CYP2D6: Where It All Began

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Abstract

This chapter discusses the genetics, metabolic actions, substrates, and inhibitors of cytochrome P450 2D6.

Cytochrome P450 (CYP) 2D6 is a member of the cytochrome P450 family of hemoproteins, which are responsible for Phase I metabolism of the majority of xenobiotics in the body. CYP2D6 accounts for about 2% to 5% of the body's P450 enzymes, but metabolizes about 25% of current drugs.[1] Most commonly, a monooxygenase reaction is catalyzed; that is the insertion of one atom of oxygen into an organic substrate – $RH + O^2 + 2H^+ + 2e^- \rightarrow ROH + H_2O$. In humans, 2D6 is expressed almost exclusively in the liver, with a small amount of activity in the intestinal wall. It is a membrane bound protein located on the cellular endoplasmic reticulum. The gene coding CYP2D6 is located on chromosome 22. Typically, substrates for the 2D6 isoenzyme are lipophilic bases.

CYP2D6 shows great phenotypic variability due to genetic polymorphism. More than 100 allelic variants with different properties have been discovered but 87% of genotypes are accounted for by five variants.[2,3] The wild-type reference is designated CYP2D6*1. Expression of the allelic variants in heterozygous or homozygous forms results in different enzyme activity levels, which are classified as: 1) poor metabolizer with little or no CYP2D6 function, 2) intermediate metabolizer with reduced function, 3) extensive metabolizer with normal function, or 4) ultrarapid metabolizer with increased CYP2D6 function. A person with two nonfunc-

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tional alleles is phenotypically a poor metabolizer. More than two functional alleles results in an ultra-rapid metabolizer. Someone with one functional copy is either an intermediate or extensive metabolizer depending on the activity of the allele. Clinical effects of drugs that are metabolized by CYP2D6 in addition to other pathways, such as oxycodone and ß-blockers, may not be impacted by genetic variability or drug interaction involving CYP2D6 unless it is the dominant metabolic path. The biological effect of a specific allele may be substrate-dependent. For example, CYP2D6*17 is usually an allele with reduced function, but it produces variable clinical outcomes when catalyzing the metabolism of substrates such as dextromethorphan, fluoxetine, codeine, and tramadol.[4] Laboratory tests can be used to distinguish genotypes (AmpliChip, Roche Diagnostics, Indianapolis, IN), or clinical activity can be evaluated by measuring the metabolism of debrisoquine, a selective CYP2D6 substrate that may be used to predict drug interactions and patients' metabolism of drugs. An extensive review of the CYP2D6 polymorphisms has been published.[1]

Ethnicity is a factor in CYP2D6 variability. About 5% to 10% of Caucasians and 2% of Chinese are poor metabolizers of 2D6 substrates.[5,6] The incidence of poor metabolizers in African populations is highly variable (0% to 34%).[7] The incidence of persons with genotypes resulting in reduced metabolism reaches 50% in Asians and 47% of children in London.[8,9] Ultra-rapid metabolizers have not been reported in Asians, but reach 9% to 30% in Africans and 1% to 7% in Caucasians.[7]

Clinically important drug–drug interactions involving 2D6 occur because of different allelic expression and/or co-administration of substances which may be inhibitors of the 2D6 enzyme. There are actually no known inducers of 2D6, which is unique among the "common" CYP450 enzymes.[10] Biological effects depend on whether the substrate is an active drug or a prodrug like codeine. The biological effect of an active drug is enhanced in poor metabolizers or by co-administration of inhibitors and reduced in ultra-rapid metabolizers or by co-administration of inducers. The biological effect of codeine, which requires 2D6 conversion to its active form morphine, is enhanced in ultra-rapid metabolizers and reduced in poor metabolizers or by co-administration of inhibitors.

Common drugs that are 2D6 substrates and may be taken by patients presenting for anesthesia are: ß-blockers, several antiarrhythmics, some selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and several antipsychotics. Some 2D6 inhibitors include: several SSRIs, 3,4-methylenedioxy-N-methylamphetamine (MDMA), ritonavir, bupropion, goldenseal, and quinidine. Medications used in the perioperative period that are 2D6 substrates include: opioids (including codeine, hydrocodone, dihydrocodone and tramadol), ondansetron, ß-blockers, and metoclopramide. Perioperative medications that are 2D6 inhibitors include celecoxib, diphenhydramine, metoclopramide, ropivacaine, cimetidine, methadone, and amiodarone.

Clinical relevance has been demonstrated. Apnea has occurred after administration of codeine to a child whose 2D6 ultra-rapid metabolizer phenotype resulted in a

higher than expected conversion of codeine to morphine.[11] Ultra-rapid metabolizers may have a higher incidence of failure of ondansetron prophylaxis of postoperative vomiting.[12] Granisetron is the only 5-HT_3 antagonist that is not metabolized by CYP2D6, and thus would confer effective anti-emetic prophylaxis to an ultra-rapid metabolizer for whom ondansetron had failed.[13] Poor and intermediate metabolizers have well-documented reduced analgesic efficacy of codeine, hydrocodone, and tramadol, each of which relies on metabolism by 2D6 to an active form to have clinical effect.[7] Patients who fail to respond to prodrug opioids metabolized by 2D6 may respond better to oxycodone, which is already an active analgesic in its "parent" form and does not require conversion via CYP2D6 to become an effective analgesic (ie, it is not a prodrug). Ropivacaine infusion has been shown to be a potent inhibitor of 2D6.[14] Patients on common selective serotonin reuptake inhibitor drugs, such as fluoxetine or paroxetine, could be predicted to experience less analgesic efficacy from opioid prodrugs. The combination of paroxetine and tramadol has resulted in development of central serotonin syndrome and seizures due to overaccumulation of tramadol, which lowers seizure threshold.[15]

Dosing and efficacy of medications that are CYP2D6 substrates may be affected by age. Liver enzymes reach maturity between the ages of 2 months and 6 months. Before that age, medications that rely on conversion to active forms, such as tramadol and codeine, may not be effective and active substrates may accumulate. Although with most drugs metabolized by CYP450, pediatric dosing correlates best with body surface area, for those drugs metabolized primarily by CYP2D6, dosing should be based on body weight.[16]

Take-Home Points

- CYP2D6 substrates and inhibitors include a broad array of commonly prescribed drugs. There are no known CYP2D6 inducers, which is unique among the "common" CYP450 enzymes.
- Coadministration of CYP2D6 substrates and inhibitors will usually produce increases in the blood levels of those substrates.
- There is great variability in the genotypic and resulting phenotypic expression of CYP2D6. At standard dosages, 2D6 poor metabolizers will generate much higher-than-expected blood levels of CYP2D6 substrates, whereas ultrarapid metabolizers will generate much lower-than-expected levels.
- Many of the commonly used analgesic agents (codeine, hydrocodone, and tramadol) are prodrugs for CYP2D6, so administering these agents to 2D6 poor metabolizers, or coadministration of potent CYP2D6 inhibitors, will result in poor efficacy. Conversely, administration of these agents to ultrarapid metabolizers can result in toxicity.

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