The practice of anesthesia has long been considered an art and a science, with interpatient variability in drug response being the rule, rather than the exception. Pharmacogenomics, which studies the role of genetics in drug response, is emerging as a discipline that may impact anesthetic management.

The purpose of this review is to provide clinicians with basic knowledge related to pharmacogenomics and its implications in anesthesia. This review focuses on pharmacogenomics related to commonly used drugs in anesthesia.

Pharmacogenomics as a predictor of drug response is increasingly used in medicine and drug development. By expanding the knowledge base of anesthesia providers, pharmacogenomic considerations have the potential to improve therapeutic outcomes and individualize drug therapy, while avoiding toxic effects and treatment failure. However, because pharmacogenomics may not fully explain variability in drug response, implementation should be in conjunction with traditional anesthesia considerations.

Keywords: Anesthesia, drug variability, pharmacogenetics, pharmacogenomics, polymorphisms.

Implications of Pharmacogenomics for Anesthesia Providers

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The practice of anesthesia has long been considered an art and a science, with interpatient variability in drug response being the rule, rather than the exception. Differences in patient response have historically been attributed to factors such as age and sex, preexisting disease and comorbidities, drug interactions, surgery type, and nutritional status. Anesthesia has been at the forefront in the discovery of pharmacogenomic disorders such as pseudocholinesterase deficiency, malignant hyperthermia (MH), and thiopental-induced porphyria, yet many anesthesia providers have limited knowledge of the topic beyond these specific disorders. Pharmacogenomics is the study of how chromosomal variations affect drug response. Although the majority of genetic alterations are benign, some have effects on drug metabolism and efficacy and may have a role in adverse reactions. The purpose of this review is to provide clinicians with current information related to pharmacogenomics and its application to drugs commonly used in anesthesia. Table 1 provides a list of key terms.

Pharmacogenomics
Pharmacogenomics has the potential to individualize drug therapy, help avoid adverse drug reactions (ADRs) and toxic effects, and improve therapeutic drug efficacy and outcomes by adjusting drug therapy to the patient’s genotype. Components of a tailored drug regimen include the right drug with the right dose to elicit the right response. Although a perfectly tailored therapy in every case may not currently exist, the goal of personalized medicine is to bring this concept to reality.

According to the US Food and Drug Administration, domestically there are more than 2 million serious ADRs

Table 1. Key Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Allele</td>
<td>Two or more forms of a gene that occupy a specific position on a specific chromosome</td>
</tr>
<tr>
<td>Chromosome</td>
<td>The DNA-containing structure of cellular organisms that contains all or most of the genes of the organism</td>
</tr>
<tr>
<td>Gene</td>
<td>The sequence of DNA that occupies a specific position on the chromosome and determines a particular characteristic in an organism</td>
</tr>
<tr>
<td>Genotype</td>
<td>A representation of an organism’s genetic makeup or the particular set of genes that the organism possesses</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>Having 2 different alleles for the same trait</td>
</tr>
<tr>
<td>Homozygous</td>
<td>Having an identical allele for a single trait</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>The study of how chromosomal variations affect drug response</td>
</tr>
<tr>
<td>Phenotype</td>
<td>The observable physical or biochemical characteristics of the organism’s genetic makeup</td>
</tr>
<tr>
<td>Polymorphism</td>
<td>A specific genetic alteration; occurs in more than 1% of the population</td>
</tr>
<tr>
<td>Single nucleotide polymorphism (SNP)</td>
<td>The most common type of genetic or allelic variation; also called a point mutation</td>
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</table>
yearly, of which there are 100,000 resulting deaths.\(^7,8\) Adverse drug reactions are the fourth leading cause of death (ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile-related deaths).\(^7,8\) Adverse drug reactions cause 1 of 5 injuries or deaths per year among hospitalized patients. Annually, ADRs cost $136 billion, which is greater than the cost of diabetic or cardiovascular care.\(^6\) For patients experiencing ADRs, costs increase in terms of average length of hospital stay and mortality.\(^7\) The application of pharmacogenomics has the potential to help providers reduce the number of ADRs patients experience, improve therapeutic drug efficacy, and prevent ADRs.\(^9\)

Although the terms pharmacogenetics and pharmacogenomics are often used interchangeably, pharmacogenetics generally refers to the variation of a single gene or relatively few genes influencing the expression of drug response, whereas pharmacogenomics refers to genome-wide alterations in drug response.\(^10\) The effect of drugs on gene expression can be studied with genomic technologies, which provides an additional perspective of the biological effects of a drug.\(^9\)

Currently, the pharmacogenomic impact of polymorphisms, which are genetic alterations (and occur in more than 1% of the population), is most noted among 3 categories: enzymes, transporter proteins, and receptors.\(^5\) The majority of drugs are metabolized by cytochrome P-450 (CYP450) enzymes, which are mostly found in the liver. Polymorphisms in CYP450 enzymes are not always significant. However, these polymorphisms become significant when a drug is dependent on the polymorphic enzyme for metabolism, when a drug is dependent on the polymorphic enzyme for bioactivation, and when drugs have a small therapeutic index.\(^2\) There are also genetic variations in transporter genes, and current research indicates that membrane transporters influence drug absorption in different areas of the body and the speed of absorption. Polymorphisms in receptor genes may influence drug affinity and response. Applications of pharmacogenomics include the identification of new drug targets, prediction of efficacy and toxicity for new drug therapy, testing for the direct influence of an agent on a specific pathway, and identification of drug responders, nonresponders, and toxic responders within a population. With the advent of pharmacogenetics—the melding of sciences, including genetics, biochemistry, and molecular pharmacology—has come the hope of personalized medicine in the future.\(^9,11,12\) Although medicine may be far from realizing that goal, there has been much scientific progress leading to the hope of one day attaining personalized medicine.

**History**

The idea of inheritance of certain traits from parent to offspring has piqued human curiosity for centuries. However, it was the scientific discoveries during the 20th century that brought about a quantum leap in the areas of genetics and pharmacology that laid the foundation for current knowledge. As the century began, William Bateson coined the term genetics, and as the century came to a close, teams of scientists revealed the entire human genome, arguably one of the greatest achievements of modern time.\(^10,12-15\) The melding of pharmacology and genetics, termed pharmacogenetics (coined in 1939 by Frederick Vogel), occurred in the 1950s primarily due to earlier clinical observations, landmark reports based on these observations, and the development of new laboratory and experimental techniques.\(^5,16\) Three genetically linked disorders in particular placed the field of anesthesiology as a major contributor to the advancement of pharmacogenetics: pseudocholinesterase enzyme deficiency, thiopental-induced porphyria, and MH.\(^3\) The 1957 writing of “Drug Reactions, Enzymes, and Biochemical Genetics” by Arno Motulsky in response to an invitation from an American Medical Association committee marked the beginning of a new discipline.\(^9,17\) Werner Kalow published the first monograph in 1962, Pharmacogenetics: Heredity and the Response to Drugs, a landmark document that contributed to the elevation of pharmacogenetics to a respected science and discipline among the other sciences.\(^18\)

**Cytochrome P-450 Enzymes**

Drug metabolism involves a biotransformation process in the liver; these reactions are termed phase 1 and phase 2. Phase 1 reactions occur by oxidation, reduction, or hydrolysis and make the metabolite more polar, or water soluble, to facilitate renal excretion. Phase 2 involves conjugation of the drug, which also makes the metabolite more polar and, thus, helps facilitate excretion in the urine. Cytochrome P-450 is used to describe a family of microsomal drug-metabolizing enzymes that are responsible for 70% to 80% of phase 1 metabolism of medications (Figure).\(^19\) CYP450 enzymes are important in the biosynthesis and metabolism of endogenous compounds such as vitamins, steroids, and lipids, and the majority of these processes take place in the liver and less frequently in the epithelium of the small intestines. There are 57 different CYP450 genes identified in humans, but only a relatively small number of the encoded proteins, primarily in the CYP1, CYP2, and CYP3 families appear to contribute to metabolism of drugs.\(^20\) The clinical relevance of the inherited variations associated with CYP450 enzymes is dependent on many environmental factors such as disease, drugs, surgery, nutritional status, and biological variations.\(^3\) The frequency of variant alleles is also significantly varied depending on race and ethnic background.\(^2\)

A unique feature of the hepatic microsomal enzymes is the capability of medications or chemicals to stimulate or induce activity levels of these enzymes.\(^21\) Examples of
agents that induce activity levels of hepatic microsomal enzymes are phenobarbital, St John's wort, polycyclic hydrocarbons, and rifamycins. Stimulation of these enzymes increases the rate of drug metabolism. On the other hand, certain medications and substances, such as calcium channel blockers, grapefruit juice, and erythromycin, inhibit the hepatic microsomal enzymes. These inducers and inhibitors add to the variability of the CYP450 enzymes and possible ADRs.

The major CYP450 enzymes of importance to anesthesia providers are CYP3A4, CYP2D6, CYP2C9, and CYP2C19. The CYP2E1 enzyme is responsible for the metabolism of inhalational agents, although variability has not been associated with genetic polymorphisms, but rather with body mass, diet, alcohol consumption, and age. The CYP3A4 family is responsible for the oxidative metabolism of around half of all medications that undergo phase 1 metabolism. This enzyme is found in large quantities in the epithelial layer of the intestines and also in the liver. CYP3A4 has the unique ability to metabolize a variety of drugs from many different classes: opioids (eg, fentanyl), benzodiazepines, local anesthetics (eg, lidocaine), immunosuppressants (eg, cyclosporine), and antihistamines (eg, terfenadine). There is an appreciable amount of genetic variability with this enzyme, yet interestingly, its distribution is continuous and unimodal and has few known clinically significant variations. Although dose adjustments are generally not needed for CYP3A4 polymorphisms, drugs metabolized through CYP3A4 are subject to inhibitors such as cimetidine, ketoconazole, and grapefruit juice. This inhibition leads to reduced CYP3A4 activity.

Another important member of the CYP450 family is CYP2D6, which is noted for extensive variability in the enzymes and its effect on the metabolism of many drugs currently used in anesthesia practice. CYP2D6 is responsible for around 25% of phase 1 drug reactions. There may be as much as a 1,000-fold difference in the metabolism of drugs by CYP2D6 between phenotypes, which may result in ADRs in patients with a polymorphism of the CYP2D6 enzyme. CYP2D6 is responsible for metabolism of many antiemetics, beta-blockers, codeine, tramadol, oxycodone, hydrocodone, tamoxifen, antidepressants, neuroleptics, and antiarrhythmics.

Testing is available to categorize a person's CYP2D6 metabolism as poor, intermediate, extensive (normal), and ultrarapid, and these designations can be helpful for clinicians to evaluate the efficacy and dosages of many medications commonly used in breast cancer treatment and psychiatry. Although testing may also be beneficial in anesthesia, associated adjustments in dosing and clear recommendations have not been fully developed and have not become standard practice. In Table 2, the different designations are described; people with poor metabolism have nonfunctional or nonexistent CYP2D6 enzymes, and people who take medications metabolized by CYP2D6 and who have poor CYP2D6 metabolism may be more likely to have ADRs, whereas people with ultrarapid CYP2D6 metabolism may have a decreased effect of a drug due to a low plasma concentration.

Drugs metabolized by CYP2C9 include phenytoin, nonsteroidal anti-inflammatory drugs, celecoxib, and warfarin. Testing is available for CYP2C9, and several studies have shown that performing and evaluating CYP2C9 genotyping can help to provide safer, more personalized warfarin treatment and to reach therapeutic levels sooner while reducing potentially life-threatening side effects.

**Table 2. Designations for Metabolism of Cytochrome P-2D6 Polymorphism**

<table>
<thead>
<tr>
<th>Designation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolism</td>
<td>Lack both copies of the functional allele</td>
</tr>
<tr>
<td>Intermediate metabolism</td>
<td>Heterozygous for 1 functional and 1 deficient allele</td>
</tr>
<tr>
<td>Extensive metabolism</td>
<td>Two partially defective alleles that cause reduced metabolism</td>
</tr>
<tr>
<td>Ultraparapid metabolism</td>
<td>Three or more functional alleles</td>
</tr>
</tbody>
</table>

Figure. Contribution of Major Human P450s to the Phase 1 Metabolism of All Drugs Currently Marketed (Reproduced with permission from Guengerich FP. Cytochromes P450, drugs and diseases. Molecular Interventions [serial online]. 2003;3(4):194-204. http://www.pharmacogenetics.org/lectures/CYP450.pdf.)
P-450 Enzymes

Table 3. Drugs Commonly Metabolized by Cytochrome P-450 Enzymes

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>Codeine, tramadol, methadone, oxycodone, hydrocodone, ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Midazolam, alprazolam, diazepam, zolpidem, fentanyl, alfentanil, sufentanil, dexamethasone, methylprednisolone, granisetron</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Celecoxib, naproxen</td>
</tr>
</tbody>
</table>

(omeprazole and pantoprazole). Table 3 provides a summary of drugs commonly metabolized by CYP450.

Pseudocholinesterase Deficiency

The first documented genetic variation in relation to an anesthetic drug was the discovery of prolonged apnea and muscle relaxation following administration of succinylcholine. Pseudocholinesterase deficiency is an uncommon disorder, which can be inherited, acquired, or iatrogenic. Other terms used interchangeably to describe this condition are plasma cholinesterase deficiency, atypical pseudocholinesterase, butyrylcholinesterase deficiency, acetylcholine acylhydrolase, and cholinesterase II deficiency. This anesthetic problem was discovered in 1950s, when it was noted that prolonged muscle relaxation occurred after succinylcholine was administered to patients with an inherited deficiency of the human serum cholinesterase enzyme.

Pseudocholinesterase is an enzyme that is produced in the liver and found also in the plasma, pancreas, heart, and the white matter of the central nervous system. This enzyme is clinically significant for metabolizing succinylcholine, mivacurium, atracurium, and some ester local anesthetics (cocaine, procaine, and tetracaine). Typically, pseudocholinesterase quickly hydrolyzes most of the succinylcholine before it reaches the neuromuscular junction in people with standard plasma levels of normally functioning pseudocholinesterase enzyme. This hydrolysis rapidly inactivates around 90% to 95% of the intravenous succinylcholine dose. The remaining 5% to 10% of the succinylcholine dose acts as an acetylcholine receptor agonist at the neuromuscular junction, which leads to prolonged depolarization of skeletal muscle. Then, as a result of prolonged depolarization, endogenous acetylcholine (released from the presynaptic membrane of the motor neuron) does not produce any additional change in membrane potential after binding to its receptor on the muscle cell. This causes flaccid paralysis of skeletal muscles develops within 1 minute. Termination of succinylcholine is the result of diffusion away from the acetylcholine receptors at the motor end plate into the extracellular fluid. The primary metabolite is succinylmonocholine, which is 1/20th to 1/90th as potent as succinylcholine and is further hydrolyzed to succinate and choline. Normally, a patient recovers fully from a typical dose of succinylcholine (0.5-1.0 mg/kg) within 3 to 5 minutes. A person with pseudocholinesterase deficiency can consequently have higher levels of intact succinylcholine molecules reaching receptors in the neuromuscular junction, causing the duration of paralytic effect to continue for up to 8 hours.

All inherited causes of pseudocholinesterase irregularity are located on chromosome 3, and all variants occur as a point mutation of this gene. The majority of the population (96%) is homozygous for the normal pseudocholinesterase genotype, also called U or usual pseudocholinesterase. The other 4% of the population carries a defective gene allele for pseudocholinesterase, which means they can have a partial enzyme deficit. This mutation is more common in persons of European descent.

To date, there are more than 50 different mutations in the pseudocholinesterase gene that have been identified. The 2 most common are the A (atypical) variant, or dibucaine resistant, and the K variant. Persons who are homozygous for the A variant are at high risk of experiencing prolonged apnea following succinylcholine or mivacurium administration. Persons who are homozygous for the K type mutation have reduced pseudocholinesterase activity due to a 66% reduction in total enzyme. Persons who are heterozygous for the K and A variant may have prolonged muscle relaxation for more than 5 minutes but less than 1 hour. Other variants of pseudocholinesterase are fluoride (F) resistant, which exhibits reduced activity, the H variant with a 10% reduced concentration, and the J variant with a reduced concentration of 33%. The most serious and rare mutation is the silent or S variant, in which a person homozygous for the S genotype will have no pseudocholinesterase activity. People with the S variant may experience prolonged apnea and muscle paralysis for up to 8 hours with a 1-time dose of succinylcholine. Generally, there will be no notable clinical significance with only a partial deficiency of pseudocholinesterase, unless there is an accompanying acquired pseudocholinesterase deficiency present that is stimulated by a physiological state or medication.

Treatment includes continuing mechanical ventilation, sedation, analgesia, and monitoring until muscle function returns to normal. When a patient has return of train-of-4 peripheral nerve stimulation, return of muscle tone, and the ability to follow commands, maintain adequate spontaneous ventilation, and perform hand grips and head lifts for more than 5 seconds, the patient may be extubated. Laboratory testing available is a plasma assay for pseudocholinesterase and the dibucaine number (the percentage of cholinesterase inhibition in serum by...
dibucaine). A normal (homozygous typical) dibucaine number is 70 to 80, a heterozygous atypical dibucaine number is 50 to 60, and a dibucaine number less than 30 indicates homozygous atypical.\textsuperscript{25} Patients should be contacted with results and provided with information about this disorder, including which drugs to avoid.\textsuperscript{27}

**Malignant Hyperthermia**

The rare hypermetabolic syndrome, MH, is an inherited genetic variation. It is a life-threatening condition that occurs when a susceptible person is exposed to triggers such as halogenated inhalation agents and/or succinylcholine.\textsuperscript{30} The triggers cause a rapid release of calcium from the sarcoplasmic reticulum, resulting in a high metabolic state, increased oxygen consumption, hypercarbia, and increased body temperature. Left untreated, MH can lead to circulatory collapse and death.\textsuperscript{31} The incidence varies from 1:5,000 to 1:50,000 in adults and around 1:15,000 in children.\textsuperscript{30,32}

Specific signs of MH include increased end-tidal carbon dioxide (early sign), marked temperature elevation (late sign), muscle rigidity (may or may not be present), myoglobinuria, and rhabdomyolysis (muscle breakdown). Nonspecific signs of MH include tachycardia, acidosis, hyperkalemia, and tachypnea. There are almost 50 mutations that have been found to be associated with MH, although the \textit{RYR1} gene mutation on chromosome 19 is the most predominant.\textsuperscript{30} Ryanodine receptors mediate calcium release from the sarcoplasmic reticulum, which is an essential step in muscle contraction. In MH, the release of calcium from the sarcoplasmic reticulum outweighs the reuptake, resulting in the inability to terminate muscle contraction. Once MH is recognized, it is imperative to act quickly to discontinue the inhalation agent, hyperventilate with 100% oxygen, administer intravenous dantrolene, cool the patient, and treat symptoms.\textsuperscript{33} Dantrolene decreases the release of calcium from the sarcoplasmic reticulum, restoring the balance between release and uptake.\textsuperscript{33}

The caffeine halothane contracture test is the most common diagnostic test for MH diagnosis. This test requires muscle biopsy and measures contracture in response to caffeine and halothane. The test is sensitive, meaning that most people with risk and susceptibility for MH will be identified. Problems with the caffeine halothane contracture test include the requirement for a fresh biopsy sample at the testing site, the invasiveness and expense of the test, and limited biopsy center locations. Currently, the 5 testing sites within the United States are located in Maryland, California (2), Minnesota, and North Carolina. Clinical molecular genetic testing is available in the United States at 2 sites, one in Pennsylvania and the other in Wisconsin. Currently, genetic testing is available to patients with a positive result of the caffeine halothane contracture test and their families and screens for the 17 most common \textit{RYR1} mutations. Although the test is very specific, only about 25% of the people at risk for MH are detected because of the multiple areas of MH mutation.\textsuperscript{34}

Obtaining a thorough anesthetic history is important before providing anesthesia for potentially susceptible patients. If there is a suspicion of MH based on patient and family history, avoidance of triggering agents is crucial. Although pretreatment with dantrolene is not recommended or necessary, having it available is crucial. Mortality has decreased from 80% thirty years ago to less than 5% today.\textsuperscript{32}

**Analgesics**

The conversion of codeine to its active metabolite morphine is mediated by CYP2D6. Codeine is the analgesic most susceptible to CYP2D6 polymorphisms because it relies on CYP2D6 for activation. People with poor CYP2D6 metabolism are unable to convert codeine to morphine, thereby rendering codeine ineffective for analgesia, yet the side effects of codeine are not altered.\textsuperscript{3} As a result of its lack of effect and presence of side effects, codeine should not be used in people with poor CYP2D6 metabolism. The metabolism of dihydrocodeine, hydrocodone, oxycodone, thebaine, and methadone can be influenced by genetic polymorphisms, leading to variability of clinical response in people with poor CYP2D6 metabolism.\textsuperscript{2}

In contrast, opioid intoxication can occur after the administration of codeine to a person with ultrarapid CYP2D6 metabolism. \textit{O}-demethylation of codeine into the active metabolite morphine by CYP2D6 accounts for a minor amount (0%-15%) of codeine metabolism.\textsuperscript{35} \textit{N}-demethylation of codeine into norcodeine by CYP3A4 (10%-15%) and glucuronidation to codeine-6-glucuronide (50%-70%) are the primary pathways of codeine clearance.\textsuperscript{35} When a person with ultrarapid CYP2D6 metabolism has concomitant inhibition of the CYP3A4 enzymes and is administered a normal codeine dose, metabolism is forced through the CYP2D6 enzyme pathway, and morphine intoxication can occur.\textsuperscript{32} Additionally, CYP2D6 ultralipid metabolism has been implicated in infant toxicity from breastfeeding during maternal codeine therapy.\textsuperscript{36}

The analgesic effect of tramadol is slightly decreased in people with poor CYP2D6 metabolism. Tramadol undergoes metabolism by CYP2D6 to N-desmethyltramadol and the active metabolite, O-desmethyltramadol. O-desmethyltramadol is considerably more potent at the μ-opioid receptor than tramadol. Because of this, tramadol is often regarded as a prodrug. Much like codeine, the person with poor CYP2D6 metabolism is slower to convert tramadol to its active metabolite, making it a less effective analgesic agent. However, because tramadol is a weak μ-opioid receptor agonist itself, decreased analgesia in people with poor CYP2D6 metabolism is less pronounced than with codeine.\textsuperscript{37,38}
Virtually all antidepressants are metabolized by CYP2D6, and many are strong inhibitors of the enzyme. Therefore, caution should be used when administering codeine, tramadol, and other drugs metabolized by CYP2D6 to people with poor or intermediate metabolism, who may experience toxic effects because of enzyme inhibition by the antidepressant.\(^1\)

CYP2C9 is responsible for metabolism of the non-steroidal anti-inflammatory drugs, celecoxib, naproxen, piroxicam, ibuprofen, and flurbiprofen.\(^4\) People with poor CYP2C9 metabolism consequently have decreased metabolism of these drugs, with the increased potential for toxicity.

The µ-opioid receptor is the main site of action for opioid agents.\(^4\) The most common polymorphism of the µ-opioid receptor (OPRM1) consists of a substitution of adenine (A) to guanine (G) at position 118. Carriers of the G118 allele have a decreased response to clinical opioid potency, decreased incidence of opioid-induced adverse effects (nausea, vomiting, sedation, pupil dilation, and drowsiness), and increased responsiveness of the hypothalamic-pituitary-adrenal axis to the antagonistic effect of naloxone.\(^1\) However, despite the presence of the G118 allele, it does not seem to affect the use of perioperative opioids.\(^39\) Rather, its usefulness may be limited to explaining why some patients require higher opioid doses.

P-glycoprotein, or multidrug resistance protein 1, is an active efflux transporter in the blood-brain barrier. Patients with altered P-glycoprotein could have enhanced entry of some drugs such as morphine, methadone, fentanyl, sufentanil, and alfentanil into the central nervous system. However, presently, experiments with substrates of P-glycoprotein have been limited to cell cultures and laboratory animals, but it could have a part in the future development of new anesthetic and analgesic agents whose entry into the central nervous system is facilitated by blocking P-glycoprotein.\(^1\)

### Postoperative Nausea and Vomiting

Approximately one-third of all patients have postoperative nausea and vomiting (PONV), with risk factors being female sex, nonsmoker, postoperative narcotic use, and a history of motion sickness or PONV. These risk factors correlate well with the incidence of PONV, with 61% to 79% having 3 to 4 risk factors for experiencing PONV. However, 10% of patients without risk factors still experience PONV.\(^40\)

Although serotonin receptor antagonists have helped to make considerable strides in decreasing the incidence of PONV, challenges remain.\(^31\) Serotonin receptor antagonists work by binding to its target, the serotonin receptor located centrally in the chemoreceptor trigger zone and peripherally at the vagus nerve terminals. The affinity of the drug for the receptor differs among the various serotonin receptors and may contribute to the differences in clinical efficacy. Currently, 4 serotonin receptor antagonists are available and approved for the clinical treatment of nausea and vomiting in the United States: dolasetron, granisetron, ondansetron, and palonosetron.\(^41\) Tropisetron is not available in the United States at this time.

Of the 5 serotonin receptor antagonists discussed, all but granisetron are metabolized to a varying extent through the isoenzyme CYP2D6. Ondansetron is metabolized by CYP2D6, CYP3A4, CYP1A2, and CYP2E1; palonosetron is metabolized by CYP2D6, CYP3A4, and CYP1A1; and dolasetron is metabolized by CYP2D6 and CYP3A4.\(^41\) Four of the serotonin receptor antagonists are active on administration except dolasetron, which must be converted by an enzyme, carbonyl reductase, into the active form hydrodolasetron.\(^42\) Genetic polymorphisms in CYP2D6 may lead to therapeutic failure in the case of people characterized as having ultrarapid metabolism; knowing that a person has ultrarapid metabolism would allow for dose adjustments or choosing another agent not metabolized by the isoenzyme CYP2D6.\(^41\) Granisetron is a serotonin receptor antagonist that is metabolized primarily by the isoenzyme CYP3A4, not the highly polymorphic isoenzyme CYP2D6.\(^42\) Because mutations in CYP3A4 have little effect on drug metabolism, dose adjustments of drugs are generally not needed. CYP3A4 is subject to inhibitors such as cimetidine, ketoconazole, and grapefruit juice, which leads to decreased action of CYP3A4 and subsequent increased drug efficacy.\(^31\)

### Pharmacogenomic Considerations for the Future

As pharmacogenomics becomes integrated into practice, it is critical to evaluate future implications. Education of clinicians in genetics, legal and ethical considerations, and financial impacts are possible areas for further consideration. To implement pharmacogenomics in a clinical setting, education of clinicians is needed to help interpret results of genetic tests. Information should be provided to aid practitioners in providing care for patients with genetic polymorphisms.\(^11\) Cost-benefit ratios will also need to be evaluated.\(^9\) Pharmacogenomics has the potential to impact many specialties, including drug companies and drug development, and how drugs will be prescribed.\(^5\)

Many questions arise as pharmacogenomics infiltrates into the healthcare field. As genetic testing becomes more advanced and available, the implications in practice are multifold. Legal and ethical questions will emerge, and the financial impact will have to be carefully evaluated.

With an improved understanding of the clinical implications of pharmacogenomics, anesthesia providers may have an increased potential to individualize therapy. Anesthesia providers may also be able to use pharmacogenomics to help reduce adverse reactions, avoid toxic effects, and improve drug efficacy. Because pharmacogenomics may not fully explain variability in drug response,
implementation should be in conjunction with traditional anesthesia considerations.

REFERENCES


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AANA Journal • October 2010 • Vol. 78, No. 5
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