Practical Pediatric Pharmacogenetics
(Dosing/Reactions/etc)

Jeffrey L. Galinkin MD, FAAP
Associate Professor
University of Colorado at Denver Health Science Center

Introduction

Nothing can put you to sleep faster than a good article on pharmacogenetics. First off it is almost impossible to understand all those words ending with –tide, -ase, etc. that we all learned and immediately forgot when we took our medical boards. Second, it is almost always impossible to figure out the point of the article and how it would actually apply to the actual practice of medicine. Thus, for this discussion I will try to summarize the current literature on this relevant drugs to our practice and present the practical aspects for us as pediatric anesthesiologist.

How all of this works

Whether you realize it or not, our profession has always been at the forefront of pharmacogenetics. The recognition of malignant hyperthermia and psuedocholinesterase deficiency in the 1950’s and 1960’s represent some of the earliest discoveries in this field. As technology has grown, so has our understanding of the interaction between individual genetic differences and drug action. This has increased our awareness that previously believed “idiosyncratic reactions” were actually related to individual differences in genotype.

The study of pharmacogenetics seeks to link differences in gene structure or genotype (polymorphisms) with pharmacologic differences in drug action (phenotype). What is seen in individual patients as a result of these polymorphism are alterations in metabolism, drug transport (how a drug gets from one part of the body to another), and receptor function. Individually each of these alterations can effect a single drugs action, collectively the issue becomes very complex and it is often difficult to discern if a polymorphism in the receptor, transporter or metabolizing enzyme is contributing to a drugs effect.

Below are listed some of the more common drugs we use and some of the basic pharmacogenetic information that we know about each of these drugs.

Medications seen in the preoperative assessment

*Diazepam: Metabolized by liver enzyme CYP2C19 (CYP = cytochrome p450). Homoygotes (two copies of the abnormal polymorphism) for the polymorphism G681A of this CYP have a 4 fold longer duration of drug effect then those non-carriers.¹*
Midazolam: Metabolized by two different enzymes present in both the liver (CYP 3A4, CYP3A5) and intestine. Thus far there is not evidence that polymorphisms in either of these enzymes cause any effect in drug action when given orally. However, coadministration of midazolam and fentanyl can cause prolongation in the action of fentanyl due to inhibition of fentanyl metabolism by midazolam’s competing metabolism at the liver enzyme CYP3A4.

Warfarin: Research into the pharmacogenetics of warfarin show the potential of genetic testing to determine drug dose. Warfarin is primarily metabolized in the liver by CYP2C9. Polymorphisms in this gene result in very low dose requirements for Warfarin. Genetic variation in the Vitamin K system (VKORC1) also alters warfarin response and between these two polymorphism much of the variability of warfarin drug dosing is explained. In a recent study polymorphisms in both of these genes were tested prior to initiation of drug therapy. Using information from these tests to establish an initial dose resulted in 83% of patients reached therapeutic, stable INR’s within 2 weeks.

Intraoperative medications

Volatile anesthetics:
Malignant hypothermia (MH) is an autosomal dominant inherited myopathy associated with abnormal intracellular calcium release in skeletal muscle upon exposure to triggering substances such as volatile anesthetics and succinylcholine. Unfortunately, there is no single polymorphism in the ryanodine 1 receptor that is singularly link to this disease. There are 170 variations in this receptor that are linked to MH susceptibility.2

Individual sensitivity to volatile anesthetics based on genetics has not been as well studied or defined. Based on research by Liem et al3 we know that many redheads have distinct polymorphisms in the melanocortin-1 receptor which make them less sensitive to desflurane (require more drug to achieve MAC). Other than this study there is little to show that any genetic variability will cause a change in sensitivity to volatile agents.

Finally, there are no specific genetic polymorphisms associated with an increased risk of halothane-induced hepatitis even though halothane metabolism is primarily mediated by CYP2E1.

Muscle relaxants:
Succinylcholine: Plasma psuedocholinesterase (butyrylcholinesterase) deficiency decreases succinylcholine inactivation in 1 in 1,500 individuals. People who are homozygous for this polymorphism (two copies of the gene polymorphism of the allele butyrylcholinesterase ASP70Gly) have prolongation of drug action up to 60 times normal. Heterozygotes (those with one copy of the polymorphism) have an increase in drug duration 3-8 times.4
**Mivacurium:** Patients with fully functional plasma pseudocholinesterase take on average 30 minutes to recover from mivacurium. This recovery time is increased by 15-30 minutes in heterozygotes and up to 6-8 hours in homozygotes.

**Opioids:**
Opioid action is very difficult to characterize by single polymorphisms. Thus, below is a brief discussion of research in each of the variables affecting the pharmacogenetics of opioid drug action.

**Metabolism:**
**Codeine:** Codeine has minimal clinical effect until it is metabolized in the liver (about 10% of drug) by CYP2D6 to morphine. Up to 10% of the population in this country are poor metabolizers of codeine and get no analgesic effect from this drug. In children this number may be as high as 36%. This may be caused by the low amount of drug absorption or additional polymorphisms reducing overall metabolism. There is also a small population of individuals, most commonly seen in persons of East African descent, who are ultrarapid metabolizers. These individuals convert the majority of codeine into morphine. For these patients respiratory depression and apnea are very real possibilities after even a single dose of drug. This is of particular concern in nursing mothers. There has been both a case report of an infant dying secondary to the use maternal codeine in a mother who was an ultrarapid metabolizer, and a study detailing the mechanism of this.

Morphine: Multiple liver cytochromes influence the metabolism of morphine. Morphine glucoronidation is the major path of first pass metabolism of morphine. An alteration in the genotype of Uridine Diphosphate Glycosyl Transferase (UDGT) causes increased glucuronidation of morphine. Theoretically, this should cause a decrease in morphine effectiveness. Most recently it was found (Candotti et al Abstract 120 at the American Academy of Pain Medicine) that CYP2D6 poor and ultrarapid metabolizers had very poor analgesia with morphine when compared to extensive and intermediate responders.

Methadone: CYP2D6 poor metabolizers have decreased clearance of drug. This decrease is not always consistent. This may be secondary to the influence of CY2B6 and CY3A4 in the metabolism of methadone. More research is currently being done to better define these effects in humans and out of the laboratory.

**Drug Transport:**
Morphine, methadone, fentanyl and meperidine are all transported (across cell membranes, to the brain etc.) by the ABC transporters specifically ABCB1 efflux transporter. Research into this polymorphism is just beginning. Early research does show that polymorphisms of this transporter can result in as much as a 2-fold increase in opioid requirements for patients with 2 copies of relevant polymorphisms.

**Mu-Receptor polymorphism:** The mu-opioid receptor is the principle site of action of opioids. The OPMR-1 gene codes for this receptor and one of the polymorphisms of this gene (A118G) result in a increased sensitivity to opioids. This work is very preliminary and more research is being generated currently to better elucidate this relationship.
Antiemetics:
Ultrarapid metabolizers of CYP2D6 have a high incidence of failure of ondansetron. This is due to the rapid metabolism of ondansetron and low overall drug exposure in these patients.

Postoperative medications

Tramadol: Metabolized by CYP2D6. Poor metabolizers maintain high tramadol levels for an extended period of time. This actually results in a diminishment of drug effectiveness. In one study, the percentage of non-responders to tramadol was significantly higher in the poor metabolizer group (46.7%) compared with the normal (extensive metabolizer) group (21.6%; p=0.005).\textsuperscript{10}

Non-steroidal Analgesics:
There has been little research in efficacy for these drugs. However, many non-steroidal drugs are metabolized by CYP2C9 (ibuprofen, naproxen, celecoxib). Individuals with two copies of the polymorphism CYP2C9*3 (homozygotes) metabolize these drugs much slower than those non-carriers and heterozygotes. Although these patients may have superior analgesia, this may be problematic since patients may also have an increase in drug side effects and toxicity.

There is also now evidence that the presence of the Human Leukocyte Antigen HLA-DRB1 polymorphism at the *11 allele may increase the risk of anaphylactoid reactions to NSAID’s.\textsuperscript{11}

How do you apply this information?

The concept of applied pharmacogenetics is still in its infancy in our specialty. Technology has not quite made it to the point that we can analyze all of the above genotypes prior to surgery and plan our anesthetic accordingly. However, you can take steps now to apply some of these concepts to your everyday practice. Avoiding drugs, when possible, with bad pharmacogenetic associated toxicity or a high non-response rate when other alternative drugs are available is an easy start. Drugs such as codeine have little place in the modern practice of medicine. It is also important to titrate drugs that have large variability in action based on genotype. Finally, do not be surprised by an unexpected long, short or absent drug action.
Reference:


