The Cytochrome P450 System in Disease States—A Brief Review

13

Catherine Marcucci MD

Abstract
This chapter briefly discusses the cytochrome P450 system in several disease states, including heart, liver, and kidney failure.

The effects of acute, severe illness as well as prolonged organ failure on the body's ability to metabolize drugs is not completely characterized at this time. However, as the sciences of solid organ transplantation, clinical pharmacology, and pharmacogenomics advance, it is clear that the competent clinician will have an increasing need for a thorough knowledge of the cytochrome P450 (CYP) system. It is very clear that diseases, from mild to frank organ failure, affect drug metabolism, but it seems as if this process varies considerably based on the organ.

Renal failure has long been associated with changes in the excretion of many drugs. What has recently been shown, however, is a possible effect of acute kidney injury on CYP-mediated drug metabolism in humans. Kirwan et al. have reported in several studies that acute kidney failure decreases metabolism of midazolam and that increasing severity and duration of renal failure are associate d with decreased midazolam elimination. They proposed a CYP3A-based etiology for these changes in drug metabolism.[1,2]

Heart failure is also associated with changes in drug metabolism and the cardiac and hepatic CYP enzymes, although the mechanisms have not been fully established and appear complicated. Zordoky et al. have suggested that heart failure may be associated with an upregulation of cardiac CYP enzymes, with the production of both protective and deleterious metabolites, and a downregulation of hepatic CYP

C. Marcucci MD
Anesthesia Services Department, Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA
e-mail: sandson.marcucci@comcast.net

C. Marcucci et al. (eds.), *A Case Approach to Perioperative Drug-Drug Interactions*, DOI 10.1007/978-1-4614-7495-1_13

enzymes due to decreased hepatic perfusion, hepatocellular damage, and release of proinflammatory cytokines.[3]

Orthotopic liver transplantation provides a set of unique clinical events with respect to drug metabolism. It is expected that hepatic failure, ranging from mild inflammatory disease to severe, chronic liver disease, would affect the body's ability to metabolize drugs. What is interesting is that the limited data show that the effect is not uniform. Adedoyin et al. studied patients with mild to moderate liver disease by using single drug probes for CYP2C19 and CYP2D6 and found selectivity in the effect of liver disease on these enzymes, with 2C19 being more sensitive than 2D6.[4] Frye et al. employed a cocktail of drugs as *in vivo* probes of the cytochrome P450 enzymes 1A2, 2C19, 2D6, and 2E1 in patients with varying severity of liver disease.[5] Again, it was determined that CYP enzyme activity is differentially affected by the presence of liver disease, with the metabolism of mephenytoin (the 2C19 probe), significantly decreased, indicating greater sensitivity of that enzyme to the perturbations of the disease state.

There is now considerable research and clinical interest in both donor and recipient 2C19 genotype and phenotype as a predictor, and marker of hepatic function, graft survival, and clinical recovery from orthotopic liver transplant.[6,7]

Finally, pregnancy is not a disease state, of course. However, there are significant physiologic changes in the gravid patient, including increased plasma volume and increased hepatic and renal flow. Obstetricians and maternal-fetal health specialists see patients who take a variety of drugs that are metabolized via the cytochrome P450 system or commonly interact with other drugs, such as psychiatric drugs, anticonvulsants, antibiotics, street drugs including cocaine, methadone, and buprenorphine, as well as HIV medications including protease inhibitors.[8] There is the growing recognition for a rigorous and science-based approach to prescribing for pregnant patients and anticipating drug–drug interactions that may occur through the choices patients make. Early studies are intriguing, such as a suggestion of induction of 2D6 during pregnancy with changes in the metabolism and response to opioids.[9] There is still a paucity of human data, especially in humans, and much work remains to be done.

Take-Home Points

- Changes in drug metabolism are possible and even probable in disease states involving the kidneys, heart, and (especially) liver.
- It has been suggested that both upregulation and downregulation of cytochrome P450 enzymes occurs in disease states.

- Both donor and recipient CYP2C19 genotype and phenotype are of clinical interest and relevancy in the situation of orthotopic liver transplant.
- Pregnancy is associated with significant physiologic changes, including possible changes in the metabolism of drugs by the cytochrome P450 system.

References

1. Kirwan CJ, Lee T, Holt DW, et al. Using midazolam to monitor changes in hepatic drug metabolism in critically ill patients. Intensive Care Med. 2009;35(7):1271–5. Epub 2009 Feb 7.
2. Kirwan CJ, MacPhee IA, Lee T, et al. Acute kidney injury reduces the hepatic metabolism of midazolam in critically ill patients. Intensive Care Med. 2012;38(1):76–84. Epub 2011 Oct 18.
3. Zordoky BN, El-Kadi AO. Modulation of cardiac and hepatic cytochrome P450 enzymes during heart failure. Curr Drug Metab. 2008;9(2):122–8.
4. Adedoyin A, Arns PA, Richards WO, et al. Selective effect of liver disease on the activities of specific metabolizing enzymes: investigation of cytochromes P450 2C19 and 2D6. Clin Pharmacol Ther. 1998;64(1):8–17.
5. Frye RF, Zgheib NK, Matzke GR, et al. Liver disease selectively modulates cytochrome P450–mediated metabolism. Clin Pharmacol Ther. 2006;80(3):235–45.
6. Chiu KW, Nakano T, Hu TH, et al. Influence of CYP2C19 genotypes on graft pathological findings and postoperative liver function in recipients after living-donor liver transplantation. Ann Transplant. 2010;15(4):38–43.
7. Chiu KW, Nakano T, Tseng HP, et al. Western blotting analysis for quantitative detection of CYP2C19 expression in liver tissues in the setting of living donor liver transplantation. Hepatogastroenterology. 2012;59(115):805–8.
8. McCance-Katz EF. Drug interactions associated with methadone, buprenorphine, cocaine, and HIV medications: implications for pregnant women. Life Sci. 2011;88(21–22):953–8.
9. Madadi P, Avard D, Koren G. Pharmacogenetics of opioids for the treatment of acute maternal pain during pregnancy and lactation. Curr Drug Metab. 2012;13(6):721–7.