# Pharmacogenomics of inhalational anesthetic agents

Pharmacogenetics is the branch of science which deals with genetic differences between individuals that can influence drug responses and overall drug metabolism in patients. The genetic factors could affect pharmacokinetics and pharmacodynamics of an administered drug due to changes in receptors, metabolism, and excretion. Thus, a therapeutic dose could be an under dose in some patients and the same dose could be either life threatening or can have undesirable adverse effects.[1] Research in pharmacogenomics has coined the concept of "personalized medicine". Here the knowledge of genetic factors is used by clinicians to prescribe medications which is appropriately tailored to patient's genetic makeup.[2] In anesthesiology, principles of pharmacogenetics have been explained for neuromuscular blocking agents, opioid metabolism, benzodiazepines, local anesthetics, post-operative nausea and vomiting, cardiovascular and hemostatic system, and pain medicine (acute and chronic).[3-5] Genetic mutations can affect the metabolism and excretion of inhalational anesthetics. This communication discusses pharmacogenomics of inhalational anesthetic agents currently used all over the world.

**Inhalational anesthetics and issues with genetic mutations:** Genetic variations and responses to inhalational anesthetics have also been studied and understood. As these agents are predominantly eliminated *via* lungs, the renal and hepatobiliary system has a little role to play. In spite of this, knowing the pharmacogenetics for inhalational anesthetics is important for perioperative physicians *i.e*. anesthesiologists. A genetic variation in an individual should be suspected if an unusual response is noticed at therapeutic concentrations. If there are no systemic conditions leading to such response like hypothyroidism, extremes of age, renal and hepatobiliary disorders; such patients and family members should be informed about such event. They should be educated and also counseled to inform the attending anesthesiologist if they are going to get exposed to any anesthetic in future about the issues faced by them during the previous exposure.

**Inhalational anesthetics: pharmacokinetics and pharmacodynamics:** Inhalational anesthetic agents are an essential component of general anesthesia because they provide amnesia and loss of awareness and also attenuate responses to noxious surgical stimuli. These agents are delivered to the patient *via* anesthetic circuit through a dedicated vaporiser. Commonly used anesthetic agents are isoflurane, sevoflurane and desflurane. The selection of agent depends on the duration of surgery, type of surgery, patient characteristics, personal preference of attending anesthesiologist and sometimes institutional protocols.

The elimination of any anesthetic from the body is by metabolism and excretion. Metabolism involves catabolic phase I reactions, *i.e*. hydrolysis, oxidation and anabolic phase II reactions involves addition of a glucuronyl or methyl group to the metabolite. Excretion of the end product is through the kidneys, hepatobiliary system, or lungs.[6] Less than 5% of inhaled anesthetic is metabolized in the body and the elimination predominantly is through lungs, *i.e*. alveolus.[7] Methoxyflurane is an exception to this as this inhalational agent also undergoes metabolism by enzymatic transformation. However, use of this agent is obsolete now.

Currently used inhalational anesthetics also undergo partial elimination through biotransformation mediated by the cytochrome family enzyme CYP2E1. However, this elimination is very negligible. Studies have shown that 20–50% of halothane, 2% of sevoflurane, less than 1% of isoflurane, and 0.1% of desflurane are metabolized by cytochrome group of enzymes.[8] Genetic variations in CYP2E1 is known but looking at the percentage of enzymatic metabolism known with inhalational anesthetics, the effects of genetic variants will be of not much clinical significance.

**Unusual responses to present inhalational anesthetics:** Sevoflurane anesthesia has been shown to cause emergence agitation which is not desirable in the postoperative period.[9] It was earlier thought that the reason of this could be different rate of recovery of sevoflurane from different areas of brain. The anesthetic effect of sevoflurane in the brain is by its effect on gamma-aminobutyric acid mediated transmission.

Park et al.[10] conducted an interesting study in 114 preschool children who underwent tonsillectomy and adenoidectomy under general anesthesia using sevoflurane. They studied the incidence of emergence agitation in postoperative period at 0, 10, 20 and 30 minutes. Genomic DNAs from peripheral leukocytes were isolated using the QIAamp Blood Minikits and the GABRgamma2 genetic polymorphisms were analyzed by performing polymerase chain reaction-restriction fragment length polymorphism method. Their results showed that AA group in the GABRgamma2-nucleotide position 3145 in intron A/G had a lower incidence of emergence agitation when compared with the non-AA group. However, the comparison was not significant statistically which could be because of small sample size.

Liem et al.[11] had reported that desflurane requirement was 20% more in red heads compared to dark hair individuals. On studying the melanocortin receptor-1 alleles in the two categories of patients, they found that mutations on the melanocortin-1 receptor gene which leads to the characteristic red hair were responsible for increased desflurane requirement in them.

**Malignant hyperthermina: a life threating entity:** Malignant hyperthermia is an autosomal dominant, pharmacogenetic disorder of skeletal muscles that manifest as a hypermetabolic response to volatile anesthetic agents and also seen with the use of depolarizing muscle relaxant succinyl choline. It is characterized by hypermetabolism, hypoxia, hypercapnia and hyperthermia due to abnormal calcium homeostasis. Soon after exposure to the triggering agent, there is a rapid release of calcium from the sarcoplasmic reticulum which leads to an uncontrolled hypermetabolic state which can eventually be responsible for cardiovascular collapse and even death if not addressed on time.[12] For this reason, dantrolene which is a skeletal muscle relaxant that inhibits calcium release from the sarcoplasmic reticulum is now kept in operating rooms and recovery areas.[13,14] The incidence of malignant hyperthermia reactions range from 1:10,000 to 1: 250,000 anesthetics. The two genes implicated with malignant hyperthermia causative mutations are ryanodine receptor 1 and calcium voltage-gated channel subunit alpha1 S.[15]

Malignant hyperthermia also precipitates in certain myopathies like myotonic muscular dystrophy (recessive inheritance), centronuclear myopathy, limb girdle dystrophies and King-Denborough syndrome. The diagnosis is suspected after an anesthetic exposure when above mentioned signs are present or muscle biopsy shows positive findings in predisposing patients. A contracture test is performed by exposing it to halothane and caffeine. Once diagnosed, the patients are issued alerts in the form of bracelets or letter from the physician after educating the patient and family members about the issue. Such patients are suitable for total intravenous anesthesia only.

**Conclusion:** Performing genetic testing and knowing every patient's pharmacogenomic profile are not feasible economically. However, a strong clinical suspicion in situations when unusual response like agitation and increased requirement is observed at therapeutic concentration is very important. Further research in pharmacokinetics and pharmacodynamics might in future offers precision medicine based inhalational anesthetics to all patients. There is a long way to go as the mechanism of action of inhalational anesthetic is exceedingly complex. Patient and family education is important in such situations so as to avoid such events during future anesthesia exposure. However patients suspected with malignant hyperthermia should be investigated thoroughly and once diagnosed an alert should be issued. Results from further research might unleash further genetic variations pertaining to use of inhalational anesthetics.

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