Pharmacogenetic in Anesthesia Drugs

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ABSTRACT

Pharmacogenetics seeks to elucidate the variations in individual’s genetic sequences in order to better understand the differences seen in pharmacokinetics, drug metabolism, and efficacy between patients. This area of research is rapidly accelerating, aided by the use of novel and more economical molecular technologies. A substantial evidence base is being generated with the hopes that in the future it may be used to generate personalised treatment regimens in order to improve patient comfort and safety and reduce incidences of morbidity and mortality.

Introduction

A drug may work well in one person, but poorly or not at all in another. One person may tolerate a drug well, whereas another develops side effects. This fact is as well known as it is unfortunate. These individual differences are largely due to our genome, the genetic blueprint that makes each of us unique. Thanks to new knowledge and techniques, medicine is now able to take greater account of these differences – thus leading to the development of more effective, safer and better tolerated drugs.1

Environmental factors, chance and above all the small differences in our genomes make each of us unique. In fact, it has been known for some time that the efficacy and tolerability of drugs vary from one person to the next. Thus, some patients need a lot more or a lot less of a given drug than most people; side effects keep occurring unexpectedly; and sometimes a drug that is usually highly effective does not work at all. Our uniqueness is reflected in our body’s response to drugs. Future drugs, it is hoped, will be better adapted to our genetic diversity and dissimilar life circumstances and will be more efficient, more specific and safer. And they will be supported by a battery of fast, simple genetic tests that will enable doctors to select the right drug for their patients’ specific needs.1

Anesthetists and other clinicians have concentrated on genetic variability that alters drug metabolizing enzymes to explain variation in pharmacokinetic responses to drug therapy. However, it is now apparent that genetic variability can affect many other important proteins such as transporter proteins and receptors. Thus pharmacogenetics plays an important role in genetic variations which is responsible to cause a variable drug response and includes the genetic
polymorphism of drug transporters, drug metabolizing enzymes, and drug receptors.

**Gene-disease relationship**

Human gene-disease studies fall into two general classes: linkage studies and association studies, based upon the nature of the inheritance pattern. Linkage studies are used in Mendelian disease, often in families with a high prevalence of a single disease that is observed early in life, in whom multigenerational trees of inheritance of disease can be traced. The basis of linkage studies is an observed principle in genetics that homologous chromosomes (i.e. both copies of say chromosome 2) in a dividing germ cell exchange large common portions of the chromosome between each other, via a molecular process called recombination. Those two chromosomes will have come from the individual's parents, and by comparing a large number (>1000) of genetic markers in multi-generational families the point of chromosomal swapping in the genome that is most significantly related to the disease can be established. This point is close to the gene responsible for the disease, but the fidelity of this technique is very limited, often giving results that cover large portions (many millions of base pairs) of a chromosome. Narrowing the region down to one or more genes involves follow-up genotyping of progressively smaller regions with greater fidelity. A good example has been using linkage analysis in families with a high incidence of breast cancer at a young age to identify the BRCA1 gene on chromosome 17. In general, linkage studies are only valuable when the disease is present at a young age and not significantly modified by environmental influences.2,3

In 2005, the first genome-wide association studies (GWAS) emerged from the combination of the HapMap project with new technologies for testing hundreds of thousands of SNPs on a single chip. The studies are undertaken by measuring say one million known SNPs in say 10,000 individuals (5,000 with the disease of interest and 5,000 without). The SNPs are roughly spaced about 1 SNP every 3,000 base pairs of the 3×10^9 base pair human genome, thus allowing mostly complete coverage of all the variation in the genome. The coverage isn't perfect; there are gaps, but we generally believe that we are able to observe about 80% of all common variation. The words common variation are important; it is likely that our ability to find associations of disease to variation that conforms to the multiple rare variant hypothesis is probably less than associations to variation that conforms to the common disease / common variant hypothesis.3,4

**Pharmacogenetics in Anesthesia**

Genes can affect drug pharmacokinetics by altering 1) the enzymes that are responsible for drug metabolism and hence drug disposition, as well as 2) the transport proteins which influence drug absorption, re-distribution and bioavailability. The major group of enzymes which catalyze the metabolism of the majority of anesthetics commonly used, are the phase 1 (cytochrome P450 enzymes, cholinesterases) and the phase 2 enzymes (uridine glucoronosyl transferases or UGT and N-acetyl transferases). The effect of gene variant on drug metabolism and clinical consequences.5,6

Numerous clinical trials and reviews have surfaced in recent years describing genetic associations with clinical outcomes in the field of anaesthesia, peri-operative outcomes and pain medicine.7,8 Nonetheless, many clinicians remain sceptical and often wonder about the relevance of genetic research, as it is often considered that titration of drugs to the desired effect works well.9,10

The Clinical Pharmacogenetics Implementation Consortium (CPIC) was created in 2009 to establish a framework for understanding levels of evidence required for pharmacogenetics to be incorporated into clinical practice, and to address the need to provide very specific guidance to clinicians and laboratories so that pharmacogenetic tests are used wisely.11
Table 1. Clinical Pharmacogenetics Implementation Consortium (CPIC) three-tier scheme for scoring of pharmacogenetics evidence. 12

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<th>Quality of evidence linking drug-related phenotype to specific genetic variations</th>
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<th>Level of evidence linking genotypes to drug dosing recommendations</th>
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**Codeine**

Cytochrome P450 (CYP450) is a super family of liver enzymes that catalyse phase 1 drug metabolism. The D6 isozyme of the CYP2 family is particularly affected by genetic variability and currently has 80 identified CYP2D6 alleles, 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, an extensive metabolism, an intermediate metabolism or a poor metabolism, 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 according to ethnicity.

Codeine is a pro-drug, and requires O-demethylation catalysed by CYP2D6 to be converted into morphine and become analgesic; this metabolic pathway 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 metabolised into morphine-6-glucuronide and morphine-3-glucuronide; both morphine and morphine-6-glucuronide display opioid activity. Codeine was initially prescribed because of the belief that being a weak opioid, it is safe and would not result in adverse outcomes. However, the death of a breastfed 13-day-old neonate through morphine overdose because his mother was taking codeine after childbirth resulted in a recent FDA warning on codeine use in nursing mothers. Toxic blood levels of morphine or its active metabolite morphine-6-glucuronide may arise in mothers and neonates who are CYP2D6 ultra-rapid or extensive metabolisers. It has been suggested that codeine be avoided in breastfeeding mothers with a CYP2D6 extensive or ultra-rapid metabolism genotype. Codeine and morphine clearance in breastfeeding mothers and their relation to CYP2D6 genotypes have since been evaluated. Other life-threatening adverse events have been reported in patients with CYP2D6 ultra-rapid metabolism and individuals in this subgroup are particularly at risk when prescribed pro-drugs with a narrow therapeutic range or concurrently with other drugs competing with critical metabolic pathways. 5,6

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. An FDA-approved genetic test (AmpliChip CYP450; Roche Diagnostics, Palo Alto, CA, USA) is commercially available to test genetic variants of CYP2D6. 7,8

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

**Morphine**

Clinicians are well aware of the large and unpredictable inter-individual variability of response to morphine. Genomic and pharmacogenetic research has considered numerous candidate genes as suitable targets for the study of pain and or analgesia. Among the numerous candidate genes that have been considered important in opioid response, the 1-opioid receptor gene (OPRM1, p.118A / G), the catechol-O-methyltransferase gene (COMT, Val158Met), several variants of the ATP-binding cassette, sub-family B member 1 gene (ABCB1) and the CYP family of enzymes have been extensively reviewed. 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. It is likely that the heterogeneity of the clinical situations (experimental pain, acute pain, labour pain, postoperative pain, chronic pain) and diversity of evaluated drugs and dosages precluded any significant findings.

Overall, the level of evidence linking gene variation to morphine response is moderate, probably due to the inherent complexity of studying a heterogenous phenotype such as pain. Limitations that have prevented strong genotype-phenotype associations from being identified in the context of pain studies include differences in pain modalities, sex differences, hurdles in extrapolating data from animal models to the response in humans, population stratification and environmental differences, in addition to the obvious polygenic nature of pain and analgesic response.

**Warfarin**

Balancing the risk of thrombosis against bleeding is a fundamental patient safety issue, and anaesthetists often assess therapeutic anticoagulation peri-operatively. Due to its narrow therapeutic window and significant variability in dose response, it is a leading cause of adverse drug reactions.

Warfarin pharmacogenetics involves both the enzyme responsible for its metabolism, CYP2C9, and its target of action, Vitamin K epoxide reductase complex 1 (VKORC1), the key enzyme of the Vitamin K cycle and the molecular target of coumadins. CYP2C9 is almost exclusively responsible for the metabolism (bio-inactivation) of the pharmacologically more active (S)-enantiomer of warfarin. The CYP2C9 genotype explains approximately 10% of the observed variability in the therapeutic warfarin dose and VKORC1 polymorphisms account for approximately 30% of the variance in stabilised warfarin dose.

In 2007, the FDA approved pharmacogenetic information to be included in the warfarin product label. The FDA proposed a relatively simple approach using genotype-stratified tables with the range of expected therapeutic warfarin doses (mg.day)1) based on CYP2C9 and VKORC1 genotypes to estimate warfarin dose; however, its accuracy has not been quantified.

Overall, the level of evidence linking gene variation (CYP2C9 and VKORC1) to phenotype (bleeding / thrombotic risk with warfarin dosing) is strong; however, there is, to date, no strong recommendation to apply pharmacogenetic testing before initiating warfarin therapy.

**Clopidogrel**

Clopidogrel is an adenosine diphosphate (ADP)-receptor antagonist, and like a pro-drug, it requires bioactivation into an active metabolite (R-130964) for inhibition of platelet aggregation. The range in response to inhibition of ADP- induced platelet aggregation with clopidogrel is extremely broad, with
a wide distribution from < 10% to almost complete platelet anti-aggregation. A recent meta-analysis reviewing clinical outcomes after clopidogrel therapy emphasised that residual platelet reactivity despite clopidogrel treatment was significantly associated with an increased risk of death and/or thrombotic recurrences.\textsuperscript{10,11,12}

Clopidogrel is metabolised in part by the enzyme CYP2C19 to achieve its antiplatelet activity. CYP2C19*1 is the wild-type genotype and results in a normal metabolic function. CYP2C19*2 and CYP2C19*3 are two common ‘loss-of-function’ alleles that result in poor metabolism. Known ethnic differences in allele distribution account for differences in clinical outcomes with clopidogrel therapy. Although platelet response to clopidogrel is highly heritable, it is not entirely explained by CYP2C19, as one analysis showed that only 12% of the variation in response to clopidogrel was explained by the commonly studied CYP2C19*2 genotype. Other genetic polymorphisms also associated with impaired CYP2C19 activity (CYP2C19*4, *5, *8) and adverse clinical events do exist although they are relatively uncommon.

On 12 March 2010, the FDA approved a new label for clopidogrel with a ‘boxed warning’ about the reduced effectiveness of clopidogrel in patients who are poor metabolisers with loss-of-function alleles CYP2C19*2 and *3, and suggested that carriers of these alleles receive a higher dose of clopidogrel or an alternative antiplatelet agent.\textsuperscript{13}

Overall, the level of evidence linking gene variation (CYP2C19) to phenotype (reduced effectiveness of clopidogrel resulting in increased myocardial infarctions and stent thrombosis) is strong; however, there is, to date, no strong recommendation to apply pharmacogenetic testing before adjusting clopidogrel dosing or switching to alternative antiplatelet therapies.

Bucindolol-treated patients who were Arg389 homozygous had a significant reduction in mortality (38% reduction) and re-hospitalisation rates during the follow-up period of 5 years; conversely, individuals carrying the Gly389 allele were found not to benefit from bucindolol therapy. A small pharmaceutical company (ARCA Biopharma, Broomfield, CO, USA) issued a patent on methods of treating heart failure patients with bucindolol administration of clopidogrel with proton pump inhibitors (CYP2C19-inhibiting drugs) decreases the antiplatelet effect of clopidogrel and might reduce clopidogrel efficacy.\textsuperscript{14,15}

\textbf{β-blockers}

In the past decade, β-blockade in the operating room has become a standard of care in at-risk patients, with the goal of improving peri-operative outcomes. However, despite numerous in vitro studies defining extensively the biological effects of the multiple genetic variants of the b1-adrenergic receptor gene (ADRB1) and the b2-adrenergic receptor gene (ADRB2). The clinical relevance for most of the numerous pharmacogenetic results for β-blockers is still inconclusive. Detailed reviews are constantly updating the body of evidence on the pharmacogenetic effects of adrenergic receptors polymorphisms on the response to β-blockers in various cardiovascular conditions.\textsuperscript{16}

Although β-blockers are widely used to treat essential hypertension, there have been too few large studies evaluating the effect of β-blockers in that clinical context based on genotype/ haplotypes of ADRB1; therefore, the level of evidence to conclude whether genetic variants of ADRB1 influence the response to β-blockers for antihypertensive therapy is overall weak. Whether the lack of consistency in findings between the various studies is due to differences in study design, population stratification (different ethnicities), the drug itself or the dose prescribed, or heterogeneity in outcome measures, a strong genetic effect of ADRB1 on blood pressure response to β-blockers remains to be determined.\textsuperscript{17,18}

Of interest and relevant to the pharmacogenetic relationship between CYP2C19 and clopidogrel response, proton pump inhibitors are often co-prescribed with clopidogrel for gastric protection. Co-
(GencaroTM) based on genetic targeting. Pending FDA approval of bucindolol with a specific indication for subgroups of the adrenoceptor genotypes, this would represent the first pharmacogenetic-guided therapy in the area of cardiovascular disease.19

Another potentially important study is that by Lanfear et al. that challenged the concept of ‘b-blockers for all’ and evaluated whether benefits from b-blockade after an acute coronary event may be different based on individuals’ genetic profile.44 Mortality rates were increased in individuals carrying certain variants of the ADRB2, raising the mortality rate to 20% at 3 years according to the haplotype combination of Arg16Gly and Gln27Glu. Patients with variants impairing b2AR down-regulation (Gly16–Glu27), indicating that receptor function does not undergo desensitisation, did benefit from b-blocker therapy. Conversely, patients with variants enhancing down-regulation (Arg16-Gln27) did not benefit from b-blockers, most likely because receptor density is lower at the cell surface, which mimics bAR antagonist activity. In fact, the administration of b-blockers to such patients appeared to unmask negative effects as suggested by the increased mortality rate in comparison with non-treated patients (not on b-blockers). Pending replication in a larger cohort with a standardised treatment, this study provides convincing evidence that genetic variability of the b2AR has direct clinical relevance for b-blockers therapy.

Conclusion
Pharmacogenetics is in initial stage of clinical practices. It is very likely that its contribution to new drug development will become reality. Common polymorphisms in drug targets dictate that DNA sequence variations will be taken into account in the genomic screening processes aimed at new drug development. This will provide new insights for the development of medications that target critical pathways in disease pathogenesis, and medications that can be used to prevent diseases in individuals who are genetically predisposed to them. This represents a migration from the traditional strategy of trying to develop medications that are safe and effective for every member of the population, but one that is a pharmacological long shot because of highly potent medications, genetically diverse patients, and diseases that have heterogeneous subtypes.

Although pharmacogenetics is unlikely to change the way anaesthesia is practised today it may help to elucidate inter-patient variability in drug response. It is undoubtedly, see its impact on other specialties on new drug development, and in drug delivery systems.

References