Clinical Utility

The cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5) account for 40-80% of total CYP in human liver and intestine, respectively. Most importantly, CYP3A enzymes metabolize 50% of commonly used drugs. CYP3A4 and CYP3A5 enzymes have overlapping substrate specificity and the contribution of CYP3A5 in the overall metabolism is smaller than the one for CYP3A4. The overall CYP3A metabolism status is expected to affect drugs that have a narrow therapeutic index.

Assay Interpretation

A limited number of variants identified within the CYP3A4 and CYP3A5 genes have been associated with significant alterations in enzyme activity and subsequent variability in therapeutic response. For CYP3A5, individuals with the less prevalent “normal metabolizer phenotype” may metabolize drugs faster than those with the more common “poor metabolizer phenotype”. This may result in increased toxicity or loss of efficacy.

The CYP3A4 *1B variant is the most studied and results in an enzyme with moderately decreased activity. It occurs in 50% of African Americans, 3-5% of Caucasians and <1% of Asians. The CYP3A4 *2, *3, *12 and *17 are also considered decreased activity alleles. Recently, the CYP3A4 *22 allele has been characterized as a decreased function allele that can be clinically relevant and is associated with a decreased clearance of substrates. The genotype phenotype relationship for CYP3A4 is not well established and individuals are predicted to have either a CYP3A4 normal or intermediate metabolic capacity.

The CYP3A5 *3 variant results in an enzyme with no activity and is the most common variant in the general population. The CYP3A5 *3B and *6 are also null alleles resulting in no enzyme activity. The CYP3A5 alleles *2, *8 and *9 result in a partially active enzyme. The CYP3A5 *1 allele produces an active enzyme and is found in 5% of Caucasians, 20% of Asians and 15-50% of Africans. Individuals with two CYP3A5 inactive alleles are classified as poor metabolizers. Individuals carrying at least one copy of a CYP3A5 active allele are either normal or intermediate metabolizers. CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians.

The reference range for CYP3A4 metabolic status is CYP3A4 *1/*1 which is consistent with a normal metabolizer.

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The reference range for CYP3A5 metabolic status is CYP3A5 *1/*1 which is consistent with a normal metabolizer. This genotype is the least prevalent in Caucasians and Asians.

Clinical Implications

CYP3A4 and CYP3A5 genotypes can help identify patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (like narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms. Fentanyl (Duragesic) is a narrow therapeutic drug that is mainly metabolized by CYP3A. There is limited evidence suggesting that the response to this drug is altered in individuals with abnormal CYP3A activity.

The following drugs used in pain management and various psychiatric conditions are metabolized extensively by CYP3A: Fentanyl (Duragesic), Oxycodone (Oxycontin) and Buprenorphine (Suboxone), Carbamazepine (Tegretol), Quetiapine (Seroquel), Ziprasidone (Geodon), Alprazolam (Xanax), Midazolam (Versed), Triazolam (Halcion), Nefazodone (Serzone), Trazodone (Olepro), Vilazodone (Vibryd), Zaleplon (Sonata) and Zolpidem (Ambien). CYP3A contributes to a small extent in the elimination of Methadone (Dolophine).

Drugs Known to Increase CYP3A Activity

| Drugs Known to Increase CYP3A Activity | $\text{Ketoconazole}$ | $\text{Itraconazole}$ | $\text{Posaconazole}$ | $\text{Voriconazole}$ | $\text{Clarithromycin}$ | $\text{Telithromycin}$ | $\text{Troleandomycin}$ | $\text{Conivaptan}$ | $\text{Nefazodone}$ | $\text{Ritonavir}$ | $\text{Lopinavir}$ | $\text{Nelfinavir}$ | $\text{Tipranavir}$ | $\text{Boceprevir}$ | $\text{Grapefruit Juice}$ | $\text{Amprenavir}$ | $\text{Aprepitant}$ | $\text{Atazanavir}$ | $\text{Darunavir}$ | $\text{Fosapenavir}$ | $\text{Erythromycin}$ | $\text{Ciprofloxacin}$ | $\text{Diltiazem}$ | $\text{Verapamil}$ | $\text{Fluconazole}$ | $\text{Imatinib}$ | $\text{Quinupristin}$ | $\text{Dalfopristin}$ |
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Drugs Known to Decrease CYP3A Activity

| Drugs Known to Decrease CYP3A Activity | $\text{Carbamazepine}$ | $\text{Enzalutamide}$ | $\text{Posphenytoin}$ | $\text{Phenytoin}$ | $\text{Phenobarbital}$ | $\text{Primidone}$ | $\text{Rifampin}$ | $\text{Rifabutin}$ | $\text{Rifapentine}$ | $\text{St. John’s Wort}$ | $\text{Artemether}$ | $\text{Bosentan}$ | $\text{Amprenavir}$ | $\text{Aprepitant}$ | $\text{Atazanavir}$ | $\text{Darunavir}$ | $\text{Fosapenavir}$ | $\text{Erythromycin}$ | $\text{Ciprofloxacin}$ | $\text{Diltiazem}$ | $\text{Verapamil}$ | $\text{Fluconazole}$ | $\text{Imatinib}$ | $\text{Quinupristin}$ | $\text{Dalfopristin}$ |
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Within the major therapeutic classes used in cardiovascular conditions, the following drugs are substantially metabolized by CYP3A: Atorvastatin (Lipitor), Simvastatin (Zocor), Lovastatin (Mevacor), Nifedipine (Procardia), Verapamil (Verelan), Nifedipine (Cardene), Felodipine (Plendil), Nisoldipine (Sular), Clopidogrel (Plavix), Prasugrel (Effient), Ticagrelor (Brilinta), Cilostazol (Pletal), Amiodarone (Cordarone), Quinidine (Qualaquin), Disopyramide (Norpace), Losartan (Cozaar), Rivaroxaban (Xarelto), Apixaban (Eliquis).

CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs. Then occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, the response and safety profiles of many CYP3A drug substrates.

References