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MaryAnne Ventura
Ohio Northern University

Lauren Desko
Ohio Northern University

Kimberly Gathers
Ohio Northern University

Ashley Overy
Ohio Northern University

David Kisor
Ohio Northern University

The Pharmacogenetics of Opioid Pain Management

MaryAnne Ventura, a fourth-year pharmacy student from Centre Hall, Pa.; Lauren Desko, a fourth-year pharmacy student from Perrysburg, Ohio; Kimberly Gathers, a fifth-year pharmacy student from Mercer, Pa.; Ashley Overy, a fifth-year pharmacy student from Grafton, Ohio; David Kisor, B.S., PharmD, professor of pharmacokinetics, chair of the Department of Pharmaceutical and Biomedical Sciences

Abstract

High rates of interpatient variability in drug metabolism and drug response for nearly all medications lead to the hypothesis that assessment of an individual patient's genotype with respect to their ability to metabolize certain drugs can be a useful tool in predicting a patient's responsiveness to certain medications. Evaluating patients using pharmacogenomics as a basis for assessment could allow pharmacists to decide which treatment options would be most efficacious in a given patient and, thereby, have significant impact in the clinical setting. This holds true especially in the case of prodrugs, which require in vivo activation to an active or more active form. Codeine is a prodrug whose clinical efficacy depends greatly on its metabolism to more active forms by both cytochrome P450 enzymes and uridine diphosphate glucuronyltransferase enzymes and is affected by the activity of transporters and the structure of its target receptor.[4] Evaluation of a patient's metabolic capacity concerning these enzymes, as well as any "abnormalities" in transporter activity or receptor structure, could indicate if the patient will receive adequate pain relief from a given dose of codeine.

Introduction

In recent years, the connection between drug metabolism and genetics has been more thoroughly validated thanks to studies on genetic variability and drug effects.[1] For nearly all medications, interpatient response variability has been found to be the rule rather than the exception. It is hypothesized that 20-40 percent of differences in patients with respect to drug response can be described by variations in a patient's phenotype, the observable traits that result from the genotype, which can include the patient's ability to metabolize drugs due to the expression of enzymes.[1,2] These variations are commonly identified through the discovery of single-nucleotide polymorphisms (SNPs), the most common genetic variations in human DNA, which occur when one single base pair replaces another.[3] Through the use of an individual's genetic background and by paying particular attention to those genes coding for proteins, such as enzymes, transporters and receptors involved in a drug's pharmacokinetics and pharmacodynamics, pharmacists and other health care providers can more thoroughly predict a patient's response to a specific medication.

A clinically relevant example of this is the metabolism of codeine. Codeine is a prodrug that requires O-demethylation by cytochrome P450 (CYP) 2D6 and glucuronidation by uridine diphosphate glucuronyltransferase 2B7 (UGT2B7) to form its more active metabolites, morphine and codeine-6-glucuronide.[4] Codeine efficacy also may be significantly affected by polymorphisms in the transporter as well as the receptor itself.

Codeine Metabolism

The CYP2D6 gene is polymorphic, which results in the metabolism of morphine being highly variable.[2] A complete lack of CYP2D6 activity is seen in 6-7 percent of Caucasians. Of the known polymorphisms, alleles *3-*8 have been classified as nonfunctional, which prevents the formation of functional CYP2D6. Alleles *9, *10 and *41 have been associated with reduced function, and *1, *2, *35 and *41 can be duplicated, which would result in a significant increase in the expression of functional CYP2D6.[5] CYP2D6 phenotype is determined by the allelic combinations that an individual patient possesses, as described in Table 1. The frequency of variant CYP2D6 alleles varies greatly interethnically. In Extensive Metabolizers (EM), approximately 10 percent of the codeine dose is converted to morphine.[4] In addition to variations in therapeutic response, an individual's genetic makeup can be used to determine the safety of codeine. For example, when compared to EMs CYP2D6, poor metabolizers (PM) experience less respiratory, psychomotor and pupillary effects, though no significant difference was seen in adverse effects, such as sedation or dry mouth, between the two phenotypes. Glucuronidation by UGT2B7 accounts for nearly 80 percent of the metabolism of a given dose, making it the main route of metabolism for codeine. As a result of this, the codeine-6-glucuronide metabolite is found at a much higher concentration in the body than codeine, as demonstrated by the fact that the area under the curve (AUC) values of codeine-6-glucuronide are 10-15 times higher than that of codeine. Although the gene that codes for UGT2B7 also has been found to be polymorphic, less than 20 allelic variants for this gene have been identified.[5] Unlike the polymorphisms associated with CYP2D6, the functional significance of UGT2B7 polymorphisms has not been well-defined with in vitro or in vivo studies. Two significant SNPs with respect to opioid metabolism are SNP G211 T of the UGT2B7 enzyme and the SNP A-842 G, which is associated with the regulatory region of the gene that encodes UGT2B7.[6] The nomenclature of SNP G211 T denotes that guanine is replaced by thymine in the DNA sequence, and SNP A-842 G means that adenine is replaced by guanine. The SNP G211 T causes a change in the amino acid sequence of the resulting protein at position 71, which changes a lipophilic residue, alanine, in the substrate binding pocket to a hydrophilic residue, serine. This substitution was studied in a comparison of two cancer patients, and this allele was shown to be present in the patient with low morphine sensitivity. The SNP A-842 G has been associated with increased promoter activity, resulting in higher levels of UGT2B7 and, thus, increased rates in morphine metabolism. This increased metabolism can be considered another reason why patients may fail to experience adequate pain relief from opioids.

Another factor that may contribute to the resistance of certain drugs is P-glycoprotein (P-gp), an efflux transporter, also known as multidrug resistant P-glycoprotein (MRP1).[2] P-gp limits the distribution and enhances the elimination of many drugs from the body in an effort to protect against a potentially toxic accumulation of the drug.[7] Morphine,

methadone, loperamide and fentanyl have all been confirmed as P-gp substrates as well as many endogenous and synthetic opioid peptides.[5] Polymorphisms that increase or decrease the levels of P-gp in membranes can alter drug effects accordingly.[6] Increased expression of P-gp would result in decreased blood concentrations of these drugs, while decreased expression would cause the opposite effect. Although P-gp is highly expressed at many apical epithelium cell membranes, including in the intestine, which influences drug absorption, its most significant impact is at capillary endothelial cells of the blood-brain barrier and blood-cerebrospinal fluid barrier, where it functions to determine CNS exposure to various substrates.[5]

The mu opioid receptor, coded for by the opioid receptor, mu 1 (OPRM1) gene, is the preferred target of many opioid drugs, especially morphine.[8] There have been more than 100 genetic polymorphisms identified in the OPRM1 gene. These variations have been noted to produce more than 20 amino acid sequences and have polymorphic frequencies of more than 1 percent.[5]

Morphine: A Case Report

According to guidelines from the World Health Organization (WHO), one of the leading pharmacological treatments for moderate to severe cancer pain is oral morphine.[6] However, the analgesic response to morphine is variable, and both genetic and non-genetic factors contribute to this unpredictability. Some of these genetic factors include variations in the genes for the drug's target receptor, drug-metabolizing enzymes and drug transporters. A published case report describes the treatment of a 55-year-old woman with lung carcinoma and bone metastases who was given morphine for the treatment of severe pain and did not experience an adequate analgesic response. Her morphine dose was increased from 20 mg/day to 75 mg/day, but her pain still was not relieved.

After undergoing genetic testing for several polymorphisms, this patient was classified as a poor responder to morphine due to the detection of several SNPs.[6] One of the SNPs identified was a genetic variation in the mu-opioid receptor (MOR-1). The patient was found to be heterozygous for the MOR-1 polymorphism A118 G, a genotype that typically results in patients needing an 18 percent higher dose of morphine compared to patients with the wildtype genotype. In addition, the patient had a genetic variation involving the UGT2B7, which altered the production of normal metabolites of morphine, one of which is active at opioid receptors and one that is inactive. This patient was homozygous for the UGT2B7 promoter polymorphism A-842 G, which causes an increase in promoter activity, therefore resulting in higher levels of the enzyme. With more of the UGT2B7 enzyme present, the patient experienced an increased rate of morphine metabolism, which contributed to her poor analgesic response. Lastly, the patient also had a SNP in the gene for P-gp, which is involved in the distribution of morphine. The patient was heterozygous for the polymorphism C3435 T, which increases the stability of the mRNA transcript and results in an expression of higher levels of the transporter. Consequently, the patient was less able to absorb and distribute morphine to various regions of the body, including the central nervous system. The overall end result of the patient having all three of these genetic polymorphisms was that she could not get adequate pain relief from morphine.

Codeine: A Case Report

Codeine does not produce an adequate analgesic response in 6-7 percent of the Caucasian population because these individuals lack functional CYP2D6 enzymes.[2] This percentage of the population is homozygous for non-functional mutant CYP2D6 alleles and, therefore, is unable to convert codeine to morphine, which provides the pain relief. In another published case report, a 65-year-old woman was given what was considered to be standard doses of paracetamol, also known as acetaminophen, and codeine for the treatment of pain. However, only minor pain relief was seen, and subsequent increases in the doses were not found to improve the analgesia and resulted in the patient experiencing undesirable side effects. The patient underwent genetic testing for CYP2D6 polymorphisms, and it was found that she completely lacked any functional CYP2D6 enzymes. Consequently, this patient was unable to get pain relief from codeine because she is part of the small percentage of the Caucasian population with this genetic variation in which morphine was not formed.

Conclusion

These case reports illustrate that there is a need to consider genetic factors when prescribing an opioid for analgesia because of the number of genetic polymorphisms in various enzymes, receptors and transporters that can significantly alter the response to this class of medications.[6] For instance, being able to use genetic tests to identify a patient as a poor responder to morphine would allow an alternative opioid to be chosen as the first-line treatment, thereby minimizing the incidence and extent of pain experienced by the patient for the duration of therapy. If point-of-care genetic testing could be done to identify patients who lack functional CYP2D6 enzymes, these patients could be prescribed an alternative drug instead of codeine, which would ultimately spare the patient from experiencing inadequate pain relief as a result of their inability to convert codeine to morphine. In the future, the use of genetic screenings prior to prescribing and dispensing opioids may allow health care providers to prevent this type of insufficient drug therapy; however, further advancements are needed in this area in order for it to have a more significant role in clinical practice. As pharmacists, we can improve patient care by providing different analgesic options to patients whose pain is not adequately controlled by opioids. These opioid resistant patients could be affected by one or more genetic factors, including having a polymorphism in either a CYP450 or UGT enzyme. Pharmacists can be the health care provider to counsel patients on this issue and provide them with other options, such as finding another pain medication that is metabolized by different CYP450 enzymes or by proposing another route of delivery for their current medication. For example, using a transdermal or buccal delivery route for a medication will avoid extensive first-pass metabolism by the liver, allowing more drug to be available for the patient. This simple change can make a substantial difference in a patient's therapy by helping to alleviate more of the patient's pain. Although this area of pharmacotherapy is still in the beginning stages of development, pharmacists have the opportunity to use pharmacogenomic methods to help improve patient care and enhance the outcome of a patient's opioid drug therapy.

Table 1. Phenotypic Designations for CYP2D6 Expression[5]

Genotype	Phenotypic Designation
Two nonfunctional alleles	Poor metabolizer (PM)
At least one reduced function allele	Intermediate metabolizer (IM)
At least one functional allele	Extensive metabolizer (EM)
Multiple copies of a functional allele and/or an allele with a mutation in the promoter region	Ultrarapid metabolizer (UM)

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