2020

CYP2D6 Polymorphisms and their Effect on Opiate Metabolism

Blair Runde
University of North Dakota

CYP2D6 Polymorphisms and their Effect on Opiate Metabolism

Blair Runde, DC, PA-S
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

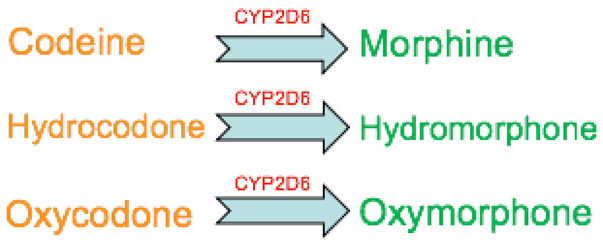
UND School of Medicine & Health Sciences
University of North Dakota

Abstract

The purpose of this research and systematic literature review is to determine if pharmacogenetic testing for the CYP2D6 enzyme responsible for the metabolism of several opiates leads to differences in serum levels, side effects, and treatment outcomes for patients with acute or chronic pain. Much of the presented research indicates an association between CYP2D6 phenotypes and differential treatment outcomes. Poor CYP2D6 metabolizers are shown to be at increased risk of analgesic failure contrasted with ultra-rapid metabolizers demonstrating better analgesic control; however, they had a higher risk of side effects and toxicity. Conflicting data is also demonstrated as well as a lack of conclusions that can be drawn for more intermediate metabolizers. It is known the gene that codes for CYP2D6 is one of many that can affect opiate metabolism. More research is needed that encompasses all of these genes in order to make the findings more applicable to clinical practice.

Introduction

Opioid involved overdose deaths have been on a steady rise nationally since the late 1990s. Unfortunately, prescription opioids acquired by both legal and illegal means have had a significant contribution to this crisis. Prescribers find it challenging to strike the delicate balance between adequately treating the patient's pain while simultaneously minimizing unwanted side effects, Pharmacogenetic testing for variations in opiate metabolism via the CYP2D6 enzyme offers a potential solution at mitigating this challenge. This literature review intends to explore how an individual's genetic variability in this enzyme influences the pharmacokinetics and pharmacodynamics of opiates.



Statement of the Problem

Pharmacogenomic testing has shown much promise as a tool that can help clinicians make better prescribing decisions. However, this testing has yet to be used clinically at the initiation of opiate therapy for pain management. Research has proven that the mechanism by which CYP2D6 polymorphisms affect opiate metabolism; however, the clinical utility of this test and the implication on patient outcomes is undetermined.

Relationship of CYP2D6 Phenotype to Activity

Metabolizer Phenotype	Total Activity Score (TAS)	Haplotype Examples
Poor (PM)	0	*4, *5, *6
Intermediate (IM)	0.5	*10, *9
Extensive (EM)	1.0 – 2.0	*2
Ultrarapid (UM)	> 2.0	*2N

Table 1 derived from "CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients," by R. Balyan, M. Mecoli, R. Venkatasubramanian, V. Chidambaran, N. Kamos, S. Clay, D. Moore, J. Mavi, C. Glover, P. Szmuk, A. Vinks, and S. Sadhasivam, 2017, *Pharmacogenomics, Volume 18*, p. 339. Copyright 2017 by Future Science Group.

Research Question

Do CYP2D6 polymorphisms lead to differences in opiate plasma levels, analgesia, and occurrence of side effects?

Literature Review

Theme 1: CYP2D6 and Pharmacokinetics

- UMs showed higher peak plasma levels, more significant analgesia, and higher rates of side effects when dosed with tramadol (Crews, 2014).
- PMs exhibited lower concentrations of tramadol, morphine, hydromorphone, and oxymorphone compared to EMs (Crews, 2014).
- Morphine is produced at a higher rate in UMs compared to EMs (Crews, 2014).
- EMs convert oxycodone to oxymorphone at a higher rate compared to PM and IMs, leading to higher oxymorphone levels (Baylan, 2017).
- PMs were only able to create 0.66 ng/ml mean plasma level (SD 1.1) of hydromorphone, compared to 7.06 mean ng/ml (SD 11.9) from UMs (Stauble, 2014).

Theme 2: CYP2D6 and Adverse Effects

- PMs and UMs are more likely to experience analgesic failure and adverse effects compared to IM and EM phenotypes (Sauver 2017).
- UM and EMs are at higher risk of toxicity and exhibited increased occurrence of side effects (Dagostino, 2018).
- UMs at risk for symptoms of toxicity from codeine and tramadol and should therefore avoid use (Vieira, 2018).
- PMs are at a lower risk of side effects compared to EMs (Crews, 2014).

Theme 3: CYP2D6 and Pain Relief

- IMs and PMs prescribed tramadol or codeine according to phenotype recommendations were more likely to have reduced pain vs trial and error; however, when all phenotypes are considered, there was no difference in pain scores (Smith, 2019).
- PMs exhibited weak analgesia with codeine compared to UMs and required higher doses of tramadol compared to EMs. UMs consumed less morphine and reported lower pain levels (Ren 2015).
- Genotypes did not affect analgesia with tramadol and there was no difference in oxycodone consumption between EM and PM participants (Ren, 2015)
- PMs showed lower analgesic response with codeine and tramadol and are at increased risk of treatment failure (Vieira, 2018).

Discussion

The evidence presented in this review suggests that those who are poor CYP2D6 metabolizers tend to have lower plasma concentrations of active metabolite that result in lower analgesic effect and incidence of side effects. Conversely, those who are ultra-rapid CYP2D6 metabolizers tend to experience higher levels of active metabolite that results in an increased analgesic effect and risk of side effects. Those who are intermediate and extensive metabolizers lie in between. Worth consideration are the numerous other genes that play a role in opiate metabolism such as the catechol-O-methyltransferase (COMT) gene that codes for enzymes responsible for opiate degradation and the OPRM-1 gene that codes for opiate receptors. Only when these variances are considered as a whole can clinical application be initiated.

Plasma Hydromorphone Concentrations in Women after C-section

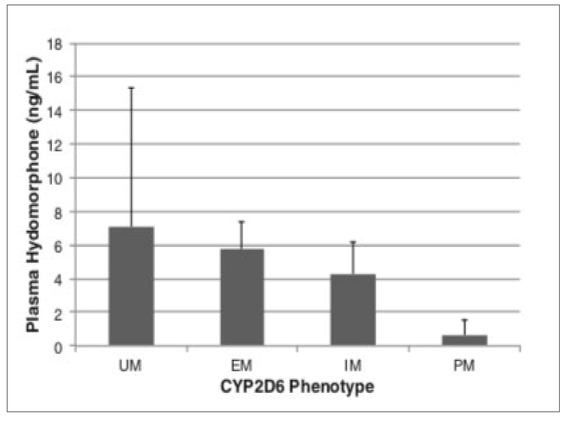


Figure 1. From "Hydrocodone in postoperative personalized pain management: Pro-drug or drug?" by M. Stauble, A. Moore, L. Langman, M. Boswell, R. Baumgartner, S. McGee…S. Jortani, 2014, *Clinica Chimica Acta, 429,* p. 28. Copyright 2014 by Elsevier.

Applicability to Clinical Practice

The evidence regarding CYP2D6 pharmacogenetic testing is promising but has lengths to go regarding the clinical application. We know there are multiple enzymes responsible for opiate metabolism, yet research that accounts for the way these enzyme polymorphisms work together to account for treatment efficacy and side effects is lacking. It has also yet to be demonstrated how these polymorphisms relate to the occurrence of opiate dependence and addiction. Who is at risk? The PMs because of their higher requirement of medication to reach treatment success, the EMs because of their increased risk of side effects and toxicity, or both? The research outlined in this review is the first of many steps required in order to find these answers.

References

Balyan, R., Mecoli, M., Venkatasubramanian, R., Chidambaran, V., Kamos, N., Clay, S., … Sadhasivam, S. (2017). CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients. *Pharmacogenomics*, *18*(4), 337–348. http://dx.doi.org/10.2217/pgs-2016-0183

Crews, K., Gaedigk, A., Dunnenberger, H., Leeder, J., Klein, T., Caudle, K., … Skaar, T. (2014). Clinical Pharmacogenetics Implementation Consortium Guidelinesfor Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. *Clinical Pharmacology &Therapeutics*, *95*(4), 376–382. http://dx.doi.org/10.1038/clpt.2013.254

Dagostino, C., Allegri, M., Napolioni, V., Dagnelli, S., Bignami, E., Mutti, A., & van Schaik, R. (2018). *CYP2D6* genotype can help to predict effectiveness and safety during opioid treatment for chronic low back pain: results from a retrospective study in an Italian cohort. *Pharmacogenomics and Personalized Medicine*, *Volume 11*, 179–191. http://dx.doi.org/10.2147/pgpm.s181334

Ren, Z., et al. (2015). The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: A systematic review and meta-analysis. *Pain Physician.18,* 131-152. https://www-ncbi-nlm-nih-gov.ezproxylr.med.und.edu/pubmed/25794200

Sauver, J., Olson, J., Roger, V., Nicholson, W., Black, J., Takahashi, P., … Bielinski, S. (2017). *CYP2D6* phenotypes are associated with adverse outcomes related to opioid medications. *Pharmacogenomics and Personalized Medicine*, *Volume 10*, 217–227. http://dx.doi.org/10.2147/pgpm.s136341

Smith, D., Weitzel, K., Elsey, A., Langaee, T., Gong, Y., Wake, D., … Cavallari, L. (2019). CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. *Genetics in Medicine*, *21*(8), 1842–1850. http://dx.doi.org/10.1038/s41436-018-0431-8

Stauble, M., Moore, A., Langman, L., Boswell, M., Baumgartner, R., Mcgee, S., … Jortani, S. (2014). Hydrocodone in postoperative personalized pain management: Pro drug or drug? *Clinica Chimica Acta*, *429*, 26–29. http://dx.doi.org/10.1016/j.cca.2013.11.015

Vieira, C., Fragoso, R., Pereira, D., & Medeiros, R. (2018). Pain polymorphisms and opioids: An evidence based review. *Molecular Medicine Reports*.http://dx.doi.org/10.3892/mmr.2018.9792

Acknowledgements

I want to extend my deepest gratitude to my advisor Julie Solberg and instructor Daryl Sieg for their guidance and encouragement that helped put this project to paper. I would also like to thank our librarian, Megan Denis, for helping me understand the ins and outs of study designs and research conduction. Lastly, I would like to thank my family and friends who offered their time, advice, and support that helped me complete physician assistant school.