

YOUR RESPONSE TO ANESTHESIA: IS IT IN YOUR GENES? PHARMACOGENETICS FOR THE ANESTHESIOLOGIST.

Mindy Cohen, MD

“For decades, anesthesiologists have been aware of individual differences in response to pharmacologic agents, perhaps more so than medical professionals in any other specialty.” –Stephen Palmer, PhD

INTRODUCTION

The field of pharmacogenetics focuses on inherited differences in medication response. Genetic variation can influence drug response and toxicity at many levels: absorption, distribution, metabolism, interaction with drug target, and excretion. While drug response is influenced by genetic factors, it is often not determined by a single gene alone and is a result of interacting genes with modifications from environmental factors. In the past several years, there has been an exponential increase in research elucidating genetic causes of some patients' widely variable response to medication.

A major goal of pharmacogenetics, is to improve medication safety and efficacy on an individualized level for each patient. In the near future, genetic testing will likely guide certain decisions about optimal perioperative care and pain management. Therefore, a basic understanding of pharmacogenetics is critical for the practicing anesthesiologist.

PHARMACOGENETICS OVERVIEW

For several decades, anesthesiologists have recognized that some patients have unexpected responses to medications. In the 1950s, a case report of prolonged apnea following succinylcholine in two brothers suggested an inherited predisposition to extended duration of action of succinylcholine [1]. We now understand that these brothers had an inherited pseudocholinesterase deficiency.

Adverse drug reactions can cause morbidity and mortality, as well as increasing the cost of healthcare. Each year, an estimated 100,000 deaths and 2 million hospitalizations are attributed to adverse drug reactions [2]. A meta-analysis of a 30 year period at several hospitals revealed a 6.7% incidence of serious adverse drug reactions resulting in prolonged hospital stay, permanent disability, or death. Episodes related to drug administration error were not included. The cost of each serious adverse drug reaction was estimated to be \$2,300-5,600 [3].

Some of these unusual drug reactions could be predicted by pharmacogenetics. Variations in DNA base pairs, known as polymorphisms or mutations, cause variability among individuals. Polymorphisms can change an amino acid building block in a protein, or alter the promoter region that controls gene expression, or change the number of copies of a given gene. Mutations may have recessive, dominant, or additive effects. Genetic variation can be found in drug absorption, drug metabolism, drug transporters, and drug receptors. Drug concentration at the target site, the number and morphology of target receptors, together with a variation in multiple downstream events will also influence response. Researchers are studying genetic variation along all points in the pathway from absorption to elimination. Complicating the picture, identification of a positive association between a specific genotype and clinical outcome does not necessarily imply causality [4]. The path from genotype to phenotype is often difficult to map reliably.

Cytochrome P450 enzymes are genetically polymorphic and cause changes in drug metabolism. CYP 2A6, CYP 2B6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 and CYP 3A4 are responsible for metabolizing most clinically important drugs. Abnormal CYP alleles can have absent, reduced, normal, or increased enzyme activity depending on the patient's genotype.

The anticipated benefits of pharmacogenetics research include: more accurate dosing, new drugs targeted to a specific genetic makeup, and improved safety. Practical applications of pharmacogenetics are already in place in the treatment of some disorders. For example, some research hospitals routinely examine groups of genes in children with leukemia before choosing the optimal chemotherapy regimen. Genetic variation can result in dramatically different responses and toxicity with chemotherapeutic treatments. Based on the results of genetic tests, oncologists can prescribe the safest and most effective drug regimen for each child. The FDA has started to modify some drug labels to include pharmacogenetic information, strongly advising that doctors customize doses for individual patients based on genotype.

PHARMACOGENETICS AND THE PRACTICE OF ANESTHESIOLOGY

Sedatives

Most benzodiazepines are metabolized by the CYP P450 pathway.

- Diazepam has a prolonged half-life in patients with certain genetic variations, which may result in prolonged sedation or delayed awakening.
 - Homozygous (2 copies) of mutation G681A in CYP 2C19 results in 4-fold longer half-life
 - Heterozygous (1 copy) of mutation G681A have 2-fold longer half-life [5].
- Midazolam is metabolized by CYP 3A4 and 3A5. However, varied clinical response is only modestly associated with genetic factors [6, 7].

Paralytics

The effectiveness and duration of succinylcholine and mivacurium are strongly associated with genetic factors.

- Patients who are heterozygous (single mutant allele) for the Asp70Gly polymorphism have 3- to 8-fold longer recovery of muscle function after succinylcholine administration.
- Homozygous expression (two mutant alleles) results in up to 60-fold longer recovery [8, 9].

Volatile Anesthetics

- Malignant hyperthermia (MH) due to volatile anesthetics is a potentially fatal pharmacodynamic abnormality due to a defect in the calcium ion release channel of the sarcoplasmic reticulum, proposed to be the ryanodine receptor gene (RYR). One in 15,000 children and 1 in 50,000 adults are susceptible to MH, caused by a variety of RYR1 polymorphisms. Genetic testing is currently impractical due to high number (>170) of known mutations.
- Decreased sensitivity to Desflurane and an increased incidence of awareness under anesthesia is seen in patients with MCR-1 variation (90% also have red-hair phenotype) [10].
- Halothane-induced hepatitis is influenced by CYP 2E1.
- Nitrous oxide causes inactivation of methionine synthase in patients with abnormal 5,10-methylenetetrahydrofolate reductase. This genetic defect was implicated in a case report of an infant boy who suffered neurologic deterioration and subsequent death after 2 anesthetics with nitrous oxide [11, 12].

Pain Tolerance

“The role of genetic factors in interindividual variability in response to opioids must consider the genetics of pain sensitivity; the genes of which also affect opioid response” [13]. Studies have found genetic factors that can predispose patients to have higher or lower pain thresholds.

- Subjects had altered sensitivity to heat and cold based on genetic makeup of vanilloid receptor subtype 1 gene, delta opioid receptor subtype1 gene, and COMT gene [14].
- Humans with non-functional melanocortin-1 receptor gene (90% also have red hair) had reduced sensitivity to noxious stimuli [15].

Opioids

- Opioid drugs are substantially metabolized, mainly by CYPs (cytochrome P450) and to a lesser extent by UDP-glucuronosyltransferases (UGTs) and COMT. CYP 3A4, CYP 2D6, and UGT 2B7 are involved in the metabolism of many of the opioids.
 - COMT metabolizes noradrenaline, adrenaline, and dopamine. Decreased oral morphine dosages were required in cancer patients with certain genetic variations [16].
- Drug transporters such as ABCB1, ABCC1, ABCC2, ABCC3, SLCO1A2, and SLCO1B3 participate in opioid transport and influence opioid efficacy and side effects [17].
 - Substrates of ABCB1/MDR1 include morphine, methadone, fentanyl, sufentanil, alfentanil, and morphine-6-glucuronide. Other transporters potentially involved in opioid distribution are MRP1, MRP2, and MRP3 (ABC transporter subfamily C), organic anion transporters (OAT1 and 3), and organic anion transporter polypeptides (OATP1 and 2, solute carrier family 21).
- Changes in μ -opioid receptor shape and copy number, can produce changes in nociceptive responses and affect opioid response.
 - Binding studies to post-mortem brain samples suggest 30-50% ranges of differences in human μ -opioid receptor densities [18].

- The μ -receptor binding ability is affected by SNP A118G in the OPRM1 gene (allele frequency 2-48% ethnicity dependent).
 - A118G mutation associated with less opioid effects (miosis, response to experimental pain, respiratory depression).
 - A118G mutation increases opioid dosage requirements in patients [19].
- The μ -receptor copy number is affected by a promoter polymorphism, G172T, associated with large interindividual differences in post-surgical opioid requirements.
- Variation in β -Arrestin 2, involved in intracellular signaling after opioid exposure, showed significant association with side effects necessitating change in narcotic regimen in chronic pain patients [18].
- Some opioids require biotransformation from a pro-drug in order to provide effective analgesia. Both codeine and tramadol require activation by CYP 2D6; however, CYP 2D6 is deficient in approximately 10% of caucasian individuals [20, 21]. CYP 2D6 genetic variation creates poor, intermediate, extensive (normal), or ultrarapid metabolizers.
 - **Codeine**
 - Codeine's analgesic properties are primarily dependent on biotransformation into morphine by CYP 2D6.
 - With CYP 2D6 deficiency, there is minimal plasma morphine after a dose of codeine [22].
 - At the other extreme, there are numerous case reports of serious respiratory depression in patients with the ultrarapid metabolizer genotype who received codeine.

"Safety of codeine during breastfeeding: **fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine.**" Madadi, P., G. Koren, et al. (2007). *Can Fam Physician* 53(1): 33-5.

A new mother was prescribed Tylenol #3 (500 mg acetaminophen and 30 mg codeine) for pain associated with an episiotomy. She took 4 the first day, and then 2 per day. Her infant developed difficulty in breastfeeding and showed lethargy on day 7. At 11 days of age, he was taken to a pediatrician owing to concerns about his gray skin color and decreased milk intake. On day 13, an ambulance team found the baby cyanotic and without vital signs. Postmortem analysis revealed a toxic blood morphine concentration of 70 ng/ml in the infant, breast milk from day 10 contained 87 ng/ml of morphine. **Mother was found to have CYP 2D6 Ultrarapid Metabolizer genotype.**

- **Tramadol**
 - Tramadol is a synthetic weak opioid metabolized by CYP 2D6 to compounds that have analgesic properties via affinity for μ -opioid receptors. Tramadol also inhibits reuptake of neurotransmitters 5HT and noradrenaline [23].
 - When treated with tramadol, extensive CYP 2D6 metabolizers experienced adequate analgesia in contrast to inadequate analgesia in poor CYP 2D6 metabolizers [24].
- **Methadone** is also metabolized by CYP 2D6. Genetic variation can cause slower metabolic clearance and increased toxicity.

Local Anesthetics

The efficacy of lidocaine was significantly reduced in patients with MCR-1 receptor mutation [25].

β -Blockers

- Metoprolol is metabolized by CYP 2D6. There is a 30-fold difference between the highest and lowest clearance values and 30-fold variability in AUC for extensive metabolizers of metoprolol.
 - Results in cardiovascular patients suggested that pharmacogenetic measures could be used to design more individualized metoprolol dosage regimen for each patient [26].
- Propranolol is mostly metabolized by the liver during its first passage through the portal circulation resulting in 25% oral bioavailability. There is great interindividual variation in the presystemic clearance of propranolol resulting in approximately 20-fold variability in plasma concentration after oral administration.
- Polymorphisms in the β 1 and β 2 receptor genes have been associated with variability in heart rate slowing and blood pressure effects with β -blockers and β -agonists [27].
 - β 1 receptor polymorphisms influence the response to metoprolol in patients with essential hypertension [28].

5-HT₃ receptor antagonists

Antagonists of the 5HT₃ receptor, such as ondansetron, have varying efficacy based on genetic variation in biotransformation enzymes, drug transporters, and 5HT₃ receptors.

- Biotransformation enzymes CYP 2D6 and CYP 3A4 are primarily responsible for breakdown of most 5-HT₃ receptor antagonists (except granisetron). CYP 2D6 genetic variation creates poor, intermediate, extensive (normal), or ultrarapid metabolizers. Ultrarapid metabolizers experience more post-operative nausea and vomiting than normal or poor metabolizers [29].
- Drug transporters such as ABCB1 (a.k.a. P-glycoprotein or MDR-1), a transmembrane efflux pump, influence the concentration of drug at the effect site. A Single Nucleotide Polymorphism (SNP) at position 3435 causes a change in ondansetron efficacy in cancer patients [30].
- The 5HT₃ receptor has genetic variability which was associated with altered ondansetron efficacy in cancer patients [31].

NSAIDs

- Ibuprofen is metabolized by CYP 2C8 [32].
- The CYP 2C9 *3 allele causes patients to metabolize celecoxib, naproxen, ibuprofen more slowly.
 - While these patients may experience more clinical benefit they are also at risk for more adverse effects associated with elevated drug levels.
- HLA-DRB1 *11 allele associated with anaphylactoid reactions to various NSAIDs [4].

Acetaminophen

- Variation in CYP 2E1 shows accelerated elimination rate in patients [33], potentially resulting in less analgesia in some patients.

GLOSSARY

Allele	Alternative forms of a gene, every individual has 2 alleles of a given gene (one from each parent)
Gene	A hereditary segment of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism
Genotype	The genetic makeup of an individual. Determined by sequencing DNA. Made of four types of nucleotides: adenine (A), guanine (G), thymine (T), or cytosine (C)
Heterozygote	Having two different alleles for a specific gene
Homozygote	Having identical alleles at a specific gene, two copies of the same allele
Mutation	A variation in the genetic code that occurs in LESS than 1% of the population
Pharmacodynamics	Varied therapeutic responses and adverse effects in each individual who was exposed to same drug dose
Pharmacogenetics	The study of how specific genes affect drug response (often used interchangeably with Pharmacogenomics)
Pharmacogenomics	The study of drug response in the context of the entire genome, looks at variations in all the genes in a group of individuals simultaneously to determine the basis for variations in drug response (often used interchangeably with Pharmacogenetics)
Pharmacokinetics	Varied plasma levels, half-lives, AUCs in each individual who was exposed to same drug dose
Phenotype	Observed variation in an individual subject. Determined by measuring drug levels, drug effect, adverse reactions, etc.
Polymorphism	Variation in the genetic code that occurs in MORE than 1% of the population
SNP (a.k.a. "SNiP")	<p>Single Nucleotide Polymorphism, substitution of a single nucleotide base for another.</p> <ul style="list-style-type: none"> ◦ A number signifies the base pair location where a single nucleotide substitution occurs, first letter signifies the "wild-type" allele, second letter represents the nucleotide found in the mutant or less common allele, example A118G, or A118 A/G, or 118 A>G ◦ Three-letter abbreviations of the altered amino acids, example Asp70Gly ◦ Numbering the different alleles as they are discovered, example CYP2D6*5 allele is the fourth identified variant in the P450 CYP2D6 enzyme

PHARMACOGENETICS INTERNET RESOURCES (URLs as of 12/30/2009)

Pharmacogenomics Knowledge Base	Collects, encodes, and disseminates knowledge about the impact of human genetic variations on drug response. Summarizes important genes and drug pathways. Curated.	http://www.pharmgkb.org/
Human Genome Project	Basic review of pharmacogenomics concepts.	http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml
Online Mendelian Inheritance in Man (OMIM)	Compendium of human genes and genetic phenotypes. Full-text, referenced overviews on over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain links to other genetics resources.	http://www.ncbi.nlm.nih.gov/omim/
Pharmacogenomics Primer	“One Size Does Not Fit All: The Promise of Pharmacogenomics” from National Center for Biotechnology Information	http://www.ncbi.nlm.nih.gov/About/primer/pharm.html
Pharmacogenetics Research Network	nationwide collaboration of scientists studying the effect of genes on responses to a wide variety of medicines	http://www.nigms.nih.gov/Initiatives/PGRN
CYP P450 summary table	CYP P450 enzyme drug interaction table	http://medicine.iupui.edu/clinpharm/ddis/table.asp

REFERENCES

- Forbat, A., H. Lehmann, and E. Silk, *Prolonged apnoea following injection of succinylcholine*. *Lancet*, 1953. **265**(6795): p. 1067-8.
- Lazarou, J., B.H. Pomeranz, and P.N. Corey, *Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies*. *JAMA*, 1998. **279**(15): p. 1200-5.
- Rodriguez-Monguio, R., M.J. Otero, and J. Rovira, *Assessing the economic impact of adverse drug effects*. *Pharmacoeconomics*, 2003. **21**(9): p. 623-50.
- Palmer, S.N., et al., *Pharmacogenetics of anesthetic and analgesic agents*. *Anesthesiology*, 2005. **102**(3): p. 663-71.
- Qin, X.P., et al., *Effect of the gene dosage of CgammaP2C19 on diazepam metabolism in Chinese subjects*. *Clin Pharmacol Ther*, 1999. **66**(6): p. 642-6.
- Shih, P.S. and J.D. Huang, *Pharmacokinetics of midazolam and 1'-hydroxymidazolam in Chinese with different CYP3A5 genotypes*. *Drug Metab Dispos*, 2002. **30**(12): p. 1491-6.
- Kharasch, E.D., et al., *Influence of CYP3A5 genotype on the pharmacokinetics and pharmacodynamics of the cytochrome P4503A probes alfentanil and midazolam*. *Clin Pharmacol Ther*, 2007. **82**(4): p. 410-26.
- Jensen, F.S. and J. Viby-Mogensen, *Plasma cholinesterase and abnormal reaction to succinylcholine: twenty years' experience with the Danish Cholinesterase Research Unit*. *Acta Anaesthesiol Scand*, 1995. **39**(2): p. 150-6.
- Cerf, C., et al., *Screening patients with prolonged neuromuscular blockade after succinylcholine and mivacurium*. *Anesth Analg*, 2002. **94**(2): p. 461-6, table of contents.
- Liem, E.B., et al., *Anesthetic requirement is increased in redheads*. *Anesthesiology*, 2004. **101**(2): p. 279-83.
- Erbe, R.W. and R.J. Salis, *Severe methylenetetrahydrofolate reductase deficiency, methionine synthase, and nitrous oxide--a cautionary tale*. *N Engl J Med*, 2003. **349**(1): p. 5-6.
- Selzer, R.R., et al., *Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency*. *N Engl J Med*, 2003. **349**(1): p. 45-50.
- Belfer, I., et al., *Candidate gene studies of human pain mechanisms: methods for optimizing choice of polymorphisms and sample size*. *Anesthesiology*, 2004. **100**(6): p. 1562-72.
- Kim, H., et al., *Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament*. *Pain*, 2004. **109**(3): p. 488-96.
- Mogil, J.S., et al., *Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans*. *J Med Genet*, 2005. **42**(7): p. 583-7.

16. Ross, J.R., J. Riley, and K. Welsh, *Genetic variation in the catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients.*, in *11th World Congress on Pain*, H. Flor, E. Kalso, and J.O. Dostrovsky, Editors. 2006, IASP Press: Seattle. p. 461-467.
17. Somogyi, A.A., D.T. Barratt, and J.K. Collier, *Pharmacogenetics of opioids*. *Clin Pharmacol Ther*, 2007. **81**(3): p. 429-44.
18. Ross, J.R., et al., *Clinical response to morphine in cancer patients and genetic variation in candidate genes*. *Pharmacogenomics J*, 2005. **5**(5): p. 324-36.
19. Bond, C., et al., *Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction*. *Proc Natl Acad Sci U S A*, 1998. **95**(16): p. 9608-13.
20. Stuvén, T., et al., *Rapid detection of CYP2D6 null alleles by long distance- and multiplex-polymerase chain reaction*. *Pharmacogenetics*, 1996. **6**(5): p. 417-21.
21. Sachse, C., et al., *Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences*. *Am J Hum Genet*, 1997. **60**(2): p. 284-95.
22. Sindrup, S.H., et al., *Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine*. *Clin Pharmacol Ther*, 1990. **48**(6): p. 686-93.
23. Stamer, U.M. and F. Stuber, *Pharmacogenetics of anesthetic and analgesic agents: CYP2D6 genetic variations*. *Anesthesiology*, 2005. **103**(5): p. 1099; author reply 1101.
24. Stamer, U.M., et al., *Impact of CYP2D6 genotype on postoperative tramadol analgesia*. *Pain*, 2003. **105**(1-2): p. 231-8.
25. Liem, E.B., et al., *Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads*. *Anesthesiology*, 2005. **102**(3): p. 509-14.
26. Ismail, R. and L.K. Teh, *The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients*. *J Clin Pharm Ther*, 2006. **31**(1): p. 99-109.
27. Libby, P., et al., eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 8th ed. 2008, Saunders Elsevier: Philadelphia.
28. Liu, J., et al., *beta1-Adrenergic receptor polymorphisms influence the response to metoprolol monotherapy in patients with essential hypertension*. *Clin Pharmacol Ther*, 2006. **80**(1): p. 23-32.
29. Candiotti, K.A., et al., *The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis?* *Anesthesiology*, 2005. **102**(3): p. 543-9.
30. Babaoğlu, M.O., et al., *Association of the ABCB1 3435C>T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists*. *Clin Pharmacol Ther*, 2005. **78**(6): p. 619-26.
31. Tremblay, P.B., et al., *Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients*. *J Clin Oncol*, 2003. **21**(11): p. 2147-55.
32. Martínez, C., et al., *The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects*. *Br J Clin Pharmacol*, 2005. **59**(1): p. 62-9.
33. Ueshima, Y., et al., *Acetaminophen metabolism in patients with different cytochrome P-4502E1 genotypes*. *Alcohol Clin Exp Res*, 1996. **20**(1 Suppl): p. 25A-28A.

Mindy Cohen, MD
Pediatric Anesthesiology, The Children's Hospital
Cohen.Mindy@tchden.org