Pharmacogenomics applications in perioperative medicine

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Introduction

The wide spectrum of pharmacologic management used in the perioperative patient presents a series of challenges for clinicians, and selection of medications to optimize therapeutic effect while minimizing risk of adverse effects can be difficult. Heterogeneity in patient response to pharmacologic treatments is attributed to differences in several factors including age, gender, race, weight, body-mass-index, disease state, use of concomitant medication(s) and genetic factors [1]. The post-genomic era following the sequencing of the human genome has brought significant advancement in our understanding of human genetics and technological advances that are shaping the fields of pharmacogenetics (the study of the effect of single genes on drug metabolism and response) and pharmacogenomics (the study of the effects of many genes as well as gene-gene and gene-environment interactions) [2]. A comprehensive understanding of the pharmacologic agent, as well as the intended dose and delivery method are critical for maximizing therapeutic efficacy and minimizing adverse effects during the perioperative period. Personalizing perioperative pharmacotherapies requires examination of genetic variations effecting drug absorption, transport, metabolism, and pharmacodynamic target(s) [3]. The purpose of this paper is to review the impact of genetic variation on perioperative drug management.

Background

Pharmacokinetics is the study of drug metabolism and is divided into three phases. In Phase 1, enzymes such as Cytochrome P450 (CYP) oxidases catalyze the addition of a polar functional group to a nonpolar drug making it more water soluble. Enzymes of the CYP system reside primarily in the smooth endoplasmic reticulum of hepatocytes. The expression of CYP enzymes is influenced by age, gender, race, disease state, genetics and epigenetic factors. In Phase II, these modified compounds are conjugated to polar compounds via transferase enzymes such as glutathione S-transferase. In Phase III, the conjugated compounds may be further processed before being recognized by efflux transporters and pumped out of cells. The goal of drug metabolism is to convert lipophilic compounds to hydrophilic compounds facilitating renal excretion.

Pharmacogenetic studies can identify genetic variations associated with drug metabolizing enzymes. Genomic DNA may include polymorphisms (i.e., variants) that result in altered transcription and/or translation of CYP enzymes resulting in variable CYP metabolism activity. Patients can be classified into phenotypic groups based on the level of enzymatic activity: extensive metabolizers have normal activity, ultra-rapid metabolizers have increased activity, intermediate metabolizers have reduced activity and poor metabolizers have little or no enzymatic activity.

Nomenclature

There are 5 common pharmacogenomic nomenclature systems: SNP nomenclature, Reference SNP (rs) nomenclature, “Star” nomenclature, Genotype nomenclature, and Haplotype nomenclature. SNP nomenclature uses letters/numbers to identify the gene such as OPMR1 - Opioid Receptor Mu 1. When a polymorphism in that gene is expressed, for example as OPMR1 304A>G, the numbers (304) following the gene OPMR1 indicate the position of the polymorphism (in this case a G substitution for A) in the gene. There are 4 nucleotides in DNA: adenine (A), thymine (T), guanine (G), and cytosine (C). In the example, OPMR1 304A>G, the first letter A indicates the original (wildtype) nucleotide and the second letter, G, represents the change in nucleotide sequence (the SNP) that characterizes the polymorphism.

The nomenclature of the CYP enzyme polymorphisms follows the “Star” nomenclature. Members of the same CYP family (those sharing > 40% similarity in amino acid sequence) are designated by number (e.g., CYP1, CYP2, CYP3). Subfamily groups (those sharing > 55% similarity in amino acid sequence) are designated by the letter following the number (e.g., CYP1A, CYP1B, CYP1C). The number following the subfamily letter designates the individual enzyme (e.g., CYP3A4, CYP3A5, CYP3A7). The nomenclature for a wild-type allele (the most prevalent allele and often having ‘normal’ enzymatic function) is given the “*1” designation (e.g., CYP3A4*1). A “*1/*1” designates homozygous wild-type genotype [3]. A number other than “1” following the “*” denotes an allele with variation in the DNA sequence. Variations can result in altered structure and/or function of the enzyme or may confer no change (i.e., “silent mutation”). Numbers are assigned sequentially as genetic variants are discovered and described in the literature, but the allele number does not reflect the functionality of the resulting enzyme (i.e., a “*2” allele could have normal, decreased, or increased enzyme function). The enzymatic activity or functionality of a given allele number designation is specific to the enzyme (e.g., the “*3” allele may designate a decrease-of-function, DOF, allele for one CYP enzyme and designate a gain-of-function, GOF, or a normal function allele for another CYP enzyme). Importantly, gene names are italicized but proteins and *designations are not (e.g., CYP2D6 is the gene that codes for the CYP2D6 enzyme; and a common loss of function, LOF CYP2D6 allele is CYP2D6∗3). Each CYP enzyme has substrate specificity but considerable overlap often exists (e.g., CYP3A4 is the primary CYP enzyme involved in the metabolism of more than 50 percent of the

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more commonly prescribed medications in the US market, but many of these are metabolized, albeit to lesser extents, also by certain other CYP enzymes [4]. The "rs" system is used by the SNP database (dbSNP) - the central database for all genetic variation information. The rs system is recommended by Human Genome Variation Society as the standard nomenclature for all genetic variation information. The rs system is used by the SNP database (dbSNP) - the central database for SNPs. When a new polymorphism is identified, the information is submitted by researchers to the dbSNP. Subsequently, the sequence data are recorded and an "rs" accession number is created.

In genotype nomenclature, the genotype refers to the two alleles inherited for a specific gene. A patient has two alleles that constitute their genotype for a given gene. If the two alleles are the same (e.g., CYP2D6 *2/*2) then they are considered homozygous carriers of *2 polymorphism. A patient with one normal (wildtype) allele and one abnormal allele may have genotype CYP2D6 *1/*2 and be referred to as a heterozygous carrier of the *2 polymorphism. In haplotype nomenclature, the haplotype refers to a combination of alleles or a set of SNPs found on the same chromosome.

The Preoperative Period

Benzodiazepines: Midazolam (MDZ) is a short-acting benzodiazepine that reversibly interacts with inhibitory gamma-aminobutyric acid (GABA) receptors in the central nervous system. It has sedative, anxiolytic, amnesic and hypnotic properties and is metabolized primarily by CYP3A4/5 in the liver to its active metabolite, 1-hydroxy-midazolam (1-OH-MDZ) [2]. A meta-analysis of 7 clinical trials reported by Miao et al. in 2009 determined that environmental factors rather than CYP3A4/5 genetic status accounted for variation in MDZ disposition [5,6]. Various studies reported by other authors, however, have determined that CYP3A genetic status does influence MDZ pharmacokinetics.

Using a 2-compartment model to examine MDZ pharmacokinetic data in 24 adult Asian cancer patients, Seng et al. determined that (1) along with total bilirubin, CYP3A5*3 genetic status was associated with MDZ clearance: CYP3A5*3 expressers (*1/*1 or *1/*3) had a 22 percent reduction of MDZ clearance compared to CYP3A5 non-expressers (CYP3A5*3 homozygotes); (2) baseline body weight was also associated with clearance and distribution volume of the metabolite 1-OH-MDZ, and (3) creatinine clearance was associated with 1-OH-MDZ glucuronide excretion [7].

Yu et al. examined the effect of CYP3A5*3 on the systemic clearance of MDZ under basal (i.e., normal), inhibited and induced metabolic conditions. The inhibited metabolic state was created by concomitant use of itraconazole 200 mg once daily for 4 days, and the induced metabolic state was created by concomitant use of rifampin 600 mg once daily for 10 days. Pharmacological profiles of MDZ and metabolites did not reveal any significant difference between basal and induced metabolic states. The CYP3A5*3/*3 group, however, had larger reduction in MDZ systemic clearance compared to the *1/*1 group. In addition, the area under the plasma concentration-time curve (AUC) ratio of MDZ metabolic ratio (1'-OH-MDZ:MDZ) was significantly lower in the CYP3A5*3/*3 group [8]. Dependent on the dose and rate of elimination, AUC reflects the actual body exposure to drug after administration and is expressed in mg*h/L. In an in vivo model reported by Shin et al., MDZ clearance was reliably predicted by CYP3A5*3 genotype [9]. In a study reported by Elens et al. of 108 cancer patients receiving MDZ, a more recently discovered CYP3A4 DOF polymorphism, CYP3A4*22, was determined to be associated with a lower MDZ metabolic ratio: 20.7% lower (95% CI: -36.2 to -6.2) for CYP3A4*22 carriers compared with CYP3A4*1/*1 patients. Combining CYP3A4*22 and CYP3A5*3 genotypes showed a 38.7% decrease (95% CI: -50.0 to -27.4; p < 0.001) in the MDZ metabolic ratio for poor (CYP3A4*22/*1-CYP3A5*3/*3) and 28.0% (95% CI: -33.3 to -22.6; p < 0.001) for intermediate (CYP3A4*1/*1-CYP3A5*3/*3) metabolizers compared to extensive (CYP3A4*1/*1-CYP3A5*1/*1) CYP3A metabolizers [10].

The Intraoperative Period

Induction Agents: Induction agents include inhalational and intravenous anesthetics. Volatile anesthetics are excreted unchanged in the lungs (less than 5% are metabolized via CYP2E1), but intravenous anesthetics undergo extensive metabolism by hepatic CYP450 enzymes including CYP2B6, CYP2C9, CYP3A4, and UGT1A9 prior to renal excretion [3].

Inhalational agents

Kayamak et al. reported that a genetic polymorphism in Glutathione S-transferase pi (GSTP1) was associated with increased serum α-glutaryl transferase (GST) levels, a marker of liver damage resulting from sevoflurane administration [11]. Although this suggests GSTP1 influences the pharmacokinetics and/or pharmacodynamics of

Table 1. Anesthesia drugs with clinically relevant polymorphisms and effect

| Drug        | Route | Gene     | SNP                  | Effect                           |
|-------------|-------|----------|----------------------|----------------------------------|
| Propofol    | IV    | CYP2B6   | CYP2B6*6              | Decreased enzyme binding, metabolism, and clearance |
| Desflurane  | IH    | MC1E     | R151C, R160W, D294H   | Increased requirement in red-headed women |
| Isoflurane  | IH    | RYR1     | Tyrosine 522          | Malignant Hyperthermia           |
| Sevoflurane | IH    | CYP2E1   | Gly2130Arg            | Renal Dysfunction                |
| Ketamine    | IV    | CYP2B6   | CYP2B6*6              | Decreased enzyme binding, metabolism, and clearance |
| Fentanyl    | IV    | OPRM1    | 304A>G                | Variable analgesic dose           |
| Succinylcholine | IV  | BChE     | 299A>G, 1615G>A       | Prolonged neuromuscular blockade  |
| Rocuronium  | IV    | SLCO1B1  | rs2206283G>G; rs1128503C>T | Increased action and recovery time; reduced elimination |
| Morphine    | IV    | UGT2B7   | C-161T, C802T         | More rapid glucuronidation        |
| Codeine     | PO    | CYP2D6   | 259A>del; G1846A; 1707T>del; A2935C; C100T | Lack of O-demethylation into morphine; loss of efficacy |
| Methadone   | IV    | CYP2D6   | G1845A*4; 1707T>del   | Slower metabolic clearance        |
| Tramadol    | PO    | CYP2D6   | G1845A*4              | Greater need for rescue analgesics after surgery |
| Oxycodeone  | PO    | CYP2D6   | CYP2D6*3/*4/*5/*6     | Increased analgesia and sedation  |
| Various NSAIDS | PO | CYP2C9   | CYP2C9*3               | Reduced metabolism of celecoxib; naproxen; ibuprofen |
| Ondansetron | IV/PO | ABCC1 | 2677TT; 3435 TT       | Increased bioavailability        |

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sevoflurane, follow-up studies supporting that GSTP1 testing may have clinical utility for guiding sevoflurane dose selection have been lacking. Polymorphisms in the melanocortin 1 receptor (MC1R) gene, however, have repeatedly demonstrated associations with increased desflurane dose requirements in more than one study [3,12].

**Intravenous agents**

Important clinical pharmacodynamic measurements associated with propofol infusion include time-to-achievement of bispectral index <70 and time-to-achievement of eye-opening. Ihom et al. determined that polymorphisms in the receptor gene GABRE (GABRE-mRNA358G, 20118C and 20326T) were not associated with systemic clearance (p = 0.82, 0.92 and 0.60, respectively) or on time to eye opening (p = 0.70, 0.82 and 0.93, respectively) [13]. Similarly, CYP2B6 did not show any significant haplotypic association with apparent systemic clearance (p = 0.48) or time to eye opening (p = 0.55) [13]. Khan et al. reported a significant association between the UGT1A9–1887T/G variant and propofol induction dose: the -1887T/G heterozygote patients required higher induction dose (p = 0.03, without correction for multiple testing) than other patients [14].

**Neuromuscular blockade**

Polymorphisms in the genes encoding certain metabolism enzymes, transporters and receptors have demonstrated significant influence on the pharmacology of the neuromuscular blockers succinylcholine and mivacurium. Both drugs are hydrolyzed by plasma cholinesterase. Heterozygous expression of the butyrylcholinesterase variant, Asp70Gly, results in a less effective plasma butyrylcholinesterase and subsequent longer (3 to 8-fold) recovery time after succinylcholine administration [15]. Prolongation was 60-fold longer in homozygous carriers [15]. Similar findings were reported for the variant gene and prolonged mivacurium-induced muscle paralysis [16].

Mei et al. studied whether genetic polymorphisms in certain transporters and in nicotinic acetylcholine receptors had a significant effect on the clinical response to the non-depolarizing muscle relaxant rocuronium in a cohort of 200 Chinese patients. The transporters, the organic anion transporting polypeptides (e.g., SLCO1B1) and the multiple drug resistance I transporter (e.g., ABCB1), are the prominent transporter types in the liver. The SLCO1B1 transporter actively moves drugs into hepatocytes, an important determinant of drug hepatic clearance as the first step in the detoxification pathway), and the ABCB1 transporter moves drugs out (exports) of hepatocytes. Mei et al. reported that variants in ABCB1, SLCO1B1, and CHRNA1 did not affect the time of onset of rocuronium [17]. Clinical duration and recovery time of rocuronium were prolonged in patients with the ABCB1 rs1128503T and the SLCO1B1 rs2306283 AG and GG genotypes [17]. The effect of the SLCO1B1 variant has biological plausibility: transport function of the SLCO1B1 enzyme is lowered by the rs2306283 A>G variant causing decreased rate of elimination, slower decline in plasma concentration, prolonged duration of action and increased recovery time. Similarly, the effect of the ABCB1 variant has biological plausibility: decreased transport resulting from the ABCB1 rs 1128503C > T variant results in decreased rate of elimination, slower decline in plasma concentration, prolonged duration of action and increased recovery time [17].

**Narcotic analgesics**

Fentanyl, a potent narcotic commonly used during the perioperative period, is metabolized by CYP3A4/5. Patient response to fentanyl is variable, and dose selection is largely empirical. Mieda et al. reported their genome-wide association study in patients undergoing laparoscopic-assisted colectomy aimed at identification of genetic factors associated with fentanyl sensitivity (patient response). A SNP, rs2076222, in the LAMB3 region was strongly associated with postoperative opioid requirements (p<0.05). The C allele (rs2076222) was strongly associated with lower sensitivity and/or higher pain sensitivity (p<0.05) [18].

Zhang et al. examined whether CYP3A5*3 was associated with postoperative response to fentanyl. They had previously reported that the CYP3A4*1G SNP was associated with postoperative analgesic response in Chinese women undergoing gynecological surgery. They reported a trend that 24-hour postoperative fentanyl consumption was lower in CYP3A5*1/*3 and CYP3A5*3/*3 compared with CYP3A5*1/*1. However, combining CYP3A5 and CYP3A4 genotypes allowed for detection of a significant association between reduced 24-hour post-operative fentanyl consumption and CYP3A5*3 carrier status (both heterozygous and homozygous *3 carriers). They also concluded that an interaction between CYP3A5*3 and CYP3A4*1G polymorphisms significantly reduces fentanyl consumption over the 24-hour postoperative period [19].

**The perioperative period**

The primary target for acute pain control in the perioperative period is the μ opioid receptor in the central nervous system (CNS). Other targets include Na-channel blockade of neurotransmission with local anesthetics (spinal and epidural blockade; peripheral nerve blockade), inhibition of prostaglandin synthesis or prostaglandin complex formation (ibuprofen; ketorolac), κ-opioid receptor blockade (butorphanol), and inhibition of serotonin and norepinephrine reuptake (tramadol). Some agents (acetaminophen) have an unknown analgesic mechanism of action [20].

Morphine sulfate is a pure μ-opioid agonist with primary actions in the brainstem, particularly the medulla, where it promotes analgesia and depression of respiratory centers [21]. The OPRM1 gene codes for the encoding for the μ-opioid receptor. The most frequent and best described SNP in OPRM1 is OPRM1 A118G. Morphine is a substrate of the P-glycoprotein transporter ABCB1, which is an ATP-dependent efflux transporter present in the brain, as well as in the liver, kidney and gastrointestinal tract. ABCB1 is coded by the highly polymorphic ABCB1 gene, which has 38 identified SNPs. P-glycoproteins in brain capillary endothelial cells act as outward transporters for morphine across the blood–brain barrier, reducing cerebrospinal fluid (CSF) morphine concentrations. A C3435T allelic variant of ABCB1, rs1045642, reduces P-glycoprotein transporter function and results in increased CSF morphine concentrations. This variant has been associated also with significant differences in interindividual pain relief achieved by morphine [22].

Patients with opioid addiction and those on narcotics for chronic pain often have the need for surgery at some point during their lives. Management of their acute perioperative pain control can be challenging due to narcotic tolerance, decreased pain threshold, and high potential for dependency. Psychological overlay and hepatic metabolism (upregulation of cytochrome P-450 enzymes and upregulation of μ-opioid receptors) contribute to the increased need for analgesics. With drug addiction and chronic opioid use there may also be changes in the structure of the μ-opioid receptor (OPRM1) due to differential expression of mRNA in polymorphic gene variants. Zhang et al. studied the role of the genetic variant OPRM1 A118G by using it as a marker to measure allele-specific mRNA expression in OPRM1 in human autopsy brain tissues. The A118 mRNA allele was 1.5 to 2.5-fold more abundant.
than the G118 allele in 8 heterozygous samples. Transfection of a cDNA resulted in a 1.5-fold lower mRNA level only for OPRM1 G118 and more than a 10-fold lower OPRM1 protein level. Their results indicate that OPRM1 G118 is a functional variant with deleterious effects on both mRNA and protein yield, and the functional relevance of this SNP in the context of addiction warrants further investigation (e.g., clinical association studies) [23]. Ideally these studies should include highly phenotyped populations of homogenous ethnic admixture with identified associations adjusted for patient demographics, risk factors and medications [24]. Many genetic association studies have examined the impact of SNPs in various target genes related to pain sensitivity and/or analgesic dosing requirements. However, original findings have not always been replicated in other cohorts. Deficiencies in study designs have included small sample size, inappropriate statistical methods, and inadequate attention to the possibility that between-study differences in environmental factors may alter pain phenotypes through epigenetic mechanisms [25]. Many reports have been limited to case-control studies and case reports. A false positive association between SNPs and phenotype is not uncommon. Basic research should focus heavily on identification of biologically plausible SNP-phenotype interactions [26]. Prospective studies are needed to further elucidate true clinical implications that may eventually warrant pharmacogenomics-guided prescribing.

Boswell et al. studied the role of the A118G SNP of OPRM1 and variability in analgesic response due to modification of receptor binding or signal transduction. After receiving spinal anesthesia (bupivacaine/morphine) or spinal anesthesia (only bupivacaine) and parenteral morphine for 24 hours post-surgery, patients received also hydrocodone/acetaminophen. Venous blood samples were obtained on post-operative Day 3 for OPRM1 A118G genotyping and serum opioid concentration measurements. Eighty-two percent of the patients were homozygous for OPRM1 118A (AA), and 17% carried the G allele (AG/GG). Pain relief was significantly associated with total hydrocodone dose in the AA group but not in the AG/GG group. Neither group demonstrated association with serum hydrocodone and analgesia. The association, rather, was for hydromorphone, a metabolite of hydrocodone, in the AA group but not in the AG/GG group. Side effects were significantly more frequent in the AG/GG group compared to the AA group [27].

Codeine, a prodrug, is bioactivated to morphine via O-demethylation and morphine is converted to morphine-6-glucuronide by the hepatic cytochrome P450 2D6 (CYP2D6). Both morphine and morphine-6-glucuronide possess analgesic properties. The conversion of codeine to morphine accounts for only 5-10% of its dose. Methadone is a synthetic μ-opioid agonist with a half-life of 8-59 hours [31]. The principle cytochrome P-450 metabolizing enzyme for the clinical elimination of methadone is hepatic CYP2B6, and CYP2B6 is highly polymorphic. Altering the metabolism and clearance of methadone, CYP2B6 polymorphisms effect plasma concentration of methadone, and the effect is greater for oral compared with parenteral route of delivery [32].

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Non-steroidal anti-inflammatory drugs (NSAIDS) are non-opioid analgesics additives often used to treat acute post-operative pain. Their clinical utility is often limited by interindividual variability of cardiovascular, gastrointestinal and renal side effects. Hepatic CYP2C9 polymorphisms may play a significant role in NSAID efficacy and toxicity. PMs (e.g., CYP2C9*3/*3) should therefore start at one-half the lowest recommended dose [5]. Prostaglandin-endoperoxide synthase 1 and 2 (PTGS1 and PTGS2) encode cyclooxygenase 1 and 2 (COX-1 and COX-2), and genetic variation in either can cause altered pharmacodynamic responses to NSAIDs [23].

The descending modulation of pain in the CNS is mediated by dopamine, epinephrine and norepinephrine. These catecholamines are metabolized by Catechol-O-Methyl-Transferase (COMT). A common polymorphism in COMT at amino acid position 158 (Val158Met) has been shown to impact analgesic response to NSAIDs. Webster et
choices throughout the perioperative period. Allowing the anesthesiologist to individualize drug and optimal dosing genotyping would be performed during the pre-operative workup significantly impact drug efficacy and drug adverse events. Ideally, perioperative patient would provide knowledge of genotypes that often reduce adverse drug reactions and increase efficacy. A future as well as a cost to the patient (financial, quality of life, morbidity and mortality). Implementation of pharmacogenomic testing can often reduce adverse drug reactions and increase efficacy. A future direction for pharmacogenomic testing in anesthesiology and in the perioperative patient would provide knowledge of genotypes that significantly impact drug efficacy and drug adverse events. Ideally, genotyping would be performed during the pre-operative workup allowing the anesthesiologist to individualize drug and optimal dosing choices throughout the perioperative period.

Conclusion
Pharmacogenomics may have important implications for medication and dose selection in each phase of the perioperative period: preoperative, intraoperative and postoperative. The perioperative period provides great diversity and density of pharmacotherapy. Each patient has a unique genetic identity based on inherited gene products that interact with drugs – metabolizing enzymes, drug transporters and drug receptors. There is significant interpatient variability in drug response due to this "pharmacological identity", and variability may translate into increased risk of adverse effects or lack of efficacy at "standard, safe, effective" dose. Empiric prescribing is not ideal. The patient is a unique individual, and his/her genetics and environmental experiences give rise to individualized pharmacokinetics and pharmacodynamics.

Lack of efficacy and adverse drugs events have a cost to society as well as a cost to the patient (financial, quality of life, morbidity and mortality). Implementation of pharmacogenomic testing can often reduce adverse drug reactions and increase efficacy. A future direction for pharmacogenomic testing in anesthesiology and in the perioperative patient would provide knowledge of genotypes that significantly impact drug efficacy and drug adverse events. Ideally, genotyping would be performed during the pre-operative workup allowing the anesthesiologist to individualize drug and optimal dosing choices throughout the perioperative period.

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