone (Avlosulfon)	Loperamide (Imodium)	Tadalafil (Cialis)
Darunavir (Prezista)	Lopinavir (Kaletra)	Tamoxifen (Nolvadex)
Dasatinib (Sprycel)	Loratadine (Claritin)	Tamsulosin (Flomax)
Delavirdine (Rescriptor)	Lovastatin (Mevacor)	Teniposide (Vumon)
Dexamethasone (Decadron)	Maraviroc (Selzentry)	Testosterone
Dihydroergotamine	Mefloquine (Lariam)	Tiagabine (Gabitril)
Diltiazem (Cardizem)	Methylprednisolone	Tinidazole (Tindamax)
Disopyramide (Norpace)	Midazolam (Versed)	Tipranavir (Aptivus)
Docetaxel (Taxotere)	Mifepristone (Mifeprex)	Topiramate (Topamax)
Donepezil (Aricept)	Modafinil (Provigil)	Triazolam (Halcion)
Doxorubicin (Adriamycin)	Nefazodone	Vardenafil (Levitra)
Droperidol	Nevirapine (Viramune)	Verapamil (Calan)
Dutasteride (Avodart)	Nicardipine (Cardene)	Vinblastine (Velbane)
Ebastine (Kestine)	Nifedipine (Adalat)	Vincristine (Oncovin)
Efavirenz (Sustiva)	Nimodipine (Nimotop)	Ziprasidone (Geodon)
Eletriptan (Relpax)	Nisoldipine (Sular)	Zolpidem (Ambien)
Eplerenone (Inspra)	Nitrendipine (Baypress)	Zonisamide (Zonegran)
Ergotamine (Ergomar)	Oxybutynin (Ditropan)	Zopiclone (Imovane)
Erlotinib (Tarceva)	Oxycodone (Percodan)	

CYP3A4 Inhibitors

Amiodarone	Erythromycin	Miconazole
Amprenavir	Fluconazole	Nefazodone
Aprepitant	Fluoxetine	Nelfinavir
Atazanavir	Fluvoxamine	Posaconazole
Chloramphenicol	Fosamprenavir	Ritonavir
Clarithromycin	Grapefruit juice	Quinupristin
Conivaptan	Imatinib	Saquinavir
Cyclosporine	Indinavir	Tamoxifen
Darunavir	Isoniazid	Telithromycin
Dasatinib	Itraconazole	Troleandomycin
Delavirdine	Ketoconazole	Verapamil
Diltiazem	Lapatinib	Voriconazole

CYP3A4 Inducers

Aminoglutethimide	Griseofulvin	Primidone
Bexarotene	Modafinil	Rifabutin
Bosentan	Nafcillin	Rifampin
Carbamazepine	Nevirapine	Rifapentine
Dexamethasone	Oxcarbazepine	St. John's wort
Efavirenz	Phenobarbital	
Fosphenytoin	Phenytoin	