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Genetics and implications in perioperative analgesia

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The wide range of patient responses to surgical pain, opioids, and anesthetic agents has puzzled anesthesiologists for many years. Much of the variation has been attributed to differences in patient size, technique, or prior drug use. However, recent genetic testing has revealed exciting clues into the basis for these variances, allowing us to start to predict which patients may have difficulties and start to select medications more rationally. In this manuscript, we discuss genetics and pain perception, genetic predisposition to pain, drug metabolism interactions, ethnogenetics, opioid metabolism, opioid receptors, genetic-related peri-anesthetic toxicity, as well as a clinical approach and a discussion regarding the future of genetic testing and anesthesia.

Introduction

Every physician, and especially those involved in providing anesthesia, is aware of the range of responses to anesthesia, surgery, and postoperative pain. Differences in the degree of pain stimulation (a fractured femur compared to a splinter in the toe) and pain sensitivity, weight and age differences, prior opioid use and tolerance, as well as the differences in bioavailability of various opioid formulations have been cited as causes for the wide variability in analgesia seen with opioids. However, even measuring blood levels of opioids does not predict analgesia [1]. The minimum effective blood level of opioids can vary widely [2]. Just as there are differences in hair and eye color, there are differences in response to pain and to analgesic medications. For instance, up to two-thirds of the variability in the interindividual response to morphine has been attributed to

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genetics [3]. We are beginning to recognize that, as is seen in much of medicine in the 21st century, genetics may explain the variability of responses and predict more effective (or less dangerous) medication choices.

Genetic primer

When discussing genetic influences, it is important to understand several terms. *Genotype* is an organism's full hereditary information; *phenotype* describes an organism's actual observed properties, such as eye color or behavior. Variations in the structure of genes are termed *genetic polymorphism*, which occurs when there are structural changes in the gene (such as deletions, duplications, and translocations). Each of these gene changes is called an *allele* of the original or *wild-type* gene; having two copies of the same allele is called a *homozygous genotype*, while having any combination of two different alleles is called a *heterozygous genotype*. The most common gene change is a *single nucleotide polymorphism* (SNP). There are several ways to name these SNPs; the easiest to understand uses the abbreviation of the gene (2D6) followed by an asterisk (2D6*) and then a number (*2D6*1*, *2D6*3*), where 1 represents the most common allele and the letter represents additional structural changes (*2D6*2A*, *2D6*2B*). However, some genes are identified by the amino acid change itself; the serotonin gene allele *5HTR* has an amino acid at position 1438 that can have an adenine or a guanine and is identified as *1438A/G*, *1438A/A*, or *1438G/G*, depending on the homozygous or heterozygous status. *Haplotype*, on the other hand, is a combination of alleles located at adjacent locations (loci) that tend to get inherited together.

Genetics and pain perception

Genetic versus environmental factors

In the classic "nature versus nurture" scenario, investigators use twin pairs, both identical and fraternal and reared together or apart, to evaluate the heritability of a feature or a condition. Several twin studies have looked at pain conditions and concluded that migraines have a 39–58% genetic contribution [4–6], low back pain a 21–67% genetic contribution [7–9], and menstrual pain a 55% contribution [10]. A recent twin study [11] looked at the response to alfentanil versus saline and found that there was significant heritability for respiratory depression (30%), nausea (59%), and drug disliking (36%), with significant familial effects detected for sedation (29%), pruritus (38%), dizziness (32%), and drug liking (26%). In general, significant familial effects account for 24–32% of the observed variance detected for heat and cold pressor pain thresholds and opioid-mediated elevation in cold pressor pain tolerance.

Genetic hypoanalgesia

There are several well-studied hereditary disorders of insensitivity to pain, including "hereditary insensitivity to pain with anhydrosis" [12], familial dysautonomia (Riley–Day syndrome) [13], Lesch–Nyhan syndrome [14,15], de Lange syndrome [16], and Tourette's syndrome [17]. More than 200 candidate genes have been identified that may be involved in pain processing.

Genetic predisposition to pain

Allele-based association studies are expected to shed light on the medical mystery of why pain persists in some patients but not others, despite seemingly identical traumas. In other words, why do some diabetic patients develop only numbness at the manifestation of their peripheral neuropathy while others with the same blood sugar fluctuations develop a painful peripheral neuropathy? Why do only some shingles patients develop postherpetic neuralgia? Why do not all of the persons in a car accident develop the same whiplash pain?

Part of the issue may be "piss poor protoplasm," a term that many young doctors learned as part of their medical training. In a study of Chinese volunteers, investigators found that an allele (*COL9A2*), which codes for a chain of collagen, was associated with a fourfold increase in the risk of developing

annular tears in people aged 30–39, and a 2.4-fold increase in the risk of developing a degenerative disc disease and end-plate herniations in people aged 40–49 years [18].

Genetics and analgesics

Drug interactions

There are three major types of enzyme interactions. A *substrate* is any medication metabolized by that enzyme. An *inhibitor* is a medication that slows the metabolism of another medication, which may result in excessively high blood levels, extended effect, and related toxicity; however, if this is a drug that has to be activated (a *prodrug*), there may be decreased effect. An *inducer* is a medication that boosts the metabolism of another medication, which may result in accelerated breakdown, increase clearance, shortened duration, subtherapeutic levels, or withdrawal; it may also cause increased activity in a prodrug.

An *adverse drug event* (ADE) or *adverse drug reaction* (ADR) is an injury that results from drug use. *Drug–drug interactions* (DDIs) are a major cause of ADRs, which can be divided into two groups: pharmacodynamic and pharmacokinetic. *Pharmacokinetic* interactions occur when one drug impacts the absorption, distribution, metabolism, or excretion of another drug, resulting in increased or decreased concentrations of one or both of the drugs. Genetics can control the metabolism as well as the transport of analgesics. *Pharmacodynamic* interactions occur when one drug modulates another drug's intended effect in the body, and these effects can be additive, antagonistic, or synergic. Pain sensitivity, opioid receptor sensitivity, and signal transduction would be examples.

Cytochrome P450 enzymes (CYP450)

The CYP450 enzyme system is a heme-containing, microsomal drug metabolism superfamily involved in the biotransformation of endogenous compounds, chemicals, toxins, and medications, and therefore are a major cause of pharmacokinetic DDIs [19–21]. There have been 57 enzymes identified in humans and they are divided into family, subfamily, isoenzymes, and allele variants [22]. Metabolism of most currently used drugs occurs by about seven clinically relevant enzymes: *CYP1A2*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP2E1*, and *CYP3A4*, all of which have different (but partially overlapping) catalytic activities. Many of the medicines commonly used are substrates (Table 1), inhibitors (Table 2), or inducers (Table 3) of medicines used in pain treatments. Phillips and colleagues identified 27 drugs

Table 1
Common substrates of CYP enzymes. Modified from Indiana University Drug Interaction Table [http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx] and Genelex web site [Oesterheld J. Cytochrome P-450 (CYP) Metabolism Reference Table. http://youscript.com/healthcare-professionals/why-youscript/cytochrome-p450-drug-table/] among others.

1A2	**2B6**	**2C19**	**2D6**	**3A4**
Amitriptyline	Bupropion	Barbiturates	Codeine	Alprazolam
Nabumetone	Methadone	Topiramate	Tramadol	Midazolam
Desipramine	Ketamine	Diazepam	Meperidine	Cyclosporine
Tizanidine	Testosterone	Amitriptyline	Oxycodone	Sildenafil
Imipramine		Imipramine	Hydrocodone	Indinavir
Acetaminophen	**2C9**	Clomipramine	Dextromethorphan	Verapamil
Cyclobenzaprine	Valproic acid	Sertraline	Amitriptyline	Atorvastatin
Clozapine	Piroxicam	Citalopram	Nortriptyline	Lovastatin
Fluvoxamine	Celecoxib	Phenytoin	Doxepin	Digoxin
Theophylline	Ibuprofen	Carisoprodol	Tamoxifen	Amiodarone
Melatonin	Warfarin	Clopidogrel	Amphetamines	Methadone
Duloxetine			Duloxetine	Erythromycin
Caffeine			Metoclopramide	Trazodone
Lidocaine			Propranolol	Fentanyl
Warfarin			Venlafaxine	Buprenorphine
Methadone				

Table 2
Common inducers of CYP enzymes. Modified from Indiana University Drug Interaction Table [http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx] and Genelex web site [Oesterheld J. Cytochrome P-450 (CYP) Metabolism Reference Table. http://youscript.com/healthcare-professionals/why-youscript/cytochrome-p450-drug-table/] among others.

1A2	2C9	2C19	2D6	3A4
Carbamazepine	Rifampin	Carbamazepine	Carbamazepine	Carbamazepine
Griseofulvin	Ritonavir	Rifampin	Phenobarbital	Phenytoin
Lansoprazole	Barbiturates	Ginko	Phenytoin	Nevirapine
Omeprazole	St. John's Wort		Rifampin	Modafinil
Ritonavir			Dexamethasone	Topiramate
Tobacco				Butalbital
St. John's Wort				St. John's Wort

frequently cited in adverse drug studies; 50% are metabolized by at least one CYP enzyme with a known poor metabolism allele [23].

Types of metabolizers

Patients can be classified by how effectively they metabolize a medication, which is based on how many copies of normal or abnormal alleles they inherited. A *normal metabolizer* (NM) (also called *extensive metabolizer* or EM) carries two active "wild-type" alleles and they respond typically when dosed at a standard dose. An *intermediate metabolizer* (IM) has one normal and one reduced allele or two partially deficient alleles. A *poor metabolizer* (PM) has two mutant alleles leading to a very limited or complete loss of activity, while the rapid metabolizer (RM) has one active and one increased activity allele and the *ultrarapid metabolizer* (UM) has multiple copies of functional alleles, leading to excess activity.

Ethnogenetics

There is an ethnic distribution of this polymorphism. Approximately 7–10% of Caucasians are *CYP2D6* deficient (PM), but only 1–2% of Asians and 2–4% of African-Americans are poor metabolizers [24], while approximately 30% of Asians and African-Americans have intermediate metabolism of *CYP2D6*. On the other hand, approximately 29% of Ethiopians, 10% of southern Europeans, and 1–2% of northern Europeans are ultra metabolizers (UMs) [25] (Table 4).

Table 3
Common inhibitors of CYP enzymes. Modified from Indiana University Drug Interaction Table [http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx] and Genelex web site [Oesterheld J. Cytochrome P-450 (CYP) Metabolism Reference Table. http://youscript.com/healthcare-professionals/why-youscript/cytochrome-p450-drug-table/] among others.

1A2	2C9	2C19	2D6	3A4
Fluvoxamine	Fluvoxamine	Fluoxetine	Duloxetine	Ketoconazole
Ciprofloxacin	Paroxetine	Fluvoxamine	Cimetidine	Erythromycin
Mexiletine	Amiodarone	Paroxetine	Sertraline	Mifepristone
Verapamil	Modafinil	Topiramate	Fluoxetine	Nefazodone
Caffeine	Tamoxifen	Modafinil	Haloperidol	Grapefruit juice
Grapefruit juice		Birth control pill	Methadone	Indinavir
			Paroxetine	Ritonavir
			Quinidine	Verapamil
			Celecoxib	Diltiazem
			Bupropion	
			Ritonavir	
			Amiodarone	
			Metoclopramide	
			Chlorpromazine	
			Ropivacaine	

Table 4
Ethnic distribution of CYP2D6 activity (multiple sources).

Ethnic group	*CYP2D6 PM*	*CYP2D6 IM*	*CYP2D6 UM*
Caucasians	7–10%		
Asians	1–2%	30%	
African-American	2–4%	30%	
Ethiopian			29%
Southern European			10%
Northern European			1–2%

Drug–gene interactions

Although usually not thought of as a drug interaction, variations in CYP genetics can change the concentrations of drugs that are principally metabolized by that particular CYP and can cause ADRs. This interaction has been called a *drug–gene interaction* (DGI) [26]. It is likely that DGIs are both common and significant since *CYP2D6*, *CYP2C19*, and *CYP2C9* are highly polymorphic and they are involved in approximately 40% of CYP-mediated drug metabolism [21]. For instance, tamoxifen must be metabolized via *CYP2D6* to endoxifen to be effective; a PM might therefore be at risk for failure of breast cancer treatment because of inadequate transformation to the active drug [27,28]. And, as we will see shortly, *CYP2D6* activity can have substantial influence on the opioids that are commonly used in pain management.

OTC and food interactions

There are also multiple potential interactions between herbs, supplements, or foods and prescription medications. For instance, intestinal *CYP3A4* concentration can be decreased by 47% within 4 h of grapefruit consumption, decreasing the absorption of many medicines, including methadone [29]. St. John's wort, commonly taken for depression, induces *CYP3A4* and *CYP2C19* enzymes. The induction of *CYP2C19* "enormously" decreases the blood levels of omeprazole [30]. St. John's wort can also decrease verapamil, midazolam, statins, methadone, digoxin, and HIV medication levels (via *CYP3A4* induction) [31] as well as potentially causing a serotonin syndrome with selective serotonin reuptake inhibitor (SSRI).

Smoking and medication

Smoking is a potent inducer of *CYP1A2*, leading to decreased caffeine levels (which may be the cause of the increased agitation seen with smoking cessation, as caffeine levels increase when the induction stops). Since methadone is also metabolized by *CYP1A2*, a smoker stabilized on methadone can have dangerous increases in methadone levels with smoking cessation [32,33]. In a study comparing smokers to nonsmokers, the smokers had higher pain scores, and took larger doses of hydrocodone, but had significantly lower serum levels of hydrocodone [34].

Drug–drug–gene interaction

A drug–drug–gene interaction (DDGI) represents an interaction derived from the superimposition of a DDI on a DGI. The term DDGI was recently coined by Kisor et al. to describe one example of how this interaction can arise [35]. They cite a case in which the concentration of a substrate drug increases when a CYP IM individual is converted to a CYP PM by adding a second drug that is a potent CYP inhibitor. This type of DDGI is also known as *phenoconversion* since the concentration of the substrate drug will be increased both by the CYP polymorphism and by the CYP inhibitor. From the genetic point of view, the individual's phenotype has been converted from a *CYP2D6* IM into a *CYP2D6* PM, hence the term phenoconversion.

Opioid metabolism

CYP2D6 and opioids

CYP2D6 is the metabolic gene associated with the metabolism of many of our opioids. There are currently at least 80 identified *CYP2D6* alleles [36], which result in the potential for enzymatic activity anywhere from 1% to 200% of the wild-type allele.

- *Codeine* is an inactive compound (a prodrug), metabolized by *CYP2D6* into its active form *morphine*. It has only a weak affinity for the mu receptor, 300 times less than morphine [37]. Therefore, *CYP2D6* PM patients and patients taking *CYP2D6* inhibitors (see Table 3) who are given acetaminophen with codeine are really being given only acetaminophen, while UM patients may have dangerously high levels of morphine after standard doses [38].
- *Tramadol* is metabolized by *CYP2D6* to its M1 metabolite, which is at least six times more potent than the parent compound [39].
- *Hydrocodone* displays weak binding capacity for the mu receptor, but the *CYP2D6* enzyme demethylates it into *hydromorphone*, which has much stronger mu binding than hydrocodone [40]. Otton et al. [41] found that subjects identified as EM reported more "good opiate effects" and fewer "bad opiate effects" than PM or EM patients pretreated with quinidine (a potent *CYP2D6* inhibitor). They concluded that the activity of *CYP2D6* may limit the abuse liability of hydrocodone. A study looking at 25,200 urine samples from patients taking only hydrocodone showed a 60-fold variability in hydrocodone/hydromorphone ratios. They identified 0.6% UM and 4% PM, with a 134-fold between-subject variability [42].
- *Oxycodone* is metabolized by *CYP3A4* to noroxycodone (which has $<$1% of the analgesia potency of oxycodone) and by *CYP2D6* to *oxymorphone*. Oxycodone is an analgesic, not a prodrug; however, oxymorphone is an active metabolite of oxycodone and may have significant impact on analgesia. In a study of experimental pain in volunteers genotyped for *CYP2D6*, the PM patients had a 2–20-fold decrease in analgesia [43]. Because oxycodone is dependent on the *CYP2D6* pathway for clearance, it is possible that toxicity and overdose can occur with *CYP2D6* inhibitors [44].

Yang et al. [45] showed that 71% of a group of postoperative patients with acute severe pain were PM for *CYP2D6*, compared to other metabolizers. They also found that PMs of *CYP2D6* who were smokers had more pain than the nonsmokers. UMs of *CYP2D6* required less morphine in the postoperative period than did any other CYP metabolizer group [46]. In addition, a wide variety of medications, including paroxetine and fluoxetine, are potent *CYP2D6* inhibitors. In fact, in psychiatry, 52% of the psychiatric and 62% antidepressant or antipsychotic drugs are metabolized by *CYP2D6* [47]. A prospective 1-year clinical study of 100 psychiatric inpatients suggested a trend toward longer hospital stays and higher treatment costs for UMs and PMs of *CYP2D6* [48].

CYP3A4 and opioids

CYP3A4 is also involved in opioid metabolism. *Fentanyl* and *buprenorphine* are excreted via *CYP3A4*, and blood levels would be expected to rise in PM patients or those receiving *CYP3A4* inhibitors [49]. *Methadone* has been widely reported to be metabolized by *CYP3A4* [50,51], though some evidence suggests that it is primarily metabolized by *CYP2B6* [52], and patients who are homozygous for the variant *CYP3B6*6* gene required lower doses of methadone than the heterozyotes or noncarriers [53].

CYP2B6

As noted above, there is new evidence that methadone may be primarily metabolized by *CYP2B6*. In addition, plasma levels of propofol metabolites show a high coefficient of variability; women have 1.9-fold higher *CYP2B6* liver levels and 2.1-fold higher levels of propofol metabolites, suggesting a relationship [54].

Opioid receptors

Mu opioid receptor

Genetic variations in the mu opioid receptor *OPRM1* have been reported to relate to the variations in morphine requirement after lower abdominal surgery. The frequency of the variant G allele varies from 10% to 48% depending on the population studied. Liu and Wang reported a prevalence of 31.3% of the AA (wild-type) genotype, 58.3% of the AG genotype, and 10.4% of the GG genotype [55]. Studies show that patients carrying the GG (homozygous variant) genotype require much higher opioid doses to achieve pain relief [56]. *OPRM1* AA patients required an average dose of 112 mg morphine/24 h, AG patients required 132 mg morphine/24 h, and GG patients required 216 mg morphine/24 h [57].

Kappa opioid receptor

The gene *OPRK1* encodes the kappa opioid receptor. Although kappa agonists such as buprenorphine can provide pain relief, binding of dynorphins to the kappa receptor has been shown to produce aversive states, which may prevent the development of opioid use reinforcement. The *36G>T* alleles are also associated with sex-specific postoperative and chronic pain [58]. The kappa receptor mediates stress response and stress increases drug craving and relapse risk. Variations in the genes encoding the kappa opioid receptor are associated with the risk for alcohol dependence [59], opioid addiction [60,61], and schizophrenia [62].

Other genetic issues

Uridine diphosphate glucuronosyltransferase

Uridine diphosphate glucuronosyltransferase (UGT) is involved in the metabolism of many drugs (such as morphine and acetaminophen) as well as the biotransformation of important endogenous substrates (e.g. bilirubin, ethinyl estradiol) [63]. *UGT2B7* metabolizes morphine into two different compounds—morphine-6-gluceronide (M6G), which is analgesic, and morphine-3-gluceronide (M3G), which actually causes pain and may account for some of the opioid-induced hyperalgesia (OIH) seen with high levels of morphine [64]. *UGT2B7* inhibition can influence the levels of M3G compared to M6G. Tamoxifen, diclofenac, naloxone, carbamazepine, tricyclic antidepressants (TCA), and benzodiazepines are all inhibitors of *UGT2B7* [65], potentially leading to opioid hyperalgesia (another reason not to use benzodiazepines).

Catechol-O-methyltransferase

Catechol-O-methyltransferase (COMT) metabolizes catecholamines and is important for dopaminergic and adrenergic/noradrenergic/serotonin neurotransmission. It has been estimated that approximately 10% of the variability in pain sensitivity is related to COMT SNPs [57]. Polymorphism at amino acid position 158 (*Val158Met*) has been shown to impact human pain response. Rakvag et al. studied the efficacy of morphine on cancer pain and noted that patients who were homozygous for the Val/Val genotype (which represents about 22% of Europeans) had lower pain sensitivities [66]. Hispanics have the highest proportion of Met/Met genotypes (and are therefore likely to have the greatest sensitivity to opioids), while African-Americans have the highest Val/Val, and therefore would be expected to require more opioid medication [67].

Diatchenko and colleagues [68] studied COMT in patients with myogenous temporomandibular joint disorder (TMD) (a condition that affects 5–15% of the adult population) [69]. They identified three major haplotypes: LPS, which is associated with low pain sensitivity, APS, which is associated with higher sensitivity, and HPS, which is associated with the highest pain sensitivity. The presence of even a single LPS haplotype diminishes, by as much as 2.3 times, the risk of developing TMD; on the other hand, 29% of the women with TMD who were studied had APS and/or HPS haplotypes, so that about one-third of the new patients with TMD could be attributed to these COMT haplotypes.

Low COMT, which results in elevated circulating catecholamines, has been associated with increased pain sensitivity (via beta2 adrenergic receptors), as well as increased depression, anxiety, and hypertension. The beta2 receptor is controlled by the *ADRB2* gene, and three different haplotypes have been implicated in the "emotional personality" seen in some pain patients [70].

GABA

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the human brain, which plays a role in regulating neuronal excitability; GABA is also directly responsible for the regulation of muscle tone. Drugs that act as GABA agonists or increase the amount of GABA typically have muscle relaxing, anti-anxiety, and anti-convulsant actions. All general anesthetics positively modulate GABA-A receptor-mediated inhibitory transmission. Changes in the GABA-A receptor subunit may account for increased anesthetic requirements [71], possibly contributing to the variable response to inhaled anesthetics.

ABCB1

Mutations of the *adenosine triphosphate (ATP)-binding cassette subfamily B* (*ABCB1*) gene (SNP *1236C>T*), an opioid transport gene, have been associated with higher methadone doses (>150 mg/d) in methadone-maintained heroin addicts [72]. There may be differences between male and female patients at this gene as well; men with the TT allele had higher beta-endorphin levels than men who had the more common CC allele, while the opposite was true in women [73], and women had a higher risk of postoperative c-section pain 3 months after surgery with the TT allele [74].

MC1R

The *Melanocortin-1 receptor* (*MC1R*) gene variants show evidence of potential for targeted analgesia based on sex. There is evidence that women, more than men, respond to kappa-induced analgesia, which is mediated by the *MC1R* [75]. Inactive *MC1R* variants have been associated with increased opioid analgesia from morphine-6-glucuronide and, in women only, of kappa opioid agonists [76]. Women carrying two nonfunctional alleles displayed greater pentazocine (kappa agonist) analgesic response. Variations in *minimum alveolar concentrations* (MAC) of volatile anesthetics and subcutaneous lidocaine efficacy have been attributed in part to *MC1R* variants [77]. Interestingly, 75% of individuals with red hair and pale skin phenotypes carry two or more inactive variants of the *MC1R*, perhaps giving support to concerns regarding increased anesthetic risks with redheads [75,78].

Genetic-related peri-anesthetic toxicity

Enzymes and transport proteins, which are genetically encoded, influence the absorption, distribution, metabolism, and excretion of medications. PM may have a decreased drug clearance leading to accumulation, or decreased activation of a prodrug leading to inadequate response. UM may fail therapy because of rapid excretion, leading to subtherapeutic blood level; however, UM can over metabolize a prodrug, leading to toxic level.

H_2 receptor agonists and proton-pump inhibitors

Anesthesiologists may choose to pretreat the patient at risk for aspiration with medications to decrease gastrointestinal (GI) acidity. In vitro studies have shown that cimetidine and famotidine are very potent inhibitors of CYP3A4, leading to decreased inactivation of oxycodone to noroxycodone, and methadone to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), potentially resulting in opioid toxicity; however, nizatidine and ranitidine did not. Omeprazole, esomeprazole, and pantoprazole also showed significant CYP3A4 inhibition, while lansoprazole selectively inhibited the CYP2D6 formation of oxymorphone from oxycodone [79].

Benzodiazepines

Midazolam is primarily metabolized by CYP3A4 and CYP3A5. Enzyme induction was found to be about 50% greater with *CYP3A5*3* homozygous genotype [77]. Diazepam is metabolized to temazepam (which is active) via CYP3A4 and to nordiazepam via CYP3A4 and CYP2C19; nordiazepam is further metabolized to oxazepam (active) via CYP3A4. Significant increases in plasma levels and half-life of diazepam have been noted in patients with one copy of the m1 variant of CYP2C19, with even higher levels if they are homozygous [80].

5HT3 antagonists

Patients who are ultrarapid CYP2D6 metabolizers (UM) have increased metabolic turnover of 5HT3 antagonists like ondansetron, resulting in increased postoperative nausea and vomiting (PONV). In a study of 250 females undergoing general anesthesia, the incidence of postoperative vomiting in UM subjects was 45.5%, significantly increased compared with PM, IM, and EM subjects (8.3%, 16.7%, and 14.7%, respectively). The authors recommended that patients who are ultrametabolizers of CYP2D6 might benefit from treatment with antiemetics that are not metabolized by CYP2D6 [81].

NSAID metabolism

Genetics also may influence the metabolism (and therefore the effectiveness) of standard NSAIDs and cox-2 inhibitors [82]. For instance, ibuprofen's clearance varies with the CYP2C9*3 genotype [77].

Warfarin

Bleeding abnormalities can cause dangerous conditions for the anesthesiologist/surgeon as well as the interventional pain physician. *CYP2C9* and the *vitamin K epoxide reductase subunit 1* (*VKORC1*) genes affect warfarin dose requirements, leading to potentially life threatening bleeding or coagulation. Warfarin is a racemic mixture of R- and S-structures (*enantiomers*), with the S-enantiomer accounting for the majority of the anticoagulation effect. *CYP2C9* genetically controls the clearance of the S-enantiomer and approximately 40% of patients have poor activity of the *CYP2C9* gene [83] (leading to delays in achieving steady state); international normalized ratio (INR) measurements may therefore be inaccurate. Genetic testing of *VKORC1* can guide the selection of a target S-enantiomer plasma level [84]; combining the two genetic tests can potentially improve anticoagulation control [85].

Local anesthetic resistance

This author described a local anesthetic skin test, utilizing subcutaneous wheals of lidocaine, bupivacaine, and mepivacaine [86]. Of almost 1200 patients interviewed, 250 patients noted a history of difficulty getting numb. Ninety patients (7.5% of the total, but 36% of those with a history of local anesthetic difficulties) were found to be numb only to mepivacaine, and an additional 43 patients (3.8% of the total) were numb only to lidocaine. In this author's practice, there appeared to be a genetic component to this resistance; one parent might be numb to all local anesthetic while the other parent would get numb only mepivacaine, with several of the children found to be positive only to mepivacaine. Subcutaneous local anesthetic resistance has been attributed in part to melanocortin-1 receptor variants [77].

Clinical approach

A genetic basis for variations in drug response and toxicity has been recognized for nearly 50 years and an FDA-approved genetic test for *CYP2D6* has been available since 2006; but the ease and cost of genetic testing has only recently allowed for routine genetic testing. The patient with a personal or family history of sensitivity or resistance to medications such as opioids is an excellent candidate for CYP testing, and there are several genetic as well as urine toxicology/genetic testing companies in the

USA (see below). Unfortunately, genetic testing takes about a week to perform, so it is difficult to obtain this information on an emergency basis. A careful history can give possible clues about the CYP status; for instance, a history of poor or limited analgesia from hydrocodone or oxycodone suggests a *CYP2D6* deficiency.

Preoperative preemptive genetic testing may be reasonable for those patients with multiple medical problems or major planned surgery. Arrays of hundreds of clinically relevant pharmacogenetic tests can be completed for about the same cost as one or two single genetic tests. Thus, reduced costs of genotyping will soon change the balance to favor preemptive genetic testing, even for rare polymorphisms. Although it is a covered service for most insurance companies, including Medicare (Baltimore, MD, USA), it is usually considered a "once-in-a-lifetime" test, which could cause problems if a patient was tested with a limited array and then new tests became available. Many clinicians are unaware of the pathways necessary for drug activation or inactivation—much less the common potential drug–drug interactions.

The future

Landau and colleagues [87] at the University of Washington are reviewing a stratification strategy for cesarean patients, using a combination of mechanical temporal summation (mTS) assessment (using a von Fry filament to identify pinprick pain), diffuse noxious inhibitory control (DNIC) assessment (using a heat thermode on one forearm and placing the other hand in hot water to assess stress-induced analgesia), and genetic testing to predict (and eventually selectively preemptively treat) pain after cesarean section.

Conclusion

In the near future, pharmacogenetic testing and approaches could facilitate a personalized approach to perioperative treatment. Both opioids and anesthesia have a narrow therapeutic index and a large inter-patient variability, with inadequate pain relief at one end of the spectrum and serious side effects, such as cardiac and respiratory depression and excessive sedation, at the other end.

Practice points

- A careful history can give possible clues as to the CYP status.
- Consider seriously the patients who describe being "sensitive" or "resistant" to medications or anesthesia.
- If one opioid is not providing adequate analgesia, consider changing to another opioid not metabolized by that enzyme system.
- Carefully review the patients medication list to spot potential drug–gene interactions.
- Avoid routine use of potent *CYP2D6* and *CYP3A4* inhibitors.
- "Titrate to effect" rather than using set doses of medication.
- Regional anesthesia failures may reflect a genetic resistance to local anesthetics rather than inadequate techniques.
- Urine or oral toxicology is now routinely performed on chronic pain patients on opioid therapy; review of the quantitative opioid metabolites can give clues as to enzyme activity. For instance, a patient on oxycodone with high levels of noroxycodone but low levels of oxymorphone is likely to be *CYP2D6* deficient, though this can also be seen in a patient taking a *CYP2D6* inhibitor.
- Because these tests may be considered "once-in-a-lifetime" for insurance reimbursement and fraught with potential fraud [88], it is important that the information be accurate and relevant. Genetic testing with oral fluid or cheek swab is available through several reputable companies, including the following:

- Quest Diagnostics® (Madison, NJ, USA) (www.questdiagnostics.com) has a "Pain management" profile for *CYP2D6* and *CYP2C19*.
- Several urine toxicology companies such as Millennium Laboratories® (San Diego, CA, USA) (www.millenniumlabs.com) have added genetic testing to their profiles.
- Genelex® (Seattle, WA, USA) (www.genelex.com) tests for *CYP2D6*, *CYP2C9*, *CYP2C19*, and *VRORC1*.
- Iverson Genetics (Seattle, WA, USA) (www.iversongenetics.com) have a "basic" panel that tests *CYP2D6*, *CYP2C9*, and *CYP2C19*, as well as an "extended" panel that adds *CYP3A4*, *CYP1A2*, *VKORC1*, and *COMT*.
- Proove™ Biosciences (Irvine, CA, USA) (www.proovebio.com) has two different profiles; one for drug metabolism that tests for *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP3A5*, and *VKORC1*, while the other looks at opioid misuse risks by testing for dopamine D1 receptor (*DRD1*), dopamine D2 receptor (*DRD2*), dopamine D4 receptor (*DRD4*), dopamine transporter (*DAT1*), dopamine beta-hydroxylase (*DBH*), 5-HT2A receptor (5-*HTTLPR*), *COMT*, *GABA*, kappa opioid receptor (*OPRK1*), mu opioid receptor, (*OPRM1*), and methylene tetrahydrofolate reductase (*MTHFR*).
- 23andMe (www.23andme.com) allows consumers to obtain a full DNA evaluation for US $99.

- Even today, the number of potential drug–drug and drug–gene interactions can seem overwhelming, and that number will only grow larger. There are currently several options available, including the following:
  - Epocrates® (San Mateo, CA, USA) (www.epocrates.com) is a free smartphone/EHR software application that warns of potential single drug–drug interactions, as well as providing drug pricing, dosing, and ICD9 codes.
  - YouScript® (www.youscript.com) is an internet-based program that combines personalized genetic data with information on potential drug–drug and drug–gene interactions. When genetic data are obtained (primarily through Genelex®), the provider can enter the patients medications (or proposed medicines) and immediately see potential harmful interactions between multiple medications as well as potential safer medication substitutions.

Research agenda

- Although population studies suggest that only about 10% of patients should be poor metabolizers of *CYP2D6*, this authors pain practice sees a much higher percentage, suggesting that chronic pain may develop from inadequately treated acute pain and that high opioid use may stem from poor opioid conversion. Performing genetic testing of consecutive pain patients in multiple pain practices should reveal the true incidence of *CYP2D6* PM status.
- A double-blind controlled study using preoperative assessment of genetic status could look at two groups of patients; both groups would be genetically tested, but only one group would be genetically assessed preoperatively and treated accordingly, while the other group would be treated standardly, looking at the incidence of ADRs as well as potential economic savings.

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