Special Article

The Clinical Implications of Cytochrome P450 Interactions With Opioids and Strategies for Pain Management

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Abstract
Pharmacokinetic differences among opioids influence a patient’s response to opioid treatment. An important element affecting a drug’s pharmacokinetics, its metabolism, may be altered under various circumstances, thereby enhancing or mitigating a patient’s response to opioids. The genetic background of the metabolic enzymes involved in opioid metabolism, comorbid medical conditions, older age, and the presence of other drugs that influence metabolism are such factors that can cause the response to opioid therapy to vary greatly from the expected response to a standard dose. As a result of the variability in individual responses to opioids, clinical management of pain with opioids must be empirical.

Introduction
Patients differ in their responses to opioid analgesics. Even in well-designed, successful clinical trials, as much as 40% of the subject population does not respond well to the analgesic being studied. Therefore, it is unsurprising that patients may require trials of several opioids before finding an agent that provides effective analgesia with acceptable tolerability. Several well-described factors contribute to this phenomenon. First, each individual presents with a unique cellular environment that includes a variety of combinations of different μ-opioid receptor subtypes. The subtypes of the μ-opioid receptor are generated through a mechanism called alternative splicing, commonly known to enhance protein diversity. The binding profiles and resulting pharmacologic effects of opioid receptor subtypes vary among μ-opioid analgesics, contributing to the observed clinical phenomena of individual variance in therapeutic response and to the incomplete cross-tolerance. Patients tolerant to one μ-opioid analgesic may retain differing sensitivity to other μ-opioids. Hence, opioid rotation can be a technique to manage patients who are unable to attain adequate analgesia from any one specific opioid.

Key Words
Adverse drug reactions, cytochrome P450, drug-drug interactions, extensive metabolizers, genetic polymorphisms, intermediate metabolizers, metabolism, pharmacokinetics, poor metabolizers, ultrarapid metabolizers, opioids
Pharmacokinetic and/or pharmacodynamic differences among opioids also influence a patient’s response to opioid treatment. An important factor affecting a drug’s pharmacokinetics, its metabolism, is altered under various circumstances, affecting a patient’s response to opioids. The genetic background of the metabolic enzymes involved in opioid metabolism, comorbid medical conditions, older age, and the presence of other drugs that influence metabolism are the factors that can cause the response to opioid therapy to vary greatly from the expected response to a standard dose. Because of the variability in individual responses to opioids, clinical management of pain with opioids must be empirical, wherein each patient is treated as an N of 1.

Besides causing 20%—40% of interindividual differences in metabolism and responses to drugs, certain genotypes are more prone to adverse drug reactions (ADRs). Indeed, different genetic variants of a gene (from as small as a single base pair change from wild type—a single-nucleotide polymorphism—to insertions or deletions) can have a wide variety of clinical consequences relevant to drug metabolism and important clinical consequences for opioids. These consequences range from drug toxicity to ADRs, extended pharmacologic effects to a nonresponse, and decreased effective dose to a requirement for higher doses to be efficacious. Metabolic variants from wild type can exacerbate drug-drug interactions, hinder a prodrug from bioactivation, or induce metabolism through alternative and potentially deleterious pathways. To minimize the potential for these negative outcomes, assays of alleles of genes involved in drug metabolism are available for clinicians to better predict drug responses and/or drug toxicities by identifying individuals as poor, intermediate, extensive, or ultrarapid metabolizers.

Taking a thorough patient history may provide a basic genetic screen for signs of the potential for drug-metabolic interactions. The prevalence of genetically based, atypical metabolic capacities that affect opioids has not been established. The most widely recognized genetic variation in P450 enzymes is in expression of cytochrome P450 2D6 (CYP2D6). Twenty-two different genetic null variants of this isoenzyme alone have been identified, and these do not encode a functional protein or have enzymatic activity. Hence, to screen for the presence of genetic polymorphisms in patients being considered for opioid therapy, a family medical history can be included. Although CYP450 genetic testing is not routinely required to manage patients with pain, it can be useful to test certain patients. These include patients who need an ultrahigh or unusual opioid regimen, those who are on a multiple drug regimen for concurrent illnesses, or those who report a history that suggests the presence of an atypical metabolic capacity for opioids. The latter would include the need for a high dosage of dental anesthesia, the limited effect of short-acting opioids (one to two hours of relief), and ADRs or the lack of response to alcohol. A diagnosis of a genetic CYP450 deficiency cannot be made definitively by a clinical history alone; a laboratory test for CYP450 deficiencies is required to make a definitive diagnosis. Still, a few screening questions regarding responses to dental anesthesia, alcohol, and opioids, such as “Do you get pain relief with codeine?” or “Are you allergic to an opioid?,” can provide a high index of suspicion.

A consideration of a patient’s ethnicity can further increase or decrease the index of suspicion for drug-metabolic interactions. There is considerable variability in the distribution of polymorphisms in genes associated with metabolism across different ethnic groups. For example, approximately 3%—5% of whites have duplications of the CYP2D6 gene, leading to a higher than normal expression of the enzyme and ultrarapid activity, whereas this phenotype is present in only 0.5% of Asians and in varying amounts—from 9% to 30%—among Africans. Extensive metabolizers have two functional copies of the CYP2D6 gene, and a standard dosing is established for this phenotype present in 70%—80% of whites. Intermediate metabolizers typically have one nonfunctional copy and one reduced function copy of the CYP2D6 gene. Approximately 10%—17% of whites are predicted to have this phenotype, although a study of a New England tertiary care center found that 54% of people were carriers of at least one deficient or nonfunctional CYP2D6 allele (the population was 87% white, 3% African American, 9% Hispanic, and 1% Asian). Last, poor metabolizers have two reduced or nonfunctional
CYP2D6 alleles and typically experience reduced clearance of drugs metabolized by this isoenzyme. Patients with poor metabolic capacity have a higher risk of adverse effects because of high systemic concentrations of active parent drugs and therapeutic failure from prodrugs, such as codeine and tramadol (which are inactive until biotransformation to their active metabolites). Although 5%–10% of whites have this phenotype, it is present in only approximately 1%–2% of Chinese and Japanese populations and in as much as 34% of African Americans. Meanwhile, age and sex also may have a significant effect on metabolic capacity. In women, systemic oxycodone levels tend to be 25% higher than those in men, given the same standard dose controlled for body weight. Perhaps initiating with a low oxycodone dose is particularly important when prescribing for female patients.

Determining the enzyme system responsible for metabolizing the opioid in question is the first step to integrating a consideration of genetic metabolic capacity into clinical practice. Next, if a polymorphic enzyme such as CYP2D6 is involved, the prevalence of the polymorphic variation of the gene within the patient population to which the patient belongs can lend insight. If a variant could be a significant problem, the predicted clinical consequences are then considered and, accordingly, clinical adjustments can be made, such as modifying the dose or dose schedule, or changing analgesics to one that uses a different enzyme system. For example, morphine, oxymorphone, tapentadol, and hydromorphone are metabolized primarily through uridine diphosphate glucuronosyltransferase and are less prone to drug interactions than those opioids eliminated using the CYP450 pathways. Alternatively, once confirming that no other drugs with the potential to elicit a metabolic interaction are being taken, then the opioid could be prescribed at a low dose and titrated slowly (for those with the potential for higher than average systemic levels), and the patient advised to closely monitor for ADRs. Metabolic genotyping can be pursued in cases of unexplained lack of efficacy or ADRs. Studies have already begun making recommendations on opioid dosage adjustments for patients with specific genotypes. Enhanced monitoring should be implemented, particularly when agents with narrow therapeutic windows are prescribed.

For patients taking more than one medication, the potential for drug interactions can be considered by referencing drug interaction databases, such as Clinical Pharmacology Online, Drug Interaction Facts, and First Databank. For a new patient who is prescribed multiple medications—particularly antidepressants or benzodiazepines—a safer approach to prescribing opioids may involve initiating with a low dose of an opioid that does not rely heavily on CYP450 enzymes for metabolism; other rational clinical practice ideas regarding opioid prescription for patients with atypical metabolic capacity are listed in Table 1. When one drug in a regimen has the potential to increase or decrease the metabolism of another, the drug with the narrowest therapeutic index should be used with caution, monitored, and adjusted as necessary. Furthermore, when a drug that induces or inhibits the metabolism of another drug is discontinued, the doses of the remaining drug(s) should be readjusted accordingly. Patient education is important to dissuade individuals from discontinuing one or more drugs themselves.

Many patients are highly concerned about the potential for negative drug-drug interactions (Fig. 1). A national random telephonic

**Table 1**

A Rational Approach to Managing Atypical Genotypes in Opioid Metabolism

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Start all opioids at a low dose and titrate slowly over time.</td>
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<tr>
<td>2.</td>
<td>Screen every patient who may need opioids with questions that may suggest the presence of a genetic-based atypical metabolic efficiency, which could affect opioid elimination and processing.</td>
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<tr>
<td>3.</td>
<td>Use opioids that primarily bypass the CYP450 enzyme system if atypical metabolic capacity is suspected or if the patient is taking multiple nonopioid drugs.</td>
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<tr>
<td>4.</td>
<td>Use a low-dose short-acting opioid to initiate the opioid treatment—particularly in a patient not well known to the practitioner.</td>
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<tr>
<td>5.</td>
<td>Closely monitor patients treated with opioids along with benzodiazepines, antidepressants, and other substances that may inhibit the CYP450 enzyme system and educate them about the dangers of combining medications and alcohol.</td>
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CYP450 = cytochrome P450.
A survey of 1004 adults conducted by the American Society of Health-System Pharmacists evaluated concerns related to being a patient in a health system. These concerns were rated on a scale from one to five, in which five represented “very concerned”; the bar chart in Fig. 1 depicts the percentage of patients who rated each concern with a score of four or five on the scale. Although the respondents were very concerned about the complications from procedures and the cost of treatment, they were most concerned about being given the wrong drug or that a drug interaction would occur. The public has a much greater level of concern about ADRs than most health care providers would suspect.

Urine toxicology testing can be a very useful way to confirm adherence to an opioid regimen (thereby helping to rule out drug diversion), and to assay for the use of other opioids, which have not been prescribed, or illicit substances. Sometimes, adherence is better confirmed by an inactive metabolite than by the parent compound. Because the CYP450 enzymes produce some active opioid metabolites that are also available by prescription, the interpretation of urine toxicology reports can sometimes be challenging. For example, taking morphine may lead to small amounts of hydromorphone content in urine (Fig. 2), and patients taking hydrocodone can test positive for both hydrocodone and hydromorphone. Monitoring patients for adherence and abuse can be simplified by prescribing an opioid that does not produce metabolites that are also available as an oral pharmaceutical, such as fentanyl, hydromorphone, methadone, or oxymorphone. Furthermore, any unclear results should be clarified with the toxicology laboratory involved. Fig. 2 is a noncomprehensive depiction of some of the metabolic products of opioids, but may explain the presence of nonprescribed opioids in the urine.

Cases of Drug-Genetic and Drug-Drug Interactions


![Fig. 1. Patient concerns about the health system in a national survey by the American Society of Health-System Pharmacists.](image-url)
Because of his immunocompromised state, bronchoalveolar lavage was used to confirm lung infection seen in radiologic findings as bilateral pneumonia limited to the inferior lobes; yeast was discovered therein. The patient was administered ceftriaxone, clarithromycin, and voriconazole for the infection along with 25 mg of oral codeine (three times per day) for cough relief.

Subsequently, the patient became unresponsive, with no neurologic improvement upon noninvasive ventilation. Laboratory results indicated normal valproic acid and serum ammonia levels, blood urea nitrogen and serum creatinine concentrations that normalized with titration, and postventilatory blood-gas concentrations outside normal limits (pO2 = 68 mm Hg, normal 80–100 mm Hg and pCO2 = 56 mm Hg, normal 35–45 mm Hg). However, upon intravenous administration of 0.8 mg of naloxone, the patient promptly made dramatic neurologic improvement. Further continuous infusion of 0.4 mg of naloxone for the following six hours led to a complete resolution of symptoms within two days. As successful treatment with an opioid antagonist would suggest, codeine seemed to be the source of the central nervous system depression. Further testing showed elevated levels of codeine and its metabolites: morphine (20-fold higher than the upper limit of normal), morphine-6-glucuronide (10-fold higher than the upper limit of normal), and morphine-3-glucuronide (8-fold higher than the upper limit of normal). The CYP3A4 enzyme eliminates 80% of codeine through glucuronidation; however, CYP2D6 converts another 10% of codeine to morphine for clearance through the kidneys. Morphine-6-glucuronide is likely more potent than morphine as an analgesic, whereas morphine-3-glucuronide can cause agitation, anxiety, and other neurocognitive effects. Morphine-3-glucuronide also can induce allodynia and hyperalgesia. Despite being given a low dose of codeine, this patient experienced neurotoxicity from opioid overdose. Because the primary mode of codeine metabolism—through the CYP3A4 elimination pathway—was inhibited by the antibiotics administered to treat the lung infection, codeine was instead diverted to the secondary pathway involving CYP2D6. Because the patient’s genotype had multiple copies of the CYP2D6 gene, as do 1%–7% of whites and more than 25% of Ethiopians, codeine was ultrarapidly metabolized into morphine and its active metabolites. Indeed, urine toxicology analyses of patients treated with codeine should show both codeine and morphine.

Individual opioids are metabolized through different enzymatic processes; furthermore, individual patients have varying capacities to metabolize individual opioids. Another case of a toxic drug interaction with antibiotics involved an individual who was noted to have reduced genetic capacity for opioid metabolism through the CYP2D6 enzyme. In these genetic circumstances, administering an opioid such as hydrocodone, which is metabolized via CYP2D6 and CYP3A4, would lead the opioid to be diverted to the latter enzymatic pathway for elimination. However, the patient with deficient CYP2D6 enzyme function was administered a potent CYP3A4 inhibitor, clarithromycin, for an ear infection, resulting in a lethal effect when hydrocodone was taken to relieve coughing. Poor metabolic capacity of CYP2D6 also was suspected in another case involving an opioid-drug interaction. In this circumstance, oxycodone—an opioid metabolized to oxymorphone primarily through the CYP2D6 pathway—was taken concomitantly with a selective serotonin reuptake inhibitor antidepressant, fluoxetine, which inhibits several CYP450 pathways, including the potent inhibition of CYP2D6. Furthermore, the activity of the other CYP450 enzyme responsible for oxycodone elimination, CYP3A4, was competitively inhibited by two other drugs that had been prescribed (diazepam for post-traumatic

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**Fig. 2. Example of the metabolism of opioids.**

stress disorder and trazodone for depression) and inhibited by fluoxetine. High systemic levels of oxycodone ensued, followed by opioid toxicity. Sadly, the patient passed away, and this resulted in a malpractice lawsuit filed against the physician involved.

Another case report focused on a drug interaction that caused opioid toxicity by the enhancement of a different CYP450 enzyme, CYP1A2. In this circumstance, a 46-year-old man on methadone therapy for back pain presented to the emergency department (ED) with altered mental status and depressed respiration. He had been a smoker for 33 years and had initiated smoking cessation a month prior. Although methadone metabolism is poorly understood, studies suggest that methadone is primarily metabolized by CYP3A4, with several other CYP enzymes: 2D6, 2B6, 2C8, 2C9, 2C19, and 1A2 implicated as well. Meanwhile, other studies have linked polycyclic aromatic hydrocarbons in tobacco smoke to induction of CYP1A2 activity. Because the patient reduced his smoking, his CYP1A2 activity would have been lowered, slowing the metabolism of methadone and increasing the systemic bioavailable levels, resulting in neurotoxicity.

Another case of near fatal respiratory depression because of an opioid-drug interaction involved transdermal fentanyl and clarithromycin in a patient with chronic obstructive pulmonary disease. A frail 81-year-old man who was taking a stable dose of transdermal fentanyl for neck pain for more than a year was treated for a Helicobacter pylori infection with clarithromycin. This antibiotic has been established as a potent CYP3A4, CYP3A5, and CYP3A7 enzyme inhibitor as well as substrate, and it is well known that fentanyl is metabolized primarily by CYP3A4. In fact, an important drug warning was issued by the manufacturer of transdermal fentanyl in 2005, highlighting the potential for fatal respiratory depression when taken concomitantly with ritonavir, ketoconazole, itraconazole, troleanomycin, clarithromycin, nelfinavir, or nefazodone.

Overall, these cases highlight the potential for toxic drug interactions with any of the opioids metabolized through CYP450 enzymes, particularly in the setting of genetically elevated or reduced enzyme activity. The following case report demonstrates an example of the influence of food-metabolic interactions on opioid metabolism.

A Case of Drug-Genetic and Drug-Food Interactions

A 58-year-old woman was admitted to the ED with altered mental status. She had regularly undergone treatment through a pain clinic for more than six years for a history of persistent low back pain after failed treatment by spinal fusion. She had a prior history of successful therapy for Hodgkin lymphoma seven years before and was felt to be in complete remission. She recently gained weight from inactivity because of pain and subsequently developed non–insulin-dependent diabetes mellitus and associated hypercholesterolemia. At the time of evaluation in the ED, she was taking the following medications: 40 mg of oxycodone extended-release twice per day, 10 mg of oxycodone immediate-release four times per day as needed, 400 mg of gabapentin three times per day, 500 mg of metformin twice per day, 40 mg of simvastatin once per day, and 5–10 mg diazepam one time per day as needed.

The husband witnessed her develop a groggy look and then collapse to the floor; he wondered whether she had had a seizure. She was evaluated and, although her vital signs were stable, she was confused and lethargic. In the ED, she responded to 1.6 mg of intravenous naloxone. A pill count was conducted while in the ED, but this did not reveal noncompliance with her prescribed opioid regimen. A urine toxicology screening did not indicate the presence of any illicit or nonprescribed drugs. Once she awoke, she vehemently denied drug abuse or overuse but rather declared that she had continued her usual drug therapies as prescribed and was exercising regularly. Yet, both her family and she herself had noticed an increase in fatigue and side effects over the course of the previous week.

During a postdischarge visit to her pain physician, the patient described how she had attempted to change her lifestyle, spurred on by her high cholesterol levels and diabetes. She had started a regimen of tight calorie restriction, exercise, and an over-the-counter dietary supplement. Further inspection showed
that the supplement was primarily grapefruit extract. A component of grapefruit juice, bergamottin, is a very potent inhibitor of CYP3A4 and CYP2C9.24

Drug testing conducted on this individual several months before admission to the ED showed the presence of oxycodone, noroxycodone, and oxymorphone in the patient’s urine. These drug toxicology results were as expected for an individual taking oxycodone, as noroxycodone is the CYP3A4 metabolite of oxycodone, and oxymorphone is the CYP2D6 metabolite.25 In comparison, the urine drug results from the hospital admission showed no measurable levels of noroxycodone, but high levels of oxymorphone and oxycodone. Normally, 80% of the metabolites of oxycodone are noroxycodone formed by an \( \text{N} \)-demethylation reaction catalyzed by CYP3A4 and 10% by CYP2D6-catalyzed \( \text{O} \)-demethylation to oxymorphone.25 A previous study established that blocking the CYP3A4 pathway can lead to tripling of the product of the CYP2D6 path, oxymorphone—a metabolite that is 14 times more potent than its parent compound.25 In this patient, the absence of the primary metabolite from the metabolism of oxycodone through CYP3A4, noroxycodone, suggests blockage of that metabolic pathway.

Furthermore, previous genetic screens established that she was a poor metabolizer via CYP2D6. Meanwhile, a study in 2010 demonstrated that blocking oxycodone metabolism through the CYP3A4 pathways shunts the opioid instead through the CYP2D6 path.25 However, in healthy individuals who are poor metabolizers via CYP2D6, diverting oxycodone from CYP3A4 can have serious clinical consequences. Indeed, blocking both pathways causes systemic concentrations of oxycodone to triple because of a 70% lower oral clearance.25 Hence, in this patient, blocking CYP3A4 with the potent inhibitor bergamottin led to acute toxicity from oxycodone because she also could not adequately eliminate the opioid through the secondary pathway involving CYP2D6.

Conclusions

Drug-drug interactions and ADRs are major burdens within clinical medicine. A few simple questions asked during a patient history may provide important information to suggest the presence of a genetic metabolic limitation that could affect a patient’s response to pharmacotherapy. Consideration of ethnicity, age, and sex also can provide important information because, for example, polymorphisms associated with widely varied metabolic capacity are not distributed equally among ethnic groups. Furthermore, whenever more than one drug is prescribed, clinicians should recognize the potential for metabolic interactions. A basic grasp of the metabolism of medications is needed to be able to predict drug-drug interactions adequately to eliminate avoidable adverse effects.

Disclosures and Acknowledgments

Dr. Brennan receives advisor and speakers bureau honoraria from Cephalon, Endo Pharmaceuticals Inc., King Pharmaceuticals, and Purdue Pharma LP. Dr. Brennan receives speakers bureau honoraria from Forest Laboratories, Johnson & Johnson, Eli Lilly and Company, and Pfizer Inc. The supplement in which this work appears was supported by an educational grant from Mallinckrodt, the Pharmaceuticals business of Covidien. Research and editorial support was provided by Miller Medical Communications, LLC, and Rebecca A. Bachmann, PhD, of BookishProse.

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