Pharmacogenetic Aspects of Anesthetic and Analgesic Agents

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Abstract

Patient's response to a particular drug therapy has been challenged with variations in clinical outcomes since long times back in past. Clinicians have always tried to get some predictive measure to know a patient's response in advance. Genetic testing of patients for drug related markers has provided one such hope. This has been greatly facilitated by technological advancements leading towards faster as well as cheaper methods of getting individual patient's genetic information and its association with drug response. Pharmacogenetics of common anesthetic and analgesic agents is reviewed with an aim to provide the reader an idea about how patient's genetic background may play a role in causing variations observed in clinical practice.

Introduction

Individual patient responses to anaesthetic drugs are shown to be affected by genetic variants for more than 5 decades.[1] As first description about anaesthesia pharmacogenetics, first review about the topic as well as the description of second gas effect and Winnie's description of the subclavian perivascular approach to brachial plexus anaesthesia occurred in the same issue of the journal Anethesiology.[2-4] Kalow's review was somewhat different than the recent developments in genetic predisposition for drug response variation. The latter studies have emerged rapidly with the revolutionary molecular biology techniques and human genome project. Kalow's work was more focused on the description of a set of rare clinical conditions following a Medelian pattern of inheritance, e.g. myotonic syndromes, pseudocholinesterase deficiency, porphyrias, and anaesthesia induced hyperthermia, now known as malignant hyperthermia (MH).[1] These conditions were found to be present in an affected individual showing strange responses towards anaesthetic agents. Generally, pharmacogenetic variants are rare and act in an individually effective fashion to cause abnormalities in drug responses. Pharmacogenomic variations are caused by common genetic variants that affect the drug response phenotype in a cumulative fashion by making individual partial contributions. Therefore pharmacogenomics is associated with the complex genetics of drug response phenotypes. The idea of personalized medicine revolves around the understanding of the pharmacogenomics variability. This review describes the pharmacogenetic aspects of common anaesthetic and analgesic agents such as neuromuscular blockers, inhalation anaesthetic drugs, opiods and Nonsteroidal Anti-inflammatory Drugs.

Neuromuscular Blocking Agents

Succinylcholine and mivacurium are commonly used neuromuscular blockers as anaesthetic agents. Their effectiveness is affected by the genetics of patient.[5] Plasma butyrylcholinesterase (pseudocholinesterase) is the enzyme for hydrolyzing these drugs and genetic variations for this enzyme are associated with inter-individual differences in the drug induced phenotypes, i.e., muscular paralysis. After administration of 1.0-1.5 mg/kg succinylcholine, normally patient recovery occurs within 5-10 minutes. In case of patients expressing only a single allele (heterozygous condition) for butyrylcholinesterase Asp70Gly polymorphism, a less efficient enzyme is produced. This results in patient's taking 3-8 times longer duration for recovery of neuromuscular functions after drug administration as succinylcholine is slowly cleared from blood. Expression of homozygous butyrylcholinesterase Asp70Gly polymorphism leads to very long recovery time as compared to that in case of normal allelic expression. This recovery time has been identified up to 60 times longer.[6] Butyrylcholinesterase gene polymorphism has a role in prolongation of muscle paralysis induced by Mivacurium.[7] The presence of variant butyrylcholinesterase alleles in patients who had been injected with mivacurium or succinylcholine for anesthesia leads to their requirements of longer durations of mechanical ventilation to normalize the neuromuscular blockade.[8] One of the beneficial use of genotyping such patients can be the avoidance of drugs for which the concern enzyme is defected. This can greatly reduce the post-operative recovery time and costs.

Benzodiazepines

The cytochrome P-450 enzymes of liver metabolize most of the benzodiazepines.[9] The polar metabolized products get excreted into bile/urine. Three genes, namely, CYP2C19, CYP3A4 and CYP3A5 are particularly important in the clearance of benzodiazepines.[9] Homozygous condition for the minor allele of CYP2C19 G681A polymorphism was found to be associated with longer half-life of the drug (up to 4 times than that in case of homozygocity of the major G allele).[10] This suggests decreased activity of the enzyme due to the polymorphism. The heterozygous individuals show intermediate diazepam effects as expected.[10, 11] Further studies have suggested the role of genetic variation in clinical manifestation of diazepam.[12] While diazepam metabolism was found to be more affected by genetic factors, this is not the case with midazolam. Genetic factors play only a modest role in metabolism of midazolam. The reason is the alternate ways of drug metabolism and its clearance. However, single nucleotide polymorphisms in the CYP3A4 and CYP3A5 genes were found to be associated with reduced clearance of midazolam.[13, 14], [15]

Inhalation Anesthetics

The pharmacogenetic studies on inhalation anesthetic drugs have been focused more on the adverse drug reaction associated genetics, e.g., malignant hyperthermia syndrome (MHS). MHS, an ailment of skeletal muscles, is initiated by intravenous administration of succinylcholine or anesthetic inhalation. It is often associated hypermetabolism and very high fever (more or around 110.0°F). The susceptibility of MHS is 1 per 15,000 children and 1 per 50,000 adults. The real prevalence is thought to be even greater because the symptoms are not shown in some susceptible individuals.[16] An important point to note about the lower incidence in adults than in children shows the complex genetic basis of MHS. Genetic variations in the

ryanodine receptor (RYR1) gene were found to be associated with MHS. Pharmacogenetic studies have revealed that nearly 50% cases of MHS have mutations in RYR1 gene. In some studies, it was found that variations in the voltage gated calcium channel genes associate with 1% MHS cases in North American population.[16, 17] As far as RYR1 SNP's are concerned, the true picture is difficult to assess as there are at least 23 SNPs associated with MHS.[18] The RYR1 polymorphisms are associated with central core disease and patients with central core disease tend to possess severe symptoms of MHS too.[19, 20] Currently genetic testing of RYR1 SNPs for detection of MHS is not being done. This is due to the fact that studies have shown that there are no known RYR1 SNPs present in MHS patients. There are variations in the frequency distribution of MHS related SNPs in different ethnic groups. This further enhances the problem of optimal anesthetic treatment in various populations. Previous studies have found RYR1 SNPs in German, Italian and American MHS patients with frequencies 70, 41 and 26% respectively.[21, 22], [23] The amount of pharmacogenetic research on adverse effects of inhalation anesthetics is huge when compared with that on the genetic influences on the therapeutic effects of inhalation anesthetic agents. This is partly because of extremely small variation in the observable inhalation anesthetic effect and our lack of complete understanding of the molecular effects of inhalation anesthetic agents.

The importance of patient's genetics in anesthetics is reflected by the case study of an infant boy's unexpected neurological deterioration and death as reported by Selzer *et al.*[24, 25] The boy was anesthetized twice with nitrousoxide within a short duration of time. His postmortem had revealed an inherited defect in folate metabolism in the form of 5,10-methylenetetrahydrofolate reductase deficiency. Two common mutations (C677T and A1298C) were found in 5,10-methylenetetrahydrofolate reductase gene along with other complex combination of mutations. These mutations are associated with decreased activity of 5,10-methylenetetrahydrofolate reductase. Nitrous oxide inhibits the activity of methionine synthase by oxidizing the cobalt atom of vitamin B12. Homocysteine and 5-ethyltetrahydrofolate are remethylated by methionine synthase to methionine and tetrahydrofolate. Methionine is an important compound for normal functioning of neurological system. Many biochemical reactions use *S*-adenosylmethionine (derived from methionine) as the main substrate for methylation. These processes include myelin sheath assembly, methyl substitutions in DNA synthesis and neurotransmitters. This infant boy presented an example of deficiency of methionine in brain and subsequent death because of complex genetic effectors and biochemical manifestation of nitrous oxide. There is a clear association of unfavorable and unexpected alterations in anesthetic outcomes with patient's genetic background.

Opioids

Opioids used for clinical effects act on the μ-opioid receptors. A118G and G-172T (promoter SNP) are the two most common variants present in Whites with a frequency of 5-10%.[26] The G allele of A118G SNP has a role in reducing the adverse drug reactions like sedation, nausea, pupil dilation and vomiting.[27, 28] Therefore G allele carriers can withstand comparatively higher doses of opiates than non-carrier patients. It has been observed that post-surgical opioid requirements vary significantly between individual patients instead of lesser genetic variation in the binding of μ-opioid receptors to opiates.[29] Full understanding of this phenomenon's molecular mechanisms is currently lacking, however, it can be partially accounted to the variations in number

of receptors. Additionally, pain perception is a complex trait involving many genes and environmental factors. Furthermore, opiate metabolism too involves influences from many SNPs, e.g., 3- and 6- glucuronidation of morphine is catalyzed by uridine diphosphate glycosyl transferase. Two linked SNPs, C-161T and C802T, in the DNA sequence of this enzyme cause rapid glucuronidation when present in homozygous state than in heterozygous or wild type state.[30]

Hepatic cytochrome P-450 2D6 (CYP2D6) is another important enzyme in opioid metabolism. About 25% of all the drugs used are processed by CYP2D6 enzyme. CYP2D6 converts codeine into morphine which has analgesic properties.[31] Gene duplication events leading to more than two copies of the CYP2D6 gene in some individuals as well as presence of many different functional/non-functional SNPs result in high amount of variability in CYP2D6 among individuals. As a result, wild type allele CYP2D6*1 allele causes more than normal level of CYP2D6 production. CYP2D6 gene duplication events vary among different populations, e.g., 4-5% in Americans, 0.5% in Chinese and 29% in Africans.[32] CYP2D6*1 is the wild type allele present in atleast a single copy in patients who rapidly convert codeine into morphine. On the other side, CYP2D6*4, *5 and *6 variants are found to be associated with poor metabolism of codeine and are present in 8% Whites. These variant alleles result in immunity to the analgesic properties of codeine.[33, 34] CYP3A4 metablizes opiates like fentanyl, alfentanil and sufentanil.[35, 36] In females, CYP3A4 is metabolized rapidly than in males by 40%. Therefore females require higher doses of opiates to achieve same level of anesthetic effect as compared to males.[37] Recent identification of the association of catechol *O*-methyl transferase (COMT) gene with the pain perception has added one more genetic factor in opioid metabolism.[38] Adrenergic and dopaminergic pathways are involved in pain transmission. These two pathways are modulated by COMT which also takes part in metabolism of catecholamine. COMT gene has an important SNP, Val158Met, conferring 3-4 fold decreased enzyme activity.[39, 40], [41] These findings revealed the potential of genetic markers in altering the efficacy of drug through modulation of receptor binding and functions.

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Hepatic cytochrome enzyme CYP2C9 metabolizes many of the NSAIDs. Two common SNPs in the CYP2C9 gene are important for decreasing the enzyme activity: CYP2C9*2 and 3. Celecoxib, naproxen, piroxicam, ibuprofen, and flurbiprofen are metabolized slowly by CYP2C9*3 carriers.[42, 43] [44, 45] [46, 47] Homozygous CYP2C9*3 alleles confer a greater reduction in enzyme activity in comparison to heterozygotes. These studies reflect that CYP2C9*3 allele carriers will retain NSAIDs for longer durations in their system. Therefore if the drug is administered in optimal amount or higher than required amount, such patients might experience greater benefit or adverse drug reactions respectively than those in patients without 3 alleles. At present, research evidence in support of this hypothesis is lacking. Some NSAIDs, like diclofenac, are not metabolically influenced by CYP2C9*2/*3 status.[43, 48] [49] A recent study has revealed same hepatic microsomal ability in CYP2C9*2/*3 heterozygous and CYP2C9*1 homozygous patients for metabolizing diclofenac.[50] There are sparse evidences association between other genes and NSAID metabolism. However, one can't completely disagree with the possibility of other unknown genetic factors that might be associated with NSAID metabolism. For example, in case of CYP2E1 gene polymorphisms, c2 allele carriers show twice rate of metabolism of acetaminophen than wild type c1 allele carriers. The c2 allele of CYP2E1 gene has a deleted

DNA segment because of which protein synthesis is affected.[51] TNF β (tumor necrosis factor β) gene mutant B2 has a protective effect in patients with acetaminophen-induced acute liver failure.[52] HLA-DRB1 is a human leukocyte antigen gene having a role in the immune response. There are possibilities of HLA-DRB1 *11 allele being associated with anaphylactoid reactions to NSAIDs.[53] Instead of these preliminary association studies, the clinical relevance and accuracy of such results can only be true based on more rigorous research.

Conclusions

Inter-individual differences in the optimal doses of anesthetic agents have been a major cause of concern among the medical professionals. Most common examples of such variations from anesthesiologist's perspective include variations in postoperative analgesic requirements, succinylcholine usage associated prolonged muscle relaxation and volatile anesthetics induced MHS. Drug absorption, distribution, metabolism, excretion, and toxicity are affected by the genetic variations as evident from the growing data on the pharmacogenetic component. Not just anesthetic agents but other drug related phenomena too are affected to some or more extent by the genetic variations. Unexplained clinical events and patterns like slow awakening in some families and patients doing better or worse recovery can now be accounted to the genetic variations. Acquiring more information about the genes affecting the drug activity can increase our ability to segregate SNPs affecting the pharmacokinetics and pharmacodynamics. In future, pharmacogenetic screening might be used for identifying sensitive patients to a particular therapy. Drug metabolism, efficacy and side effects can be predicted accurately to a greater extent by such pharmacogenetic fingerprinting. However, cost to benefit ratio is a limitation at present for pharmacogenetic testing. But, high throughput, advanced and cheaper genotyping technologies can answer the cost to benefit ratio issue. Before pharmacogenetic testing becomes routine part of clinical practice, questions on the time it should be done, adjustments of dosing and its alternatives should be further explored to enhance the confidence among patients and clinicians. For all these issues to be properly addressed, prospective clinical trials and sufficiently powered genetic association studies are required in well defined segregated patient groups. Only then, real benefits of pharmacogenetic testing would become evident and we can then make sure that these methods can be safely as well as effectively applied in real world scenario.

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