CYP1A2: The Switch-hitter

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Abstract

This chapter discusses the genetics, metabolic actions, substrates, inducers, and inhibitors of cytochrome P450 1A2

Cytochrome P450 (CYP) 1A2 is a monooxygenase that is found almost exclusively in the liver.[1] It accounts for 10% to 15% of major cytochrome p450 enzymes.[1,2] By means of hydroxylation or de-alkylation reactions, CYP1A2 metabolizes endogenous compounds such as steroids, retinols, melatonin, and arachidonic acids; it also metabolizes approximately 4% to 20% of commonly prescribed medications, and contributes to bioactivation of many procarcinogens.[1,2]

The genetic sequencing for CYP1A2 is located on chromosome 15. 1A2 is a highly polymorphic enzyme with greater than fifteen 1A2 alleles identified to date.[3] Single-point mutations in the 1A2 allele can cause changes in enzyme expression. For example, the wild-type allele *CYP1A2 *1A* exhibits normal enzyme inducibility, the *CYP1A2*1C* allele exhibits decreased enzyme inducibility, and the *CYP1A2*1 F* allele exhibits increased enzyme inducibility.[3] Allelic frequencies may vary with ethnicity. For example, four distinct single-nucleotide mutations of 1A2 were screened in 459 Caucasians and found to be significantly different from distributions seen in other ethnicities.[4] Predicting clinically significant drug–drug interactions (DDIs) or adverse drug events related to 1A2 may be complicated by the fact that 1A2 enzyme expression may vary up to 40-fold from individual to individual.[5]

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This interindividual variability is attributable to genetic and ethnic factors, as well as enzyme induction or inhibition by foods, environmental toxins like tobacco smoke, and medications.

Dietary effects on 1A2 include enzyme induction by brassica vegetables, char-grilled meats, and grape juice. Apiaceous vegetables, caffeine, and grapefruit juice inhibit 1A2 enzyme activity.[6] The degree of dietary 1A2 induction or inhibition may vary considerably from individual to individual; clinically relevant drug interactions may only occur with drugs having narrow therapeutic windows.[6] Cigarette smoking is a potent inducer of 1A2.[7] Human CYP1A2 has the ability to activate heterocyclic amines to carcinogenic and mutagenic products.[8] In multiple studies, 1A2 function was shown to be strongly induced by polycyclic aromatic hydrocarbons, some of which are found in tobacco smoke.[7,9,10] Plasma levels of the 1A2 substrates olanzapine, and clozapine have been shown to decrease in the presence of cigarette smoking.[9,11] Some investigators suggest that practitioners consider 1A2 substrate dosage reduction for persons who quit smoking and dosage increases for persons who commence smoking.[12]

Commonly prescribed medications that induce 1A2 include carbamazepine and (in persons with the *CYP1A2*1 F* allele variant) omeprazole.[13] Fluvoxamine, quinolone antibiotics (eg, norfloxacin, enoxacin, and ciprofloxacin), and oral contraceptives inhibit 1A2 enzyme activity.[13] Drugs that are preferentially metabolized by 1A2 include caffeine, clozapine, olanzapine, tacrine, and theophylline.[13] Drugs that are to a lesser degree metabolized by 1A2 include clomipramine, duloxetine, imipramine, naproxen, ondansetron, propafenone, R-warfarin, and verapamil.[13]

Concomitant use of CYP1A2 substrates, inhibitors and/or inducers has been shown to produce significant pharmacokinetic interactions.[7,11,12,14] However, medication dose adjustments may not be uniformly necessary, particularly if the drugs in question have high therapeutic indices. For example, one study showed that although plasma concentration of duloxetine significantly increased with concurrent administration of fluvoxamine, these combinations were generally well tolerated by the human research subjects.[14]

Take-Home Points

- CYP1A2 accounts for approximately 10% to 15% of major cytochrome P450 enzymes and metabolizes 4% to 20% of commonly prescribed medications.
- Interindividual variability in enzyme expression of CYP1A2 can be related to genetic, dietary, environmental, and medication effects and this variability in enzyme expression may affect drug metabolism and clinical effects.

- Concomitant use of CYP1A2 substrates, inhibitors, and inducers may necessitate medication dosage adjustments for drugs with narrow therapeutic windows or low therapeutic indices.

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