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Genetic Influences on Anesthetic Drug Response: Pharmacogenomic Considerations for Personalized Anesthesia

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Abstract: ***Genetic variations significantly influence how individuals respond to anesthetic agents, affecting drug efficacy, metabolism, and safety. Pharmacogenetics examines these genetic factors and guides anesthetic decisions to minimize adverse reactions. This review highlights key genetic polymorphisms that alter the pharmacokinetics and pharmacodynamics of commonly used anesthetic drugs. It also explores the growing role of precision medicine, bioinformatics tools, and machine learning in tailoring anesthesia plans. Integrating pharmacogenomic insights into clinical practice enhances patient safety, optimizes outcomes, and represents the future direction of personalized anesthesia care. (1, 2, 3, 4, 5, 6, 7, 8)***

Keywords: Genetics, pharmacogenomics, anesthesia, mutations, polymorphism

1. Introduction

'If it were not for the great variability among individuals, medicine might as well be a science and not an art.' Sir William Osler 1892. (9)

Despite the fact that all human beings are 99.9 percent genetically identical, genetic variations are responsible for the variations in individual characteristics as well as for susceptibility to diseases or drug responses.

Specific enzymes are required to convert prodrugs into their active form. A genetic deficiency of these substrates can render the administered drug ineffective, partially effective or even toxic. Drugs administered in their active form may depend on specific enzymes for their biotransformation. If this substrate is absent or insufficient, that medication may accumulate in the body and have adverse side effects. Since overdosages or adverse drug effects are implicated in over 50% of anesthesia-related deaths, genetic screening becomes exceedingly vital before anesthetic administration. (10, 11)

Pharmacogenomic integration into clinical anesthetic will certainly improve patient safety as anaethetic drug selection will become precise to minimize adverse events and ensure better outcomes by eliminating postoperative complications significantly. (12, 13)

Understanding the genetic underpinnings of anesthetic response is critical for reducing adverse drug events, improving patient outcomes, and advancing the practice of precision medicine in anesthesiology.

2. Genetics in Anesthesia

The hepatic cytochrome P450 enzyme systems metabolize a majority of anesthetic agents. Glutathione S-transferases (GSTs), sulphotransferases (SULTs), Uridine 5'-diphospho glucuronosyltransferases (UGTs), Nicotinamide adenine dinucleotide phosphate {NAD(P)H} and quinone oxidoreductase (NQO1) also participate in drug biotransformation to a lesser degree. (14)

1) Propofol

Propofol (2,6-diisopropylphenol) is a widely employed short acting intravenous making it a rapid-onset, short-duration induction agent with a favorable safety profile. A greater portion of propofol is conjugated to glucuronide (70 %), while the remainder is hydroxylated by CYP2B6. The CYP2B6 A785G gene variant in some elderly individuals delays this biotransformation, resulting in higher propofol plasma concentrations. These patients need a 50% reduction in its infusion rate for maintenance of general anesthesia. In another subset of patients with UGT1A9–331C/T and UGT1A9–1818T/C genetic variant, exhibit a faster propofol clearance that results in a slow onset of its action and, therefore, a higher dosage for the desired effect. (15)

Sedation and amnesia is mediated by the GABAA receptor. Genetic mutation in the beta 1 and 2 subunit of this receptor can alter patient response to propofol and etomidate. (16)

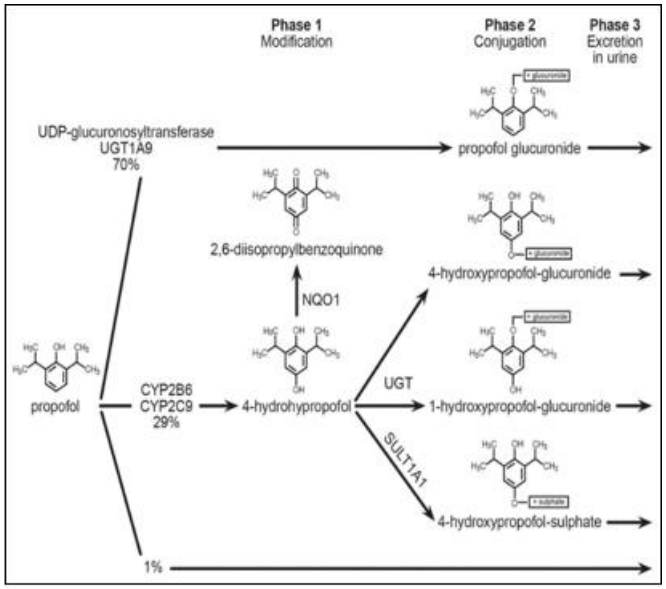

Figure 1: Metabolic pathway of propofol

2) Narcotics

The hepatic cytochrome P450 enzymes catalyze the oxidation and metabolism of a broad range of anesthetic medications. Of the four subforms of CYP3A, CYP3A4, CYP3A5, CYP3A7, and CYP3A43, CYP3A5 exhibits genetic variations in 20% of the population. This leads to inter-individual differences in drug metabolism, impacting drug efficacy and safety. Patients with the CYP2D6 variant are poor metabolizers of specific narcotic drugs and exhibit resistance to the analgesic effects of codeine. This drug is dependent on the enzyme for its conversion to morphine. Some other variants of the enzyme result in accelerated of the drug, resulting in greater toxic effects due to excessive active metabolite formation. (17, 18) Narcotic drug addiction potential has been observed in individuals with single-nucleotide polymorphisms (SNP) in rs3495 and rs 1803274 of the butyrylcholinesterase gene (BCHE).

The μ-opioid receptor (MOR) is a protein encoded by the OPRM1 gene. It is the primary target for many opioids, both natural and synthetic. Genetic variations and polymorphisms in the OPRM1 gene can lead to variations in individual response to opioids and also on pain susceptibility and addiction potential. Those with the G allele OPRM1 A118G rs1799971 genetic variation exhibit reduced sensitivity to pain. Their higher pain threshold merits lower analgesic requirements. Since tapentadol and methadone have dual mechanisms of action, these drugs may be preferred over conventional narcotic drugs for those with OPMRI variations. Individuals with the G/G genotype for the rs13093031 and rs6961071 SNPs exhibit reduced sensitivity to fentanyl. (19, 20, 21, 22, 23, 24)

3) Muscle Relaxants

Butyrylcholinesterase (BChE or pseudocholinesterase) breaks down acetylcholine and the BCHE gene on chromosome 3 is responsible for manufacturing the enzyme in the liver. Hereditary BChE deficiency is an autosomal recessive genetic disorder. Patients with the enzyme deficiency exhibit slow metabolism of muscle relaxants like succinylcholine and mivacurium and also to the ester-group local anesthetic agents like procaine and tetracaine. The "atypical" or "A" variant is associated with profound enzyme deficiency whereas the "K" (BCHE-K) variant carriers have a 33% reduction in plasma BChE activity and susceptible for prolonged apnea with depolarizing muscle relaxants. Fresh blood transfusion from non-carrier donors can restore respiration in these patients. (25, 26, 27)

4) Sedatives

The gamma-aminobutyric acid (GABA) is a major target for general anesthetics and sedative drugs. The GABA type A receptors (GABAARs) form the majority of inhibitory neurotransmitter receptors in the central nervous system. Structurally, these receptors comprise of two α subunits, two β subunits, and one additional subunit from either γ or d, arranged in a counterclockwise fashion as γ2β2α1β2α1 chloride (Cl-) selective channel. (Fig 2) Multiple GABAAR subunit subtypes and variants exist, each with distinct biophysical and pharmacologic properties.

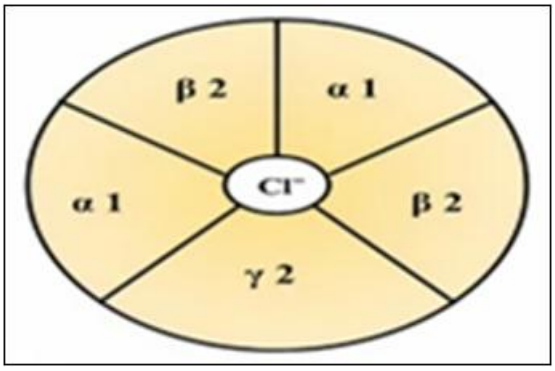

Figure 2: Structure of the GABA type A receptors

Benzodiazepines act on the α+/γ− interface of the $GABA_A$ receptor, while etomidate binds to its β+/α− interface, and barbiturates target the α+/β− and γ+/β− interface. Anesthetic drugs enhance receptor-mediated synaptic transmission and interrupt the thalamocortical transmission. Abnormal GABAAR function results in a spectrum of neurological conditions such as sleep disorders, seizures, cognitive and mood disorders, and loss of neuroplasticity. Further research on aspects of this receptor will result in highly specific sedative and anesthetic drugs and newer therapeutic modalities. (28)

5) Malignant Hyperthermia Susceptibility

The RYR1 gene provides instructions for the manufacture of the ryanodine receptor 1 (also referred to as the RYR1 channel). Upon activation, it causes release of positively charged calcium ions from storage sites within the sarcoplasmic cells and plays a critical role in skeletal muscle function.

Malignant hyperthermia is a pharmacogenetic disorder triggered by certain halogenated anesthetic agents in genetically predisposed individuals. Approximately 70 % of these individuals carry mutations in the RYR1 gene. This can predispose them to greater risk of developing malignant hyperthermia after halothane and suxamethonium administration. Most of these mutations change single amino acids in important regions of the ryanodine receptor 1 protein. As a result, large amounts of calcium ions are released from the sarcoplasmic reticulum inside muscle

cells, generating heat and causing hyperthermia, rigidity and severe acidosis. (29)

Mutations in RyR1 render the channel leaky (unable to close properly) to calcium (Ca^{2+}) and responsible for a variety of muscle weakness known as RyR1-related disorders (RyR1-RD). Some of the known subtypes are central core disease (CCD), multiminicore disease (MmD), centronuclear myopathy (CNM), congenital fiber-type disproportion (CFTD), King-Denborough syndrome (KDS), rhabdomyolysis-myalgia syndrome, late-onset axial myopathy, atypical periodic paralysis and statin-induced myopathy. (30, 31)

3. Conclusions

By incorporating pharmacogenetic insights, anesthesia management can be tailored to individual responses, enhancing the safety and effectiveness of anesthesia across diverse patient populations. As genetic research continues to provide deeper insights into anesthetic responses, it is likely to lead to even more targeted and effective anesthesia practices in the future.

Using bioinformatics tools like the Pharmacogenomics Knowledgebase (PharmGKB), anesthesiologists can make genetically driven decisions to increase the predictability and safety of anesthesia. Machine learning computational models can convert genetic data and clinical information to predict drug responses, reduce risks and improve outcomes. Consideration of genetic differences is critical for the optimization of pharmacotherapy and precision public health. Pharmacogenomic advancements benefit society by enabling more effective and individualized patient.

Integrating pharmacogenetic insights into anesthesia practice enhances patient safety by accounting for genetic variability in drug response. Tools such as PharmGKB and machine learning models enable anesthesiologists to anticipate drug behavior, personalize care, and reduce complications. As precision medicine evolves, its incorporation into anesthetic planning will likely become a standard practice, contributing to safer and more effective clinical outcomes.

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