CYP2B: 2B or Not 2B?

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Abstract

This chapter discusses the genetics, metabolic actions, substrates, inducers, and inhibitors of cytochrome P450 2B6.

The functions of the cytochrome P450 (CYP) 2B family of enzymes have not been, until relatively recently, well characterized in humans. Located on chromosome 19, CYP2B6 is the only known isoform present in humans, and comprises between 1% and 10% of the P450 enzyme system.[1,2] Although CYP2B6 was originally thought to be negligible in importance in humans, it is becoming more evident that the presence of CYP2B6 is ubiquitous, but expression and inducibility are highly variable among individuals, depending on age and ethnicity.[3]

Expression of CYP2B6 is closely regulated by the constitutive androstane receptor (CAR), the pregnane X receptor, and glucocorticoid receptor.[4] CYP2B6 has been detected not only in liver, but also lung, kidney, and intestine, where it participates mostly in *N*-demethylation and hydroxylation of its substrates.[5] This has important implications for many anesthetic drugs that are metabolized by CYP2B6.

There are more than 40 substrates for CYP2B6, and the list is growing.[3] Some well-known substrates are the antidepressant bupropion, the antineoplastic agents cyclophosphamide and ifosfamide, and the antiretroviral efavirenz.[2] Clinically important inhibitors include the selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline, estradiol, thiotepa, ticlopidine, and clopidogrel.[2,6,7]

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Inducers of CYP2B6 include the anticonvulsants phenobarbital, phenytoin, and carbamazepine, as well as rifampin, ritonavir, and some glucocorticoids such as dexamethasone.[8]

A profoundly important role for CYP2B6 is evolving in anesthesia. For instance, CYP2B6 is a high-affinity, high-capacity enzyme for propofol, and appears to be the major cytochrome P450 enzyme for propofol metabolism.[9] Presence of CYP2B6 in other major organs appears to be a significant factor in the extrahepatic metabolism that occurs with propofol.

Ketamine metabolism to its analgesic metabolite, norketamine, is mostly mediated via CYP3A4 at higher concentrations. However, at lower, subanesthetic doses, CYP2B6 plays a relatively larger role, since it appears to have a higher affinity for ketamine than 3A4.[10]

CYP2B6 is responsible for about 57% of the conversion of meperidine to its neurotoxic metabolite, normeperidine.[11] Thus, great caution is warranted when giving meperidine to individuals also taking CYP2B6 inducers.

CYP2B6 has recently been shown to be the main mediator in P450 metabolism of methadone.[12] It preferentially dealkylates the S enantiomer of methadone, increasing the R/S ratio. Since the R enantiomer is responsible for the analgesic effects of methadone, interindividual variation of the drug's effects can be remarkable based on the relative activity of CYP2B6.

It is clear that the importance of CYP2B6 within the cytochrome P450 system has been relatively underestimated in the past. We are now beginning to learn how much of a major player it is, especially in the realm of anesthesiology.

Take-Home Points

- The importance of the CYP2B6 enzyme is only starting to be fully elucidated.
- Important substrates of CYP2B6 include propofol, ketamine, meperidine, and methadone.
- Important inducers of CYP2B6 are phenobarbital, phenytoin, carbamazepine and dexamethasone.
- Interindividual variations in CYP2B6 expression and inducibility can produce variable effects.

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