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Drug Interactions Mediated by Cyp2b6

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Abstract

More and more evidence suggests that CYP2B6 is more involved in drug metabolism in humans than previously thought. There has been a growing interest in the genetic and xenobiotic factors that influence the enzyme's expression and function due to the discovery of numerous important CYP2B6 substrates and polymorphic differences. The liver's xenobiotic receptors, pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are the primary regulators of CYP2B6 expression. These receptors not only mediate the inductive expression of CYP2B6, but also of CYP3A4, several important phase II enzymes and drug transporters. Clinically used drugs like cyclophosphamide and ifosfamide, anesthetics like propofol and ketamine, synthetic opioids like pethidine and methadone and antiretrovirals like nevirapine and efavirenz have been shown to be metabolized by CYP2B6.

Keywords: Cyclophosphamide • Anesthetics • Efavirenz

Introduction

There is a lot of variation between people in how the human CYP2B6 gene is expressed and how it works, which can affect how well CYP2B6-substrate drugs work in patients. Genetic polymorphism and xenobiotic intervention are two of the many causes of these variations. In this review, we will discuss the major players in the expression and function of CYP2B6, as well as recent advancements in the evaluation of the clinical implications of significant CYP2B6-mediated drug–drug interactions. The human cytochrome P450 (CYP) superfamily is made up of 18 families and 43 subfamilies containing 57 genes and 59 pseudogenes1. CYP2B6 is expressed primarily in the liver and represents one of the approximately fifteen CYP enzymes, distributed amongst P450 families 1–4, predominantly responsible for xenobiotic metabolism.

Literature Review

Alongside CYP2B7, a related pseudogene, CYP2B6 is located on the long arm of chromosome 19 within a CYP2B cluster3, 6. Orthologs of the human CYP2B6 genes can be found in other species including rats, mice and dogs, which are termed Cyp2b1, Cyp2b10 and CYP2B11, respectively. Notably, unlike in other species, CYP2B6 is the only isozyme of the CYP2B subfamily with metabolic function in humans [1].

Historically, CYP2B6 has been believed to be relatively inconsequential with respect to human xenobiotic metabolism. However, in recent years, the discovery of important substrates, robust chemical-mediated induction and genetic polymorphisms of this CYP isozyme has triggered significant academic and industrial research interests. The number of drugs known to be metabolized by this enzyme has drastically increased since the development of effective monoclonal antibodies, the establishment of bupropion as a selective marker of CYP2B6 catalytic activity and the utilization of recombinant DNA techniques. Current estimates indicate that CYP2B6 accounts for 2%–10% of total hepatic CYP content and is, in fact, involved in the metabolism of a significant number of drugs in humans, estimated to be around 8% of all commercially available drugs. Known CYP2B6 substrates include but are not limited to a number of clinically utilized therapeutic agents such as cyclophosphamide (CPA), artemisinin, bupropion, ketamine, pethidine, propofol, methadone, nevirapine (NVP) and efavirenz (EFV) (Table 1), as well as endogenous chemicals and environmental compounds [2,3].

Discussion

CYP2B6 expression can be induced or inhibited by a variety of chemicals and drugs, either directly or through the transcriptional activation of nuclear receptors. In the hope of altering the expression of drug-metabolizing enzymes and transporters in a manner that is beneficial for the treatment of cancer and other disorders, recent studies have begun to investigate the potential of these nuclear receptors as targets for combination therapies. The effects of genetic and pharmacological modulation of CYP2B6 expression on drug disposition are gaining more attention as more CYP2B6 substrates are discovered. The potential for clinically significant DDI by CYP2B6 modulation has been highlighted in this review. It is essential to point out that, despite the fact that experiments have shown that many drugs may be susceptible to CYP2B6-associated DDI, the number of clinically significant DDI mediated by CYP2B6 is small [4].

To this end, the only CYP2B6–drug pairing that is supported by compelling clinical evidence across various ethnic groups appears to be the role of CYP2B6*6 in the therapeutic efficacy and toxicity of EFV. Patients receiving EFV-based treatment would ultimately benefit from the clinical implementation of a CYP2B6 genotyping test due to the fact that EFV is still at the forefront of HIV treatment. CYP2B6 has been discovered to be a catalyst for numerous biotransformation reactions over the past two decades, despite the fact that it was previously thought to have little effect on human drug metabolism. Because CYP2B6 is highly inducible and polymorphic, its expression and function vary widely from person to person, resulting in different drug metabolism and disposition. CYP2B6 polymorphisms can increase drug toxicity and plasma drug concentrations both of which are frequently linked to loss of function. Regarding CYP2B6 metabolism, EFV and CPA are two of the drugs that have received the most research and are better understood. The therapeutic indices of these two commonly used drugs are extremely narrow and variations in CYP2B6 expression and function significantly alter the drug plasma concentrations of each agent. Additionally, these drugs have associated toxicities. In the case of CPA, an increase in the active moiety's circulating concentrations may be beneficial as a result of an increase in CYP2B6 expression or function. However, in the case of EFV, elevated metabolism may result in circulation concentrations that are not therapeutic45. On the other hand, the enzyme's decreased metabolic capacity may result in the circulation of toxic levels of EFV or non-therapeutic levels of the active CPA moiety [5,6].

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Conclusion

CYP2B6 has been discovered to be a catalyst for numerous biotransformation reactions over the past two decades, despite the fact that it was previously thought to have little effect on human drug metabolism. Because CYP2B6 is highly inducible and polymorphic, its expression and function vary widely from person to person, resulting in different drug metabolism and disposition. CYP2B6 polymorphisms can increase drug toxicity and plasma drug concentrations, both of which are frequently linked to loss of function.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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