Opioid Response in an Individual with Altered CYP2D6 Activity: Implications of a Pharmacogenomics Case

Tyler Ballinghoff[1], Kevin Bain[1], Adriana Matos[1], Chandni Bardolia[1], Jacques Turgeon[1], and Nishita Amin[1]

[1]Tabula Rasa HealthCare

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Abstract

The benefits of opioid use in older adults to manage chronic non-cancer pain must outweigh the risks as these individuals are more susceptible to the side effects and drug interactions associated with opioids. Pharmacogenomic testing supports clinicians to select an appropriate opioid therapy while minimizing these risks.

Key Clinical Message

This article describes a simulated case involving Pharmacogenomics implications for a patient prescribed opioids for chronic non-cancer pain, and provides Pharmacogenomics based recommendations to optimize treatment.

Introduction

Given the widespread use and unfortunate misuse of opioids in the United States, the appropriate management of chronic non-cancer pain (CNCP) has been extensively debated in recent years. It is estimated that nearly 50% of older adults have CNCP, and approximately 5% to 10% of them chronically use opioids to manage pain.[1] Older adults tend to have more persistent or severe pain and are more susceptible to the side effects and drug interactions associated with opioids than younger adults with similar CNCP.[2] Therefore, it is imperative that the benefits are optimized and the risks are minimized when it comes to opioid use for CNCP in older adults.

The use of pharmacogenomics (PGx) testing is effective in optimizing the benefits of certain drugs, such as antidepressants, clopidogrel, and warfarin.[3] PGx testing minimizes the risks associated with the opioid codeine, and could be used to balance the benefit-risk profile of not only codeine, but all opioids that are metabolized by CYP2D6. [3] This article describes a simulated patient case modeled after numerous encounters in our practice involving the clinical application of PGx for CNCP opioid optimization. We also provide examples of PGx-based recommendations to optimize treatment. This case serves as instructional guidance for clinicians only; medical decision-making will vary based on each individual patient case. Additionally, this case provides context about the clinical utility of PGx to guide opioid analgesic drug selection and demonstrates the impact of genetic variations and concomitant medications on drug interactions and phenoconversion.

Case Report & Results

A 67-year-old Caucasian female presented with a past medical history of chronic, intractable lower back pain, hypertension, anxiety, and heart failure. Her physician prescribed several medications to manage her various conditions, including oxycodone tablets, 15mg four times daily; duloxetine capsules, 60mg once daily; lorazepam tablets, 1mg twice daily as needed; metoprolol succinate tablets, 50mg once daily; and lisinopril

tablets, 10mg once daily. At a follow-up appointment with her physician, she reported experiencing on going uncontrolled pain. Following multiple increases in her oxycodone dosage, from a total daily dose of 20mg to 60mg, she continued to experience inadequate pain control. When her physician sought assistance, the clinical pharmacist suggested that PGx testing would be helpful to assess appropriateness of opioid therapy and guide medication changes. The physician then ordered a PGx test.

A DNA sample was collected by buccal swab and analyzed by a genetics laboratory. The results were then interpreted by the clinical pharmacist. The patient was identified as an intermediate metabolizer (IM) for the cytochrome P450 2D6 (CYP2D6) drug-metabolizing enzyme, with a **9|*40* genotype (Table 1).

Considering the patient's previous unsuccessful trials of non-opioid treatments (e.g., nonsteroidal anti-inflammatory drugs, skeletal muscle relaxants), the clinical pharmacist recommended that the physician consider an alternative opioid such as oxymorphone, hydromorphone, or morphine, which are not metabolized by the CYP2D6 drug-metabolizing enzyme. After her physician changed the opioid from oxycodone to hydromorphone 2mg four to six times per day as needed, the patient's pain control improved significantly.

Importantly, the dose of hydromorphone was established as if the patient was opioid naïve, since metabolic transformation of oxycodone into oxymorphone was impaired due to genetic polymorphisms, drug-drug interactions and drug-drug-gene interactions. A direct dose calculation using morphine milligram equivalent dose algorithms was not applied, considering that the dose of oxycodone was increased up to 60mg per day.

Discussion

The opioids codeine, hydrocodone, tramadol, and oxycodone are metabolized by the CYP2D6 enzyme to active metabolites that are primarily responsible for their analgesic effects (morphine, hydromorphone, O-desmethyltramadol and oxymorphone, respectively). Consequently, CYP2D6 IMs have reduced enzyme activity that alters the CYP2D6-mediated activation of these opioids, thereby reducing analgesic effects and increasing risk of side effects.[4,5] Figure 1 illustrates how the Medication Risk Mitigation Matrix allows users to view simultaneous multi-drug interactions, drug-gene interactions, and PGx results, when present. From this illustration, it can been seen that this patient was taking duloxetine and metoprolol which are known substrates with higher affinity than oxycodone for CYP2D6. Hence, when these drugs are taken concomitantly with oxycodone, competitive inhibition of CYP2D6 enzyme could occur.[8] Under these conditions, phenoconversion is observed (a disconnect between the genotype-predicted phenotype and likely phenotype observed clinically), and the patient's CYP2D6 enzyme behaved like that of a poor metabolizer (PM), which further reduced the activation of oxycodone into oxymorphone.

Several studies have demonstrated that single nucleotide polymorphisms, or genetic variations, in the *CYP2D6* gene can significantly affect the efficacy and safety of opioids.[4,5] There are numerous variant alleles, or different forms, of the *CYP2D6*gene that an individual can possess that will result in decreased or increased enzyme function and, consequently, reduced or enhanced capacity to convert the aforementioned opioids to their active metabolites.

Studies have shown that individuals carrying copies of the *CYP2D6*loss-of-function alleles, otherwise known as CYP2D6 PMs, exhibit lower concentrations of opioid active metabolites than normal metabolizers (NMs), resulting in reduced analgesia and poor pain control.[4,5] Another study in the post-surgical setting found that compared with CYP2D6 ultra-rapid metabolizers (UMs; individuals carrying multiple copies of the functional alleles), CYP2D6 PMs required a 33% higher dose of tramadol in the recovery room.[6] In an experimental study among a small group of healthy volunteers, researchers demonstrated a 1.5 to six-fold increase of analgesic effect in CYP2D6 UMs when compared to NMs; when NMs were compared to PMs, the PMs experienced a two to 20-fold reduction of analgesic effects.[4]

Yet another study showed that CYP2D6 UMs, had higher hospitalization rates than CYP2D6 NMs.[7] Due to increased rates of overdoses and fatalities among infants of breastfeeding mothers who were CYP2D6 UMs and prescribed codeine and among children who were CYP2D6 UMs receiving codeine, this opioid now carries a Black Box Warning in its prescribing information.[9]

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international organization facilitating the use of PGx for patient care. CPIC developed evidence-based guidelines for using PGx information to guide codeine and alternative opioid therapy. [3] These recommendations are summarized in Table 1 at the end of this article.

For CYP2D6 IMs or PMs, CPIC recommends choosing an alternative opioid that is not metabolized by CYP2D6, such as hydromorphone or morphine. The rationale is that the use of codeine, and other opioids such as hydrocodone, tramadol, and oxycodone in patients with CYP2D6 IM or PM status is associated with a high risk of reduced efficacy and poor pain control.

This case highlights the value of utilizing PGx information to enhance clinical decision-making and potentially improve therapeutic outcomes in patients with CNCP whose pain cannot be controlled with non-opioid therapy require opioid therapy.

Conclusion

In summary, *CYP2D6* genetic variations and concomitant drug interactions leading to phenoconversion can significantly affect therapeutic outcomes of patients receiving opioids. As illustrated by this simulated case, some patients are unable to metabolize certain opioids to their active metabolites, which may result in poor pain control and diminished quality of life. The use of PGx information and drug-gene interaction data can assist prescribers and other healthcare practitioners in selecting the most precise opioid therapy for patients.

Author Contributions

TB and KTB contributed to conceptualization; TB, KTB, and AM contributed to case development; TB, KTB, AM, CB, JT and NSA contributed to case interpretation; TB and KTB contributed to writing—original draft; AM, CB, JT, and NSA contributed to writing—review & editing; TB, KTB, and AM contributed to resources; JT and NSA contributed to supervision.

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Table 1: Adapted CPIC Recommendations to Guide Codeine and Possibly Alternative Opioid Therapy Using PGx Information [2]

CYP2D6 Phenotype	**Implications and Clinical Interpretation**	**Recommendation**
Poor Metabolizer (*e.g.,*4|*4, *3|*6*)	CYP2D6 PMs may experience reduced analgesic effects from certain opioids (e.g., codeine, tramadol, oxycodone, hydrocodone) due to reduced production of the active metabolites.	Select alternate or monitor closely for symptoms of insufficient pain relief.
Intermediate Metabolizer (*e.g., *9|*40, *2|*4*)	CYP2D6 IMs may experience reduced analgesic effects from certain opioids (e.g., codeine, tramadol, oxycodone, hydrocodone) due to reduced production of the active metabolites.	Select alternate drug or monitor closely for symptoms of insufficient pain relief.
Normal (Extensive) Metabolizer (e.g., *2/*2, *1/*41)	CYP2D6 NMs will likely experience the desired effects of certain opioids (e.g., codeine, tramadol, oxycodone, hydrocodone) due to normal formation of the active metabolites.	Continue to follow label recommended dosing.
Ultra-Rapid Metabolizer (*e.g., *2|*2 XN, *1|*1 XN*)	CYP2D6 UMs may experience enhanced analgesic effects from certain opioids (e.g., codeine, tramadol, oxycodone, hydrocodone) and an increased risk for toxicities due to increased production of the active metabolites.	Select alternate drug or monitor closely for adverse drug events (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention).

Abbreviations: CPIC = Clinical Pharmacogenetics Implementation Consortium, PGx = pharmacogenomics

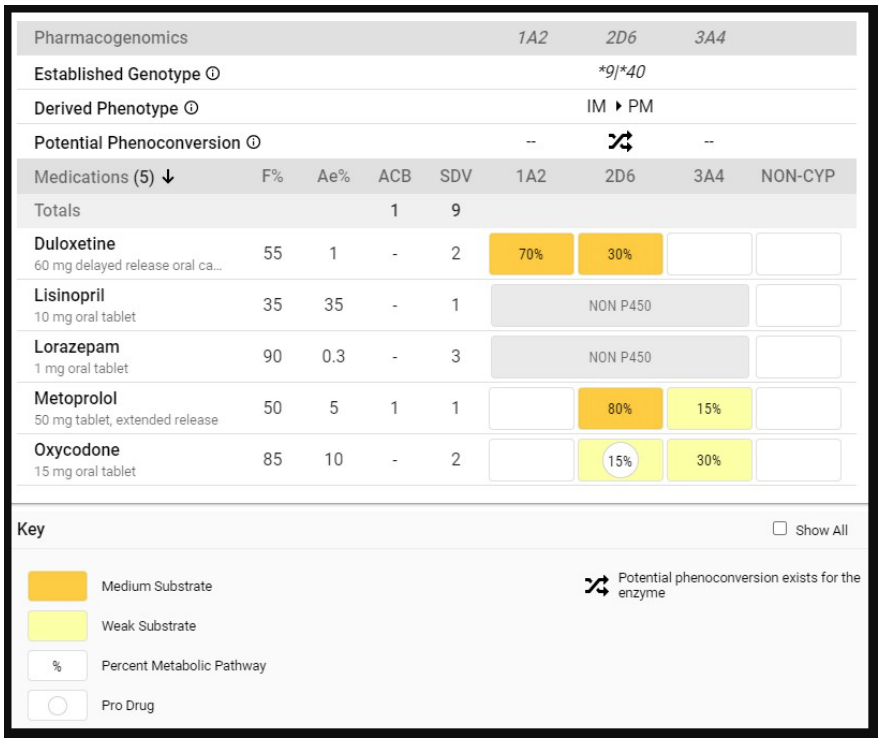

Figure I: View of the Medication Risk Mitigation Matrix Incorporating Genetic Results and Phenoconversion

Abbreviations: IM – intermediate metabolizer, PM – poor metabolizer, F% - absolute bioavailability, Ae% - amount excreted in urine, ACB – Anticholinergic Burden Score, SDV – Sedative Burden Score