Opioid Metabolism and Pharmacogenetics: Clinical Implications

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FOR MANY WHO HAVE worked in the ambulatory setting in the past, discharging patients, especially pediatric patients, with a prescription for a codeine product for postoperative pain has been a fairly common practice. The use of codeine, especially in children, had started to decline in recent years as warnings about potential risks started to arise. A dramatic decline in the prescription of codeine products and tramadol may be noted this year since the Food and Drug Administration (FDA) issued its strongest warning in April 2017, requiring changes in the labeling of codeine to treat pain or cough and tramadol to treat pain, stating that these products are contraindicated in children younger than 12 years.[1] The FDA also announced that tramadol is contraindicated in the treatment of pain after adenotonsillectomy in those aged less than 18 years. Additional warnings about the use of codeine and tramadol in adolescents aged between 12 and 18 years who are obese or have obstructive sleep apnea or significant pulmonary problems were also announced.[1] Furthermore, warnings against the use of codeine or tramadol by breast feeding mothers was strengthened because of risks of serious adverse effects, including respiratory arrest and death, in their breastfed children.[1]

These FDA announcements illustrate the significance of the evolving recognition of the genetic influences of opioid metabolism and their impact on clinical practice. For those working in perioperative settings, an understanding of genetic influences on analgesic metabolism is helpful in explaining the phenomena in which patients may not receive pain relief from high doses of one opioid, yet will have excellent pain relief when even small doses of a different opioid are used. An increase in the practice of personalized medicine may be seen in some perioperative settings as health care providers and patients recognize that not all people will have the same response to the same medication. Personalized medicine involves the use of medications specifically selected for an individual patient, based on the patient's genetic makeup for sensitivity to and metabolism of the medication.[2]

Perianesthesia nurses daily observe variability in patients' individual responses to medications that are used to provide analgesia. Some patients may be very sensitive to very small doses of some opioids and experience significant analgesia, but risk adverse effects such as excessive sedation and respiratory depression, whereas others despite significant dose increases have unrelieved pain, but may also be at risk for adverse outcomes due to the use of high doses. It is well recognized that there is significant variability in the ways people respond to different medications.[3] Although variability in individuals' responses to analgesics may be attributed to multiple factors including age, gender, culture, mood, activity, environmental exposure, drug-drug interactions, drug bioavailability, and pain stimuli, research has offered insight into the impact of genetics on medication effects.[4-7]

Genetic variability has been found to impact both pain susceptibility and analgesic responses,[5] and in recent years, there has been an explosion in research in the field of genetics and pain. With rapidly evolving interest and research in this area, these findings have begun to impact the delivery of care. It may be expected that standard prescribing practices or order sets in which "one

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size fits all" will decline as awareness of the impact of genetic variability increases.

Pharmacogenetics is the study of how allelic difference in single genes may be associated with variability in specific medication responses, whereas pharmacogenomics is the study of the inherited genetic differences that result in individual responses to drugs.[2,6] To demonstrate the growing impact of genomic science, there are a number of guidelines now published that address use of genetic testing in clinical practice.[2] In the field of pain management, there is increasing interest in the role of genetics on drug targets and metabolism.[6] Variations in the structure of genes are called *genetic polymorphisms*.[8] A gene that has been altered by a polymorphism is referred to as an *allele* of the original gene.[8] Extensive research is underway in examining the gene variants or polymorphisms that affect the absorption, distribution, metabolism, and elimination (pharmacokinetics [PK]) of the same medications on different people.[7,9] Polymorphisms can also influence the effects or actions of medications (pharmacodynamics [PD]) brought on by receptor binding properties of a particular drug, including adverse drug effects and efficacy.[9] The differences in PK and PD are commonly seen in clinical trials with medications, illustrated by the fact that it is acceptable and expected in standard drug trials for 30% to 40% of the subjects to not have a response to the drug. Polymorphisms in some individuals may occur within proteins, including those that involve drug transporters and the mu opioid receptors, and cause variability in the effects of opioids.[3] Studies on genetic variability that influence drug transport and the mu opioid receptors are providing insight into the role of genetics on pain and analgesia, but this topic is beyond the scope of this article.

The focus of this article is on opioid metabolism and the impact of polymorphisms on patients' responses to opioid medications. Great research and clinical interest exist in the area of polymorphisms that affect the metabolic enzymes that process and eliminate opioids and their metabolites, thus impacting an individual's response to opioids. It is possible that these genetically induced changes in drug metabolizing enzymes may account for 10 to 10,000-fold variability in the activity of drugs.[5] Knowledge of genetic polymorphisms and opioid metabolism influences the choice of opioids in an analgesic plan and has better informed our understanding of drug-drug interactions. In addition, patients are becoming increasingly aware of genetic influences on medication metabolism, and some have received the results of simple genetic testing that they expect health care providers will understand and consider in their analgesic treatment plans.

To illustrate the impact of genetic polymorphisms in the perioperative setting, consider a situation in which a patient has been taking an opioid, such as oxycodone for more than a 12-month period of time without any significant adverse effects, however, if an equivalent analgesic dose of a different opioid is given postoperatively, the patient may develop significant sedation or respiratory depression. It is possible that this effect, which is termed incomplete cross-tolerance, may be explained by pharmacogenetics.[3] Similarly, pharmacogenetics may explain the phenomena in which a patient who no longer has pain relief from an opioid that has been taken for a period of time then experiences effective analgesia when rotated to a different opioid.[3] To better understand the impact of genetic polymorphisms on the variability of opioid PD and PK analgesia, a basic understanding of drug metabolism is needed.

Opioid Metabolism

The main site of opioid action is in the central nervous system, and opioids need to be fat-soluble or lipophilic to cross over the blood-brain barrier. However, for these medications to be excreted, these compounds need to be changed via a chemical process to make them more water-soluble for excretion, mostly in urine. To make opioids more water-soluble or hydrophilic, there are two phases of metabolism that must take place: phase I includes hydrolysis and oxidation, whereas phase II completes the reaction by conjugation into a water-soluble compound.[10,11] Table 1 provides a summary of commonly used opioids, their phase I and phase II of metabolism, and their active metabolites.

Phase I hepatic metabolism for opioids is mostly via an oxidative metabolism. This metabolism is catalyzed by a particularly important enzyme, the cytochrome P450 (CYP450) family of enzymes. The P450 system is responsible for metabolism of approximately 90% of all medications including