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Pharmacogenetics in Anesthesia Drugs: A Narrative Literature Review

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A B S T R A C T

Pharmacogenetics plays an essential role in genetic variations, which are responsible for causing a variable drug response and include the genetic polymorphism of drug transporters, drug-metabolizing enzymes, and drug receptors. This literature review aimed to describe pharmacogenetics in anesthesia drugs. Human gene-disease studies fall into two general classes; linkage studies and association studies, based on the nature of the inheritance pattern. Linkage studies are used in Mendelian disease, often in families with a high prevalence of a single disease observed early in life, in whom multigenerational trees of inheritance of disease can be traced. In conclusion, pharmacogenetics is in the initial stage of clinical practice. Its contribution to new drug development will likely become a reality. Common polymorphisms in drug targets dictate that DNA sequence variations will be considered in the genomic screening processes for new drug development. This will provide new insights for developing medications that target critical pathways in disease pathogenesis and medications that can be used to prevent diseases in individuals genetically predisposed to them.

1. Introduction

A drug may work well in one person but poorly or not 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 primarily due to our genome, the genetic blueprint that makes us unique. Environmental factors, chance, and the slight differences in our genomes make each of us unique. 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.[1-3]

Our uniqueness is reflected in our body's response to drugs. It is hoped that future drugs will be better adapted to our genetic diversity and different life circumstances and will be more efficient, specific, and safer. They will be supported by a battery of fast, simple genetic tests enabling doctors to select the right drug for their patient's specific needs. Anesthetists and other clinicians have concentrated on genetic variability that alters drug-metabolizing enzymes to explain variations in pharmacokinetic responses to drug therapy. However, it is now apparent that genetic variability can affect many other vital proteins, such as transporter proteins and receptors. Thus pharmacogenetics plays an essential role in genetic variations, which is responsible for causing a variable drug response and includes the genetic polymorphism of drug transporters, drug-metabolizing enzymes, and drug receptors.[4-6] This literature review aimed to describe pharmacogenetics in anesthesia drugs.

Gene-disease relationship

Human gene-disease studies fall into two general classes; linkage studies and association studies, based on the nature of the inheritance pattern. Linkage studies are used in Mendelian disease, often in

families with a high prevalence of a single disease 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 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. By comparing a large number (>1000) of genetic markers in multigenerational families, the point of chromosomal swapping in the genome most significantly related to the disease can be established. This point is close to the gene responsible for the disease. However, the fidelity of this technique could be improved, 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.[6,7]

In 2005, the first genome-wide association studies (GWAS) emerged from combining the HapMap project with new technologies for testing hundreds of thousands of SNPs on a single chip. The studies are undertaken by measuring 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 3×109 base pair human genome, thus mainly allowing complete coverage of all the variation in the genome. The coverage is imperfect; there are gaps, but we generally believe we can observe about 80% of all common variation. The common words variation are essential; 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.[3,4,8]

Pharmacogenetics in anesthesia

Genes can affect drug pharmacokinetics by altering the enzymes that are responsible for drug metabolism and hence drug disposition, as well as the transport proteins which influence drug absorption, re-distribution, and bioavailability. The primary group of enzymes that catalyze the metabolism of most anesthetics commonly used are phase 1 (cytochrome P450 enzymes, cholinesterases) and 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 recent clinical trials and reviews have surfaced describing genetic associations with clinical outcomes in anesthesia, peri-operative outcomes, and pain medicine.[7,8] Nonetheless, many clinicians remain skeptical 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 the levels of evidence required for pharmacogenetics to be incorporated into clinical practice and to address the need to provide precise guidance to clinicians and laboratories so that pharmacogenetic tests are used wisely.

Morphine

Clinicians know the large and unpredictable inter-individual response variability to morphine. Among the numerous candidate genes that have been considered necessary in opioid response, the l-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 one gene (ABCB1) and the CYP family of enzymes have been extensively reviewed. Limitations that have prevented strong genotype-phenotype associations from being identified in the context of pain studies include differences in pain modalities, sex

differences, population stratification, and environmental differences, in addition to the apparent polygenic nature of pain and analgesic response.[11,12]

Warfarin

Balancing the risk of thrombosis against bleeding is a fundamental patient safety issue, and anesthetists 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.[2] Warfarin pharmacogenetics involves the enzyme responsible for its metabolism, CYP2C9, and its action target, Vitamin K epoxide reductase complex 1 (VKORC1), the key enzyme of the Vitamin K cycle and the molecular target of coumadin. CYP2C9 is almost exclusively responsible for the metabolism (bio-inactivation) of warfarin's pharmacologically more active (S)-enantiomer. 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 stabilized warfarin dose.[9]

In 2007, the FDA approved pharmacogenetic information on 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) based on CYP2C9 and VKORC1 genotypes to estimate warfarin dose; however, its accuracy has yet to be. Overall, the evidence linking gene variation (CYP2C9 and VKORC1) to phenotype (bleeding/thrombotic risk with warfarin dosing) is vital; however, there is, to date, no solid recommendation for applying pharmacogenetic testing before initiating warfarin therapy.

Clopidogrel

Clopidogrel 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 comprehensive, with a wide distribution from < 10% to almost complete platelet anti-aggregation. A recent meta-analysis reviewing clinical outcomes after clopidogrel therapy emphasized that residual platelet reactivity despite clopidogrel treatment was significantly associated with an increased risk of death and thrombotic recurrences.

Clopidogrel is metabolized partly 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 are also associated with impaired CYP2C19 activity (CYP2C19*4, *5, *8), and adverse clinical events do exist, although they are relatively uncommon. In 2010, FDA approved a new label for clopidogrel with a 'boxed warning' about the reduced effectiveness of clopidogrel in patients who are poor metabolizers 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.[13]

β-blockers

In the past decade, b-blockade in the operating room has become a standard of care in at-risk patients to improve peri-operative outcomes. However, numerous in vitro studies defined 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 of most of the pharmacogenetic results for b-blockers still needs to be discovered. Detailed reviews are constantly updating the body of evidence on the pharmacogenetic effects of adrenergic receptors polymorphisms on the response to b-blockers in various cardiovascular conditions.[14]

Although b-blockers are widely used to treat essential hypertension, there have been too few extensive studies evaluating the effect of b-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 b-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 robust genetic effect of ADRB1 on blood pressure response to b-blockers remains to be determined.[12-14]

Bucindolol-treated patients who were Arg389 homozygous had a significant reduction in mortality (38% reduction) and re-hospitalization 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 treating heart failure patients with bucindolol (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 cardiovascular disease.

Another potentially important study evaluated whether benefits from b-blockade after an acute coronary event may differ based on individuals' genetic profiles. Mortality rates were increased in individuals carrying specific variants of the ADRB2, raising the mortality rate to 20% at three 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 desensitization, 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. Administering b-blockers to such patients appeared to unmask adverse effects, as suggested by the increased mortality rate compared to non-treated patients (not on b-blockers). Pending replication in a larger cohort with a standardized treatment, this study provides convincing evidence that genetic variability of the b2AR has direct clinical relevance for b-blockers therapy.[10-12]

2. Conclusion

Pharmacogenetics is in the initial stage of clinical practice. Its contribution to new drug development will likely become a reality. Common polymorphisms in drug targets dictate that DNA sequence variations will be considered in the genomic screening processes for new drug development. This will provide new insights for developing medications that target critical pathways in disease pathogenesis and medications that can be used to prevent diseases in individuals genetically predisposed to them. Although pharmacogenetics is unlikely to change the way anesthesia is practiced today, it may help to elucidate inter-patient variability in drug response. Undoubtedly, it is its impact on other specialties on new drug development and drug delivery systems.

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