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Pharmacogenetics and Obstetric Anesthesia and Analgesia

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1. Introduction

Approximately 50 years ago, pharmacogenetics emerged as a new field of medicine that may explain human drug action. Anesthesia, in particular, played a key role in these early investigations. An understanding of how an individual's genetic footprint influences drug metabolism and effectiveness may allow tailored prescriptions, improving outcomes and safety; and such concepts, which form the backbone of personalized medicine, have raised a lot of hope. The ultimate goal of pharmacogenetics research is to offer 'tailored personalized medicine' with a view to improving the efficacy of medication as well as patient safety by helping predict risks of adverse outcomes.

In this Chapter, we first present a selection of historical landmarks related to anesthesia as a catalyst for the development of pharmacogenetics, we then cite practical examples of relevant candidates genes and common polymorphisms that are known to alter the response to medication prescribed in the perioperative and peripartum period as well as clinical outcomes in the parturient. To conclude, we hope to present current views and potential exciting perspectives that may arise from the application of pharmacogenetics to the daily practice of obstetric anesthesia and pain medicine.

2. The history of pharmacogenetics related to anesthesia

Medical genetics began with the 20th century rediscovery of Gregor Mendel's original 19th century work on plant genetics [1]. In 1949, the landmark paper in *Science* by Linus Pauling and colleagues linked sickle cell anemia to a derangement in a specific protein [2], and was the first proof that a genetic change alters the structure and function of a protein and results in a human disease. This set the stage for the birth of pharmacogenetics, a field first described by Arno Motulsky in 1957 [3], named by Friedrich Vogel in 1959 [4], and established by Werner Kalow in 1962 [5]. These scientists defined pharmacogenetics as the study of the variability in drug response due to genetic variability. In the early 1950s, prolonged apnea after succinylcholine was one of the drug responses that provided a starting point from which the new field of pharmacogenetics would launch. In 1956, *The Lancet* published a paper that was the first to suggest a genetic basis for prolonged apnea after succinylcholine [6]. Werner Kalow reported soon after the occurrence of prolonged postoperative muscle relaxation

following the administration of succinylcholine for endotracheal intubation, and described how an inherited variation of drug metabolism involving the enzyme butyrylcholinesterase affects the response to succinylcholine [7]. Malignant hyperthermia after succinylcholine or inhaled volatile anaesthetics is another example of an adverse reaction important to the history of pharmacogenetics. To date, 30 causative mutations have been identified on the ryanodine receptor gene (*RYR1*) that are associated with malignant hyperthermia [8,9]. Guidelines proposed by the European Malignant Hyperthermia Group were the first to describe comprehensive genetic screening for a pharmacogenetic test in the field of anesthesia [10].

3. The pharmacogenetics research network

Since the first reports ten years ago describing initial findings from the Human Genome Project [11,12], and its completion in 2003 [13], promises that these discoveries would translate into tangible clinical tests that may change drug prescriptions have been somewhat unfulfilled. Working towards this translation, the pharmacogenetics research network has established a pharmacogenomics knowledge base (PharmGKB) with the goal to collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response, curate primary genotype and phenotype data, annotate gene variants and gene-drug-disease relationships via literature review, and summarize important pharmacogenetic genes and drug pathways (http://www.pharmgkb.org) (Figure 1).

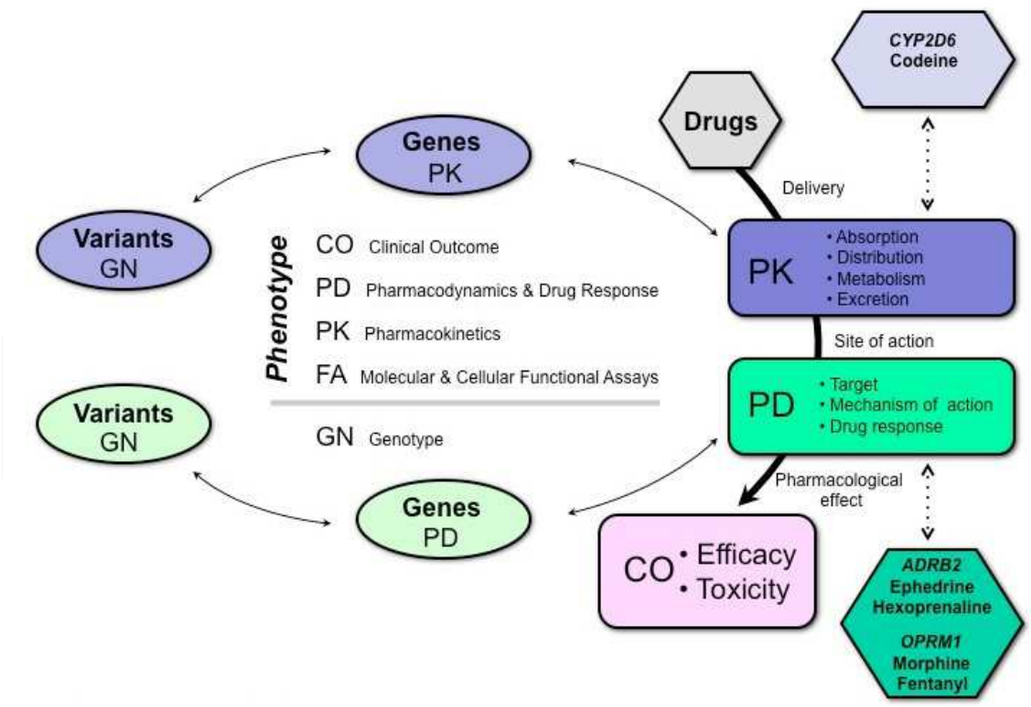

Fig. 1. Pharmacogenomics (PGx) information flow
Adapted from the NIH Pharmacogenomics Research Network – Pharmacogenomics Knowledge Base (http://www.pharmgkb.org)

4. The relevance for obstetric anesthesia and analgesia

Numerous clinical trials and reviews have surfaced in recent years describing genetic associations with clinical outcomes in the field of anesthesia, peri-operative outcomes and pain medicine [14-28]. An overview of all the drugs utilized in the peri-operative and peripartum period is beyond the scope of this review. For this Chapter, we selected several clinical examples for which gentoype/phenotype effects have been evaluated and present their relevance for clinical practice.

4.1 The β_2-adrenergic receptor genotype

Several single nucleotide polymorphisms (SNPs) that have been described in the gene encoding the human β_2-adrenergic receptor (β_2AR) affect the function of the receptor *in vitro*. Substitution of glycine for arginine at position 16 (Arg16Gly) has been associated with enhanced agonist-induced desensitization, while substitution of glutamic acid for glutamine at position 27 (Gln27Glu) has been associated with resistance to desensitization [29]. Significant differences in the response of individuals to β_2AR therapeutic manipulation related to the particular genotype/haplotype of the β_2AR have been demonstrated. The β_2AR is of particular interest for obstetric anesthesia, since drugs that are given to ensure hemodynamic stability at the time of delivery, as well as drugs to promote uterine quiescence (tocolysis) act via β_2-agonism.

4.1.1 Vasopressor requirement during spinal anesthesia for Cesarean delivery

Numerous clinical trials have evaluated the response to vasopressors to prevent and or treat hypotension during spinal anesthesia for elective Cesarean delivery [30]. For decades, ephedrine has been considered the safest and probably the sole acceptable strategy, based on classic studies in sheep that suggested deleterious effects of pure α-adrenergic agonists on uteroplacental blood flow. Ephedrine has been widely used in a variety of regimens (different bolus doses, infusions and in combination with phenylephrine) although no consensus has ever been achieved as to which of these modes of administration provides the most reliable and effective response. Ephedrine is a sympathomimetic amine, the principal mechanism of its action relies on its direct and indirect actions on the adrenergic receptor system (both an α- and β-adrenergic agonist).

A pharmacogenetic study in an obstetric population showed that the incidence and severity of maternal hypotension after spinal anesthesia for Cesarean delivery and the response to treatment is clearly affected by β_2AR genotype/haplotype [31]. Women Gly16 homozygous and carrying one or two Glu at position 27 (heterozygous or homozygous for the minor Glu27 allele) were found to require significantly *less* vasopressors (ephedrine) for treatment of hypotension during spinal anesthesia. The two haplotypes that seem to 'protect' women from requiring higher doses of ephedrine are relatively common in Caucasians, and in this study 20% of the women carried either one of these haplotypes. This pharmacogenetic effect may explain in part why the numerous studies trying to prevent or treat hypotension during spinal anesthesia for Cesarean section failed to define one single optimal strategy (fluid loading, ephedrine or phenylephrine) that would 'fit all'.

Since the incidence of spinal hypotension and vasopressor use is reduced in preeclampsia [32,33], it has been further hypothesized that haplotypes of β_2AR gene influence hemodynamics

during spinal anesthesia for Cesarean delivery in women diagnosed with severe pre-eclampsia. In a prospective case-control study, we compared the incidence of hypotension and vasopressor requirements in a predominantly African-American cohort [34]. Despite a trend towards fewer pre-eclamptic women requiring vasopressors, the total vasopressor dose was *higher* in those in whom treatment was indicated. However, no woman in the pre-eclamptic group carried the Gly16Gly/Glu27Glu haplotype, and since this was one of the two haplotypes that predicted less vasopressor requirement in normotensive women [31], this might provide an explanation for these unexpected results. Whether these findings are specific to African-American women remains to be determined in larger studies in other ethnic groups. These findings illustrate the importance of ethnicity when assessing genetic associations, and similar interactions between ethnicity and genetics have been suggested for other SNPs presented in this review (μ-OR). In the long term, if these findings are confirmed, clinical implications could involve using haplotype of β_2AR to predict spinal hypotension and to guide hemodynamic management in women with compromised cardiovascular function and altered uteroplacental perfusion.

4.1.2 Ephedrine-induced neonatal acidosis

Meanwhile, the direct effects of ephedrine on the fetus have been revisited recently [35]. Evidence that ephedrine crosses the placenta to a greater extent and undergoes less early metabolism and redistribution than phenylephrine (a direct α-adrenergic agonist) causing direct fetal metabolic acidosis has made ephedrine less desirable as a first-line treatment [36]. The proposed mechanism is that direct fetal β-adrenergic stimulation increases anaerobic glycolysis and causes a hypermetabolic state. The hypothesis that neonatal *ADRB2* genotype may directly influence the degree of neonatal acidemia in response to ephedrine given to the mother prior to delivery has just recently been explored. The most clinically relevant and intriguing finding of a study conducted in Asian woemen was that umbilical artery (UA) pH was overall higher and UA lactate was lower in neonates that were Arg16 homozygous as compared to neonates with the two other genotypes of *ADRB2* [37]. Furthermore, among babies born to mothers receiving ephedrine, ephedrine dose was associated with neonatal acidemia (decreased UA pH) only in neonates carrying a Gly16 allele, but not in neonates who were Arg16 homozygous. Since there was no significant difference in ephedrine concentration as determined by maternal and umbilical cord assays among genetic groups, any difference in metabolic markers are unlikely to have resulted from differential transplacental transfer of drug or a pharmacokinetic effect. Arg16 homozygous neonates seem to be protected from the risk of developing acidemia when exposed to ephedrine, irrespective of the dose given to the mother (Figure 2). These findings provide interesting insight on fetal acidosis and metabolic responses in neonates born to mothers who have received β-agonists (ephedrine and/or other β-stimulants prescribed for tocolysis or bronchodilation) prior to delivery.

4.1.3 Tocolytics for management of preterm labor and delivery

Stimulation of the β_2AR results in uterine smooth muscle relaxation, and thus the β_2AR has long been a therapeutic target for the treatment of preterm labor. β_2-agonist therapy, in common with virtually all tocolytics, has not been consistently successful at stopping preterm labor or prolonging pregnancy, in part due to the multifactorial nature of preterm labor, and possibly because of a wide variability in therapeutic response within the

population. The mechanisms involved in regulation of myometrial smooth muscle contraction and relaxation in preterm labor or even at term are not yet fully elucidated. Genetic variability of *ADRB2* has been evaluated in several studies in the context preterm labor and delivery. Arg16 homozygosity of *ADRB2* appears to confer a protective effect against preterm delivery while the minor allele at position 27 (Glu) increases the risk for preterm delivery [38-40]. Furthermore, a pharmacogenetic effect, with a better response to $\beta_2$agonist therapy (hexoprenaline) for tocolysis in women Arg16 homozygous with idiopathic preterm labor between 24 and 34 weeks gestation has been demonstrated [41]. This had a significant impact on neonatal outcomes, with higher birth weights and less neonatal intensive care unit (NICU) admissions for respiratory or other complications due to prematurity in babies born to mothers with that genotype. Meanwhile, a variety of genomic studies have examined the influence of genetic variants on the incidence of preterm labor [42], and proteomic studies to validate biomarkers that could identify women at risk for preterm delivery and serve as predictive tools are ongoing [43,44].

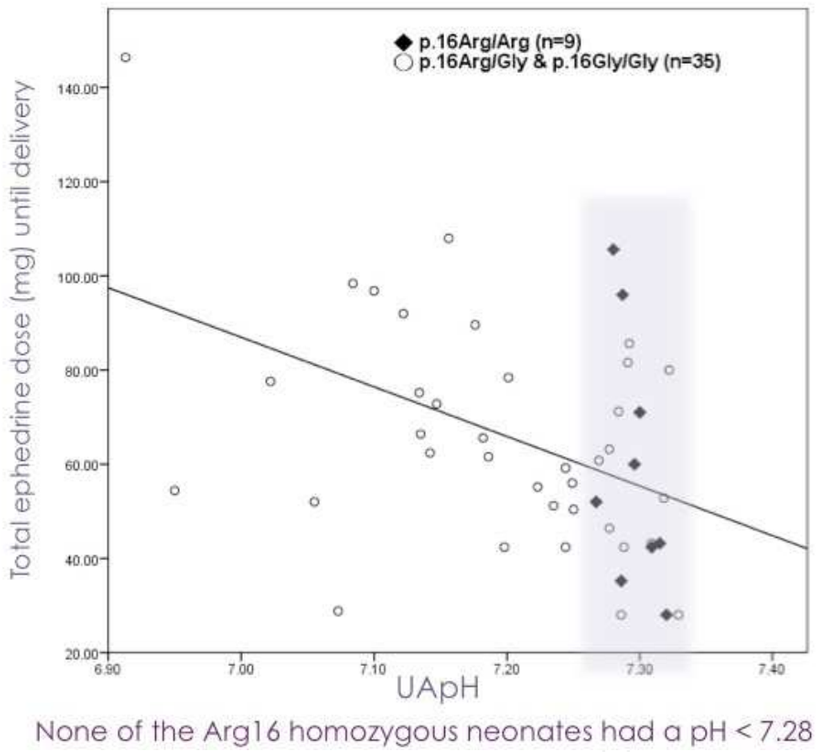

Fig. 2. Ephedrine-induced neonatal acidosis according to p.16Arg/Gly of *ADRB2*
From Landau R, Liu SK, Blouin JL, Smiley RM, Ngan Kee WD: The Effect of Maternal and Fetal β_2-Adrenoceptor and Nitric Oxide Synthase Genotype on Vasopressor Requirement and Fetal Acid-Base Status During Spinal Anesthesia for Cesarean Delivery. Anesth Analg 2011; 112: 1432-7

4.1.4 Course of labor and delivery

Recent studies have confirmed that *ADRB2* haplotype is important not only in the context of preterm onset of labor and delivery, but also on the course of labor and delivery in the term parturient. In a recent observational study in North-American women enrolled between 34-40

weeks gestation, the progress of active labor was found to be slower in women homozygous for Arg16 [45]. In women at term, the rate of cervical dilatation and duration of labor was shown to be slower in women carrying the wild-allele (Gln) at position 27 [46]. Taken together, both studies confirm that uterine quiescence during pregnancy and progression of cervical dilatation during labor are strongly associated with *ADRB2* haplotype.

5. Analgesia and pain-related candidate genes

Interindividual variability in pain perception and sensitivity to analgesic therapy with a large unpredictability in efficacy, side effects and tolerance profiles to opioids is well described. Genomic and pharmacogenetic research has considered numerous candidate genes as suitable targets for the study of pain and or analgesia [47]. Among the numerous genes and specific polymorphisms that have been considered important in opioid response, the A118G polymorphism of the μ–opioid receptor gene (*OPRM1)*, a common variant of the catechol-O-methyltransferase gene (Val158Met of *COMT*), several genetic variants of the ATP-binding cassette, sub- family B gene *(ABCB1)* and genetic variants of the cytochrome P450 family of enzymes have been extensively reviewed [22,24,48]. In addition, a genetic database of *knock-out* mice allowing the study of genetic variations in the context of specific pain phenotypes was made public [49].

Recently an extremely rare phenotype characterized by a total absence of pain perception ('congenital indifference to pain') with no associated neuropathy has been associated with the mutations in the gene SCN9A, encoding the α-subunit of the voltage-gated sodium channel, $Na_v1.7$ [50-52]. Individuals with loss-of-function mutations of the $Na_V1.7$ lack protective mechanisms that allow tissue damage detection and suffer severe injuries because they do not learn pain-avoiding behaviors. This discovery opens new directions for development of novel generations of drugs with blocking $Na_v1.7$ proprieties, which should provide more selective and safe analgesia. Meanwhile, we are still in the era of opioid therapy, and the analgesic effect may be influenced by alterations in the metabolism of analgesic drugs (cytochrome P450), variants coding for the μ-opioid receptor (μOR) as well as other targets.

5.1 Cytochrome P450 and the codeine story

Cytochrome P450 (CYP450) is a super-family of liver enzymes that catalyze phase 1 drug metabolism. The D6 isozyme of the CYP2 family is particularly affected by genetic variability and currently has 80 identified CYP2D6 alleles (http://www.cypalleles.ki.se/), resulting in a variable enzymatic activity ranging from 1 to 200%. As a result, each individual can be classified as having an "ultra-rapid metabolism" (UM), an "extensive metabolism" (EM), an "intermediate metabolism" (IM) or a "poor metabolism" (PM) and microarray technology is available to classify individuals according to their metabolic phenotype. Furthermore, it is important to note that the distribution of CYP2D6 phenotypes varies with race, since mutated alleles differ among racial and ethnic groups. Of note, approximately 7 to 10% of Caucasians have no CYP2D6 activity (poor metabolism) because of deletions, frameshift, or splice-site mutations of the gene. On the other end of the spectrum, 1 to 3% of Middle Europeans and up to 29% of Ethiopians have duplications of the *CYP2D6* gene and are classified as ultra-rapid metabolizers [53]. Ultra-rapid metabolizers have up to 50% higher plasma concentrations compared to extensive metabolizers [54].

Codeine is a pro-drug and needs to be converted into morphine to elicit its analgesic effect; therefore 'poor metabolizers' do not achieve analgesia with codeine while they may encounter side effects such as nausea and vomiting. Codeine is converted to morphine through *O*-demethylation catalyzed by CYP2D6, and accounts for 10% of codeine clearance. The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation represents approximately 80% of codeine clearance. Morphine is further metabolized into morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), and morphine and M6G have opioid activity. While codeine is undoubtedly not a wonder analgesic, it was initially prescribed because of the belief that being a weak opioid, it is safe. There was a recent FDA warning on codeine use in nursing mothers following the death of a breastfed 13-day-old neonate thought to have suffered a morphine overdose because his mother was taking codeine [55]. Toxic blood levels of morphine or its active metabolite morphine-6-glucuronide (M6G) may arise in mothers and neonates that are CYP2D6 ultra-rapid or extensive metabolizers. The infant in this case report was categorized as a CYP2D6 extensive metabolizer (extensively metabolizing the pro-drug codeine to morphine) and had a blood concentration of morphine at 70ng/mL; neonates breastfed by mothers receiving codeine typically have concentrations of 0-2.2ng/mL. The mother was categorized as a CYP2D6 ultra-metabolizer and her breast milk had a morphine concentration of 87ng/mL – the typical range being 1.9-20.5ng/mL at doses of 60mg codeine every 6 hours. Therefore, the infant had two reasons for having supranormal morphine levels. In light of these findings, it has been suggested that codeine be avoided in breastfeeding mothers with a CYP2D6 extensive or ultra-rapid metabolism genotype. Reports followed that studied the rates of codeine and morphine clearance in breastfeeding mothers and their relation to *CYP2D6* genotypes [56-58]. Other life-threatening adverse events have been reported in individuals who are CYP2D6 ultra-rapid metabolizers [59,60].

Since 2007, the FDA requires manufacturers of prescription codeine products to state in the "Precautions" section of the drug label the known risks of prescribing codeine to breastfeeding mothers [61]. An FDA-approved genetic test (AmpliChip CYP450: Roche Diagnostics, Palo Alto, CA, USA) is commercially available to test genetic variants of *CYP2D6* [62].

Overall, the level of evidence linking gene variation (*CYP2D6)* to phenotype (increased biotransformation of codeine into morphine) is strong, however there is no randomized clinical trial assessing the benefits of genetic testing prior to codeine therapy at large. Currently, the only recommendation for risk aversion is a cautionary insert to avoid codeine in breastfeeding mothers (or to apply genetic testing in mothers/neonates if codeine is prescribed).

5.2 The μ-opioid receptor genotype

The μ-opioid receptor gene (*OPRM1*) is probably the most well studied gene in the context of post-operative and labor analgesia [63]. The most common polymorphism of *OPRM1* is a single nucleotide substitution at position 118, with an adenine substitution by a guanine (A118G) reported to occur with an allelic frequency of 10–30% among Caucasians [64], a higher prevalence among Asians [65] and a lower one in African-Americans [66]. Clinicians are well aware of the large and unpredictable inter-individual variability in response to opioids [67]. A recent meta-analysis of all pain studies evaluating the impact of A118G polymorphism of *OPRM1* on the response to opioids did not identify a strong association between this polymorphism and the response to opioids [63]. It is likely that the heterogeneity of the clinical

situations (experimental pain, acute pain, labor pain, post-operative pain, chronic pain) and diversity of evaluated drugs and dosages precluded from any significant findings.

5.2.1 Response to intrathecal and systemic morphine for post-Cesarean analgesia

The response to an intrathecal solution containing morphine and fentanyl for post-Cesarean analgesia according to *OPRM1* genotype was evaluated in a North-American cohort [68]. There was no difference in the duration of spinal morphine analgesia or need for analgesic supplementation over 72 hours in women carrying the minor allele (G118). The time for first opioid rescue analgesia was on average 22 hours regardless of genotype. The incidence of nausea was similar between groups, however pruritus was less frequent during the first 24 hours in women carrying the minor allele (G118).

In two studies from Singapore in women undergoing Cesarean deliveries under spinal anesthesia (with morphine), women with the minor allele allele exhibited *increased* consumption of iv PCA morphine 24 hours post-delivery [69,70]. Women were given upon arrival in the post-anesthesia care unit (PACU) a morphine iv PCA pump and no other analgesics were prescribed. In the first study on 588 Chinese Singaporean, 24 hours post-operative morphine iv PCA consumption was lowest in women homozygous for the wild-type allele (A118) [69]. Distribution of morphine use over time (doses were recorded in 4 hour time intervals) demonstrated that most of morphine use occurred in the PACU during the first 4 hour after spinal anesthesia. It is possible that this early iv morphine use reflects lack of analgesia upon arrival in the PACU. Consequently, initial differences in iv morphine use may be due to differences in pain perception rather than impaired spinal morphine analgesia in women carrying the minor allele (G118), while differences of morphine use at 24 hour reflect either differences in intrathecal morphine duration and/or efficacy or more likely differences in iv morphine efficacy. The overall incidence of nausea was low; nonetheless it was higher in women homozygous for the wild-type allele (A118).

In the second publication, 994 women from the three main ethnic groups in Singapore were evaluated (n=617 Chinese, n=241 Malays and n=136 Indians) [70]. The authors reported a large inter-individual range with 65 women not using any morphine, 129 using only one dose, while another 122 administered 2 doses. Total iv morphine use over the first 24 hours was significantly higher in women homozygote for the minor allele (G118), and incidence of nausea was again lower in this genotypic group. In a multiple regression analysis, the most important factor contributing to morphine usage was maximum pain score, followed by ethnicity and A118G polymorphism. After correction for genotype, ethnicity was still a significant contributing factor, with Indian women reporting higher pain scores and using higher doses of iv morphine.

This apparent discrepancy between the North-American study reporting no effect of *OPRM1* A118G polymorphism on intrathecal morphine analgesia and the Singaporean results may be explained by differences in ethnicity, study design and primary outcomes. In the Singaporean studies, the intrathecal solution did not include fentanyl therefore it is possible that onset of intrathecal analgesia occurred after women arrived in the PACU. Since women were given iv PCA morphine as the initial rescue analgesic (rather than ibuprofen as in the North-American study), such study design was more likely to evaluate the effect of A118G polymorphism on iv morphine analgesic rather than intrathecal analgesic response.

Another obvious explanation may be that *OPRM1* genotype interacts differently with opioid analgesia in different ethnic groups.

Study	Subjects (N)	Study cohort	Route of administration	Measured outcomes	Observed associations
Landau (34)	223	Nulliparous women in early labor	Spinal (up-down sequential and randomized doses)	ED50 (median effective dose providing 60min of early labor analgesia)	G118 carriers requested analgesia at later stage (greater cervical dilatation) and required *less* spinal fentanyl
Wong (35)	147	Nulliparous women in early labor	Spinal (25mcg)	Duration of effective analgesia in early labor	No difference in duration of analgesia between genotypes
Fukuda (36)	280 (183 women)	Healthy Japanese, orodental surgery	• Pre-op IV test: (2mcg/kg) • Post-op iv PCA (40mcg/10min)	• Cold-pressor test before vs after iv dose • 24h post-op iv PCA consumption	• Pre-iv test: decreased sensitivity in A118 • Post-iv test: enhanced analgesic effect in A118 • Reduced fentanyl sensitivity in women vs men • No difference in VAS scores and 24h post-op fentanyl consumption between genotypes
Wu (37)	189 (97 women)	Han Chinese, laparoscopic abdominal surgery	• Pre-op IV (5mcg/kg) • Intra-op IV (1mcg/kg/30min) • Post-op IV (1mcg/kg)	• Post-op pain scores (15, 30, 45, 60min) • Time to awakening • Respiratory depression • PaCO2	• Lower pain scores in A118 (at 15 and 30min) • Longer time for awakening in A118 • Higher PaCO2 in A118 subjects
Zhang (38)	174	Han Chinese, hysterectomy	• Pre-extubation (1mcg/kg) • Post-op IV PCA (continuous 5mcg/h bolus 20mcg/5min)	• Pre-op electrical pain threshold • 24h post-op VAS scores • 24h post-op IV PCA consumption	• No difference in pain threshold • Lower electrical pain tolerance threshold in G118 carriers (gene-dose dependant effect) • No difference of initial post-op or averaged 24h pain scores • Higher consumption of post-op fentanyl in G118 homozygotes • Trend for higher incidence PONV in A118 subjects

Table 1. Recent studies evaluating *OPRM1* A118G SNP and fentanyl analgesic effect
From Landau R, Kraft JC: Pharmacogenetics in obstetric anesthesia. Curr Opin Anaesthesiol 2010; 23: 323-9

5.2.2 Response to intrathecal fentanyl for labor analgesia

Using the up-down sequential allocation model to identify differences in analgesic requirement according to *OPRM1* genotype in a Swiss cohort of nulliparous women requesting neuraxial analgesia early in labor, women carrying the minor allele (G118) required substantially lower doses of intrathecal fentanyl [71]. The ED50 (median effective dose providing labor pain relief defined on a 0-10 verbal numerical pain scale as being < 1 for at least 60 minutes) of intrathecal fentanyl given as part of a combined-spinal epidural (CSE) was 1.5 fold higher in A118 homozygotes versus that in women carrying at least one minor allele (G118). Moreover, this finding was replicated using random-dose allocation (doses ranging from 2.5-35µg), with a 2.1-fold difference between genetic groups. Of note, cervical dilatation at the time of analgesia request was significantly *less* in women homozygote for wild-type allele (A118) than in women carrying one or two minor alleles (G118). This is of interest because women received the CSE analgesic when they requested pain relief at the time they experienced painful contractions. It has previously been demonstrated that epidural analgesic requirements increase with progress of labor and cervical dilatation, therefore women carrying the variant G118 allele should have greater analgesic requirements due to the greater cervical dilatation at which they requested analgesia; our finding that these women require *less* fentanyl may actually underestimate the true effect of genotype. Since provision of optimal labor analgesia remains an ongoing challenge for obstetric anesthesiologists, the variability in ED50 according to genotype is clearly relevant from a clinical standpoint. These findings suggest genotyping may help improve the administration of labor analgesia with 30% of Caucasian women (and probably a vast majority of Asian women) potentially requiring lower doses of intrathecal fentanyl for effective analgesia during labor and delivery.

In a North-American cohort, the effect of the A118G polymorphism on the duration of intrathecal fentanyl analgesia in early labor and found no difference between genotypes [68]. The severity of nausea, pruritus or incidence of vomiting was also not different between genetic groups. While the A118G polymorphism may influence intrathecal fentanyl potency, there may be no pharmacokinetic effect altering duration of analgesic action.

Overall, the level of evidence linking gene variation to morphine or fentanyl response is moderate, probably due to the inherent complexity of studying pain (different nociceptive modalities, gender differences, limitations in extrapolating data from animal models to the response in humans, interethnic and environmental differences) in addition to the obvious polygenic nature of pain and analgesic response. The design and execution of large clinical studies analyzing multiple haplotypes simultaneously remains to be the true challenge to date. Meanwhile, a genome-wide study in the context of acute post-operative pain was published [21], the possible impact of epigenetics-based strategies for pain therapy is proposed [72] and researchers are actively working on gene therapies for chronic pain [73-75]. It will also be of interest to see the new insights and developments brought by more research on the SCN9A gene, a gene involved in channelopathies that result in the inability to experience pain, and potential targeted therapies [76].

6. The future of personalized medicine

Perhaps the most exciting yet challenging development of personalized medicine emerged with the highly sophisticated technology that now allows whole genome sequencing at a

cost that is no longer prohibitive. Therefore, extensive considerations are needed to decide how to best utilize whole genome sequencing data in clinical practice [77]. Among these challenges, patients will need to receive complex and detailed genetic counseling before they can decide whether they wish to undergo such genetic risk assessment, and effective ways to convey meaningful information to patients about the many implications of their whole-genome sequences need to be developed. In addition, interpretation should take into account the limits of the sequencing method used. Databases with easily accessible and well validated information about the associations between genomic sequences and diseases needs to be created, maintained, and frequently updated to incorporate new information about disease risks, and changes in assessment will have to be communicated to patients.

A fascinating report on the first integrated analysis of a complete human genome in the clinical context of a 40 year old male who presented with a family history of coronary artery disease and sudden death addressed these issues [78]. Disease and risk analysis of the genome for this individual study was focused on variants associated with genes for known Mendelian disease, novel mutations, variants known to have a pharmacogenetic effect, and SNPs previously associated with complex disease. The subject was found to have an increased genetic risk for myocardial infarction, type II diabetes and certain cancers. With this report, the authors developed tools to integrate the subject's clinical characteristics, his family history and the results from whole genome sequencing including 2.6 million SNPs and 752 copy number variations to assist clinical decision-making. Large-scale implementation of such sophisticated methodology will require multidisciplinary approaches that include medical and genetic professionals, ethicists and regulatory agencies.

7. Conclusions

There is no doubt that genetic variants affect drug responses to an extent that can have relevant implications beyond just the efficacy of a prescribed drug. For the clinician, and in particular for the anesthesiologist providing anesthesia and post-operative pain management, there are to date no guidelines or recommendations that suggest any pharmacogenetic testing prior to administering any anesthesia-related drug. Consequently, it is still too early to foresee immediate implications of pharmacogenetics in general and pharmacogenetic diagnostic tests specifically, but one can hope that future discoveries in the field of genomics will soon aid anesthesiologists and other clinicians in predicting efficacy or toxicity for some drugs.

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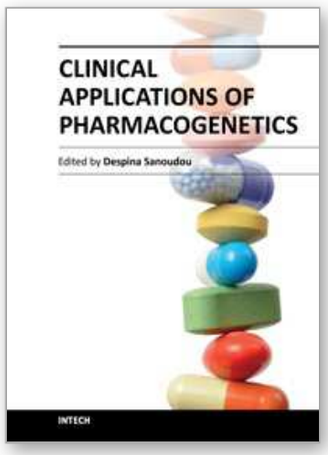

Clinical Applications of Pharmacogenetics

Edited by Dr. Despina Sanoudou

ISBN 978-953-51-0389-9

Hard cover, 292 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

The rapidly evolving field of Pharmacogenetics aims at identifying the genetic factors implicated in the inter-individual variation of drug response. These factors could enable patient sub-classification based on their treatment needs thus expediting drug development and promoting personalized, safer and more effective treatments. This book presents Pharmacogenetic examples from a broad spectrum of different drugs, for different diseases, which are representative of different stages of evaluation or application. It has been designed so as to serve both the unfamiliar reader through explanations of basic Pharmacogenetic concepts, the clinician with presentation of the latest developments and international guidelines, and the research scientist with examples of Pharmacogenetic applications, discussions on the limitations and an outlook on the new scientific trends in this field.

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