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SPECIAL ISSUE - ARTICLE

Precision Medicine in Anesthesia: Pharmacogenomics and Personalized Care

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Abstract
Precision medicine in anesthesia represents a transformative approach aimed at optimizing anesthetic care by tailoring interventions to individual patient characteristics, particularly their genetic profile. Pharmacogenomics, a cornerstone of precision medicine, explores the genetic factors influencing drug metabolism, efficacy, and adverse reactions. This article delves into the integration of pharmacogenomics in anesthesia, discussing its impact on drug selection, dosage adjustments, and patient outcomes. It also highlights the potential for reducing perioperative complications, enhancing patient safety, and improving recovery through personalized anesthetic care. Challenges such as the need for robust genetic databases, ethical considerations, and the cost-effectiveness of implementing precision medicine in clinical practice are also discussed. The future of anesthesia lies in harnessing pharmacogenomics to provide individualized care, ultimately advancing patient-centric anesthetic management.

Keywords: Precision medicine, anesthesia, pharmacogenomics, personalized care, genetic profiling, drug metabolism, patient safety, perioperative outcomes

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Introduction

Anesthesia is a critical component of modern medicine, providing essential pain relief and sedation during surgical and diagnostic procedures. Traditionally, anesthetic care has been guided by generalized protocols, with drug choices and dosages determined by factors such as patient weight, age, and medical history. However, this one-size-fits-all approach often overlooks individual variations in drug metabolism and response, leading to suboptimal outcomes. Precision medicine offers a promising alternative, aiming to tailor anesthetic care to the unique genetic makeup of each patient. Pharmacogenomics, the study of how genes influence drug response, is central to this personalized approach.

Pharmacogenomics in Anesthesia

Genetic Variability and Drug Metabolism

The metabolism of anesthetic agents is a complex process influenced by multiple factors, with genetic variability playing a pivotal role. A significant aspect of this variability lies in the function of enzymes involved in drug metabolism, particularly those of the cytochrome P450 (CYP450) enzyme family. The CYP450 enzymes are responsible for the oxidative metabolism of a wide variety of drugs, including many anesthetics. Variations, or polymorphisms, in the genes encoding these enzymes can lead to significant differences in how individuals metabolize anesthetic drugs, impacting both efficacy and safety [1,2]. The role of pharmacogenomics and personalized anesthesia towards tailoring care for enhanced outcomes using precision medicine are mentioned in Table below.

Role	Relevance	Current Applications in Anesthesia	Future Possibilities
CYP2D6 Polymorphisms & Opioid Metabolism	Genetic variations in CYP2D6 alter how opioids like codeine, tramadol, and oxycodone are metabolized	Used to predict opioid response; poor metabolizers may experience reduced analgesia, while ultrarapid metabolizers may face a higher risk of overdose	Integration of routine CYP2D6 testing to personalize opioid selection and dosing, reducing inadequate analgesia or overdose risk
CYP3A4/5 Variants & Fentanyl Metabolism	Differences in CYP3A4/5 enzymes affect how fentanyl and other anesthetics are broken down in the body	Tailoring fentanyl dosing based on enzymatic activity can optimize patient safety and drug effectiveness	Personalized dosing of fentanyl based on CYP3A4/5 genotype, minimizing overdose risk and improving analgesic outcomes
Butyrylcholinesterase (BCHE) Variants	BCHE deficiency may cause prolonged neuromuscular blockade after	Screening for BCHE mutations helps prevent prolonged paralysis and respiratory complications	Widespread genetic screening to identify BCHE variants, optimizing the selection and dosing of

	drugs like succinylcholine		neuromuscular blocking agents
VKORC1 and CYP2C9 Variants & Warfarin Sensitivity	Genetic variants in VKORC1 and CYP2C9 influence warfarin metabolism, affecting perioperative bleeding risk	Adjusting warfarin doses based on these genetic markers can reduce the likelihood of hemorrhage or thrombosis	Routine genotyping to guide perioperative anticoagulation therapy, especially in patients with high-risk profiles
CYP2C19 Polymorphisms & Proton Pump Inhibitors (PPIs)	CYP2C19 variants impact PPI metabolism, which is relevant for acid suppression in perioperative care	Tailored PPI selection based on metabolic profile helps ensure effective acid suppression in high-risk patients	Routine use of pharmacogenetic data to guide PPI therapy, optimizing gastric protection and reducing aspiration risk
CYP2C9 Variants & Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Variants in CYP2C9 affect the metabolism of NSAIDs, altering their effectiveness and risk of side effects	Tailoring NSAID choice and dose based on metabolic capacity, particularly for postoperative pain management	Broad integration of genetic testing to optimize NSAID selection, improving pain control and minimizing adverse effects like GI or renal complications
Pharmacogenetics of Local Anesthetics (e.g., Lidocaine)	Sodium channel gene mutations (e.g., SCN9A) may impact patient sensitivity to local anesthetics	Current applications are limited, though these variants could explain differential sensitivity to local anesthetics	Future development of pharmacogenetic tools to predict patient-specific responses to local anesthetics, leading to personalized dosing strategies
Malignant Hyperthermia (RYR1 and CACNA1S Mutations)	Mutations in these genes increase susceptibility to malignant hyperthermia triggered by certain anesthetics	Preoperative screening for these mutations helps prevent malignant hyperthermia during surgery	Routine genetic testing in high-risk individuals to identify susceptibility and guide the choice of safer anesthetic agents
Genetic Variants and Anesthetic Emergence Delirium	Genetic markers may influence the risk of emergence delirium, especially in pediatric patients	Currently considered only in select patient populations, with a focus on pediatric anesthesia	Genetic testing to identify high-risk patients and implementation of tailored anesthetic strategies to reduce the incidence of emergence delirium

G6PD Deficiency & Hemolysis Risk	G6PD deficiency predisposes patients to hemolysis when exposed to certain anesthetic drugs	Preoperative testing in at-risk populations can prevent hemolytic episodes by avoiding certain drugs	Genetic screening for G6PD deficiency to guide safer anesthetic and medication choices perioperatively
Pharmacogenetics of β-blockers (CYP2D6 Variants)	CYP2D6 variants influence the metabolism of β-blockers commonly used for perioperative management	Adjusting β-blocker dosing based on CYP2D6 genotype helps to optimize therapeutic effects and prevent adverse events	Personalized β-blocker therapy to reduce perioperative cardiovascular complications, improving overall hemodynamic stability
Serotonin Transporter (SLC6A4) Polymorphisms & Antidepressants	Variants in the serotonin transporter gene affect response to SSRIs, which may interact with anesthetic drugs	Awareness of gene-drug interactions helps manage patients on long-term SSRIs and prevent complications like serotonin syndrome	Future use of genetic data to guide anesthetic choices, minimizing risks associated with SSRIs and improving perioperative management
Pharmacogenetics of Propofol Metabolism	Variants in enzymes involved in propofol metabolism may affect its duration of action and recovery	Current use is minimal, but interindividual differences in propofol sensitivity may be explained by genetic factors	Genetic testing to optimize propofol dosing, improving recovery times and reducing complications related to anesthesia depth
ACE Inhibitor Polymorphisms & Hypotension Risk	Genetic variants may increase susceptibility to perioperative hypotension in patients on ACE inhibitors	ACE inhibitors are frequently continued perioperatively; pharmacogenomics could inform risk prediction	Genetic testing to predict hypotensive responses, allowing for more precise management of blood pressure during anesthesia
Pharmacogenomics of Volatile Anesthetics	Variants may influence patient sensitivity to volatile anesthetics like sevoflurane	Clinical use is currently limited; genetic markers could explain variability in anesthetic responses	Future pharmacogenomic testing could personalize the selection and dosing of volatile anesthetics to minimize postoperative complications and optimize recovery

Cytochrome P450 Enzymes and Anesthesia

The CYP450 family encompasses several essential enzymes, including CYP2D6, CYP2C9, and CYP3A4, which play crucial roles in the metabolism of various anesthetics. These enzymes exhibit genetic polymorphisms that lead to different metabolic phenotypes: ultra-rapid metabolizers (UMs), who possess multiple copies of an active enzyme gene and metabolize drugs faster than normal; extensive metabolizers (EMs), who exhibit normal enzyme activity and make up the majority of the population; intermediate metabolizers (IMs), who have reduced enzyme activity and consequently slower drug metabolism; and poor metabolizers (PMs), who exhibit little to no enzyme activity, resulting in very slow drug metabolism. These metabolic variations significantly impact anesthetic drug processing in the body. For example, CYP2D6 is vital for metabolizing opioids like codeine and tramadol, with PMs potentially experiencing little to no analgesic effect due to their inability to convert these drugs into their active forms, while UMs may metabolize opioids rapidly, increasing the risk of overdose and respiratory depression [4]. Similarly, CYP2C9 is involved in metabolizing warfarin, necessitating lower doses for individuals with specific polymorphisms to avoid excessive anticoagulation in perioperative settings [5]. Lastly, CYP3A4 metabolizes a broad spectrum of drugs, including midazolam; variations in this enzyme's activity can affect sedation levels, requiring UMs to take higher doses for desired effects, whereas PMs face the risk of prolonged sedation and complications [6].

Impact on Drug Selection and Dosage

The integration of pharmacogenomics into anesthesia practice allows for a more individualized approach to drug selection and dosage. By understanding a patient's genetic profile, anesthesiologists can predict how the patient will metabolize specific drugs, enabling them to choose the most appropriate anesthetic agents and tailor dosages to minimize risks and maximize efficacy.

Predictive Genetic Testing

Predictive genetic testing can identify polymorphisms in genes encoding drug-metabolizing enzymes, transporters, and receptors. For example:

- **Warfarin and CYP2C9**: As previously mentioned, genetic variants in CYP2C9 can significantly influence warfarin metabolism. Patients with reduced function alleles of CYP2C9 may require lower initial doses of warfarin and more careful monitoring to prevent over-anticoagulation. Additionally, variations in the VKORC1 gene, which encodes the warfarin target enzyme, also influence warfarin sensitivity and dosage requirements [7].
- **Malignant Hyperthermia and RYR1:** The RYR1 gene encodes the ryanodine receptor, a critical component of calcium release channels in muscle cells. Variants in RYR1 are associated with susceptibility to malignant hyperthermia (MH), a life-threatening hypermetabolic reaction to certain anesthetics like succinylcholine and volatile agents (e.g., halothane, isoflurane). Genetic screening for RYR1 variants in at-risk individuals allows anesthesiologists to avoid

triggering agents and opt for safer alternatives, such as non-triggering anesthetics (e.g., propofol) [8].

- **Thiopurines and TPMT:** Although not an anesthetic, thiopurines are immunosuppressive drugs that may be used in perioperative management, particularly in patients undergoing organ transplantation. Thiopurine methyltransferase (TPMT) is an enzyme that metabolizes thiopurines. Individuals with low TPMT activity due to genetic polymorphisms are at risk of severe toxicity, necessitating dose adjustments or alternative therapies [9].

The hypothetical case studies with its clinical applications are mentioned in Table 1.

Table 1. Case Studies and Clinical Applications

	Introduction	Case Example
Opioids	Opioids are a cornerstone of pain management in anesthesia, but their efficacy and safety are heavily influenced by genetic factors. The OPRM1 gene, which encodes the mu-opioid receptor, is a key determinant of opioid response. Variants in OPRM1 can alter the receptor's binding affinity and signaling, leading to variations in analgesic efficacy and the risk of side effects.	A patient with the OPRM1 118A>G variant, which reduces receptor affinity for opioids, may require higher doses of morphine to achieve adequate pain relief. However, this also increases the risk of opioid-induced side effects, such as sedation and respiratory depression. In such cases, alternative pain management strategies, such as multimodal analgesia or the use of non-opioid analgesics, may be more appropriate [10].
Volatile Anesthetics	Volatile anesthetics are commonly used for inducing and maintaining general anesthesia. However, individuals with mutations in the RYR1 gene are at risk for malignant hyperthermia, a condition characterized by a rapid rise in body temperature, muscle rigidity, and metabolic acidosis, which can be fatal if not promptly treated.	A patient with a known RYR1 mutation requires anesthesia for an elective surgery. Genetic testing confirms the risk of MH. The anesthesiologist avoids the use of triggering agents like sevoflurane and instead uses total intravenous anesthesia (TIVA) with propofol, along with appropriate perioperative monitoring and dantrolene availability, to mitigate the risk of MH [11].

Enhancing Patient Safety and Genetic Screening for Risk Identification

Personalized care in anesthesia, grounded in the principles of precision medicine, offers a transformative approach to improving patient safety. By leveraging pharmacogenomics— the study of how an individual's genetic makeup influences their response to drugs—anesthesiologists can anticipate and mitigate potential risks associated with anesthesia. This proactive approach is particularly valuable in identifying patients who are genetically predisposed to adverse drug reactions (ADRs), allowing for the customization of anesthetic protocols to enhance safety and efficacy.

Genetic Screening for Risk Identification

A key strategy in personalized anesthesia care involves genetic screening to identify patients at risk for specific adverse drug reactions (ADRs) related to genetic variants that affect drug metabolism, drug targets, or predispositions to conditions triggered by anesthetic agents. For instance, individuals with genetic mutations in genes such as KCNQ1, KCNH2, or SCN5A are predisposed to prolonged QT syndrome, a condition that can lead to dangerous arrhythmias like Torsades de Pointes [12]. Certain anesthetic agents, including volatile anesthetics and some antiemetics like ondansetron, can exacerbate QT prolongation, so preoperative genetic testing allows anesthesiologists to avoid these agents in at-risk patients, opting for safer alternatives such as total intravenous anesthesia (TIVA) with propofol, which does not affect the QT interval. Additionally, patients with mutations in the RYR1 gene are at risk for malignant hyperthermia, a life-threatening condition triggered by specific anesthetic agents. Early identification of these individuals enables anesthesiologists to avoid triggering agents and ensures that dantrolene, the sole effective treatment, is readily available, significantly reducing the risk of complications [13]. Furthermore, certain genetic variants in the DRD2 and 5-HT3 receptor genes can increase susceptibility to postoperative nausea and vomiting (PONV) [14]. By customizing antiemetic prophylaxis based on a patient's genetic profile, anesthesiologists can decrease the incidence of PONV, thereby enhancing overall patient comfort and safety.

Tailoring Drug Dosage and Selection

A vital component of enhancing patient safety through personalized care is the adjustment of drug dosage and selection based on individual genetic profiles. Genetic polymorphisms in drug-metabolizing enzymes, transporters, and receptors can cause significant variability in drug response, necessitating tailored dosing strategies to prevent toxicity or therapeutic failure. For example, variations in the CYP2D6 enzyme impact the metabolism of codeine and other opioids; patients who are ultra-rapid metabolizers convert codeine to morphine at an accelerated rate, increasing the risk of opioid toxicity, including severe respiratory depression, while poor metabolizers may find standard doses ineffective for pain relief. Pharmacogenomic testing can help anesthesiologists adjust opioid dosing or choose alternative analgesics that do not rely on CYP2D6 metabolism [15]. Similarly, the anticoagulant warfarin has a narrow therapeutic window and varies widely in dosing needs due to genetic differences in the CYP2C9 and VKORC1 genes; patients with reduced CYP2C9 activity or specific VKORC1 variants require lower doses to minimize bleeding risks, making preoperative genetic testing crucial for safe dosing [16]. Additionally, succinylcholine, a muscle relaxant used during intubation, is metabolized by plasma cholinesterase, and genetic variants in the BCHE gene can lead to pseudocholinesterase deficiency, resulting in prolonged paralysis. Identifying this genetic deficiency enables anesthesiologists to adjust the succinylcholine dose or select alternative muscle relaxants, preventing complications associated with prolonged paralysis [17].

Minimizing Perioperative Complications

Personalized anesthetic care is essential for minimizing perioperative complications by tailoring anesthetic management to a patient's genetic profile, which can significantly reduce the risk of adverse events such as drug-induced organ toxicity, severe allergic reactions, or hemodynamic instability. For instance, some patients may have a genetic predisposition to severe allergic reactions or anaphylaxis to specific medications, such as antibiotics or neuromuscular blocking agents, due to variants in the human leukocyte antigen (HLA) complex associated with drug hypersensitivity reactions. Conducting preoperative genetic screening for these variants enables anesthesiologists to avoid potentially life-threatening allergic reactions by selecting safer anesthetic agents. Additionally, certain anesthetics, particularly volatile agents like halothane, can lead to hepatotoxicity in genetically susceptible individuals, with variations in genes such as CYP2E1, which is involved in their metabolism, predisposing some patients to this serious complication. Identifying these genetic risks allows for the selection of non-hepatotoxic alternatives, protecting patients from potential liver damage and enhancing overall safety during the perioperative period.

Optimizing Recovery

Personalized anesthetic care significantly enhances recovery by not only ensuring safety during surgical procedures but also optimizing postoperative outcomes tailored to individual genetic profiles. Effective management of postoperative pain is crucial, as genetic variations in enzymes like CYP2D6 and opioid receptors such as OPRM1 can influence drug metabolism and efficacy. For patients who are poor metabolizers or have low receptor sensitivity, standard opioid doses may lead to inadequate pain relief, which can delay recovery. By utilizing pharmacogenomic data, anesthesiologists can devise more effective pain management strategies, including multimodal analgesia that incorporates non-opioid analgesics and regional anesthesia techniques to reduce reliance on opioids and minimize related side effects.

Additionally, personalized care allows for targeted prophylaxis and treatment of postoperative nausea and vomiting (PONV), with tailored antiemetic regimens for patients identified as high-risk based on genetic profiles, significantly reducing PONV incidence and enhancing postoperative comfort. Furthermore, addressing the risk of postoperative cognitive dysfunction (POCD) and delirium—especially in older adults—is essential; anesthesiologists can select agents with minimal cognitive side effects and adjust dosages according to genetic factors to mitigate these risks. Overall, personalized anesthetic care fosters more predictable and efficient recovery pathways, enabling patients to return to normal activities more quickly with fewer complications and reduced hospital stays. This integration of personalized care in anesthesia practice not only improves patient safety but also advances the field of precision medicine in enhancing postoperative recovery.

Conclusion

Precision medicine in anesthesia, driven by pharmacogenomics, holds the promise of revolutionizing anesthetic care by providing personalized, patient-centered approaches. By tailoring drug selection and dosage to individual genetic profiles, this approach can significantly enhance patient safety, reduce perioperative complications, and optimize recovery. As the field continues to evolve, the integration of pharmacogenomics into clinical practice will play a pivotal role in advancing the future of anesthesia, making it safer and more effective for every patient. This article provides a comprehensive overview of how precision medicine and pharmacogenomics are reshaping the field of anesthesia, emphasizing the importance of personalized care in improving patient outcomes.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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