Pharmacogenomics in Anesthesia

Ramsey Saba, MD[a], Alan D. Kaye, MD, PhD, DABA, DABPM, DABIPP[b], Richard D. Urman, MD, MBA[a,*]

KEYWORDS

• Allele • Homozygous • Heterozygous • Genotype • Phenotype
• Pharmacogenomics • Polymorphisms • Single-nucleotide polymorphisms (SNP)
• Genetics

KEY POINTS

- There are a growing number of genomic variations that alter the standard expected course of neuromuscular blocking agents.
- Three common points of genomic expression that lead to opioid interpatient variability include opioid transportation, receptor molecules, and enzymes involved in opioid metabolism.
- There is growing evidence characterizing pharmacogenomics interactions associated with malignant hyperthermia and postoperative nausea and vomiting.
- Better understanding of genetic predisposition to bleeding and arrhythmias following cardiac surgery may change management recommendations.

INTRODUCTION

Much of clinicians' daily practice involves the science of drugs and how to tailor them to each individual patient. It is well documented that different drugs can have much interpatient variability related to various environmental factors, including diet, social habits, and geographic influence. Clinicians are now looking more into the intrinsic causes of variability; notably, differences in a patient's genome. A better understanding of genomic influences on anesthesia may allow a more individually tailored anesthetic and ultimately lead to better outcomes, decreased hospital stays, and improved patient satisfaction. In this article we review several studies and discuss the current role of genetics in drug response-specifically within the realm of anesthesia.

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[a] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; [b] Department of Anesthesiology and Pain Medicine, LSU Health Science Center, Louisiana State University School of Medicine, 1542 Tulane Avenue, Room 659, New Orleans, LA 70112, USA
* Corresponding author.
E-mail address: urmanr@gmail.com

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The concept of pharmacogenetics was first described by geneticist Friedrich Vogel[1] in the late 1950s. He described polymorphisms in the acetylation of isoniazid. This antituberculosis drug is metabolized by acetylation in the liver. Some individuals were slow inactivators of the drug and some were faster. As one would expect, failure rates were higher for fast-activators and slow-inactivators had a higher incidence of toxicity.[2] In this example, the study of inherited differences in drug metabolism is referred to as pharmacogenetics. In a much broader sense, pharmacogenomics refers to the many different genes that determine drug behavior. It is a description of how chromosomal variations affect pharmacologic responses.[3] Much of this translates to polymorphisms that cause variations in drug transporters, metabolizing enzymes, and receptors.[4]

NEUROMUSCULAR BLOCKING AGENTS

In 1957, Kalow and Gunn[5] described an inherited variation in drug metabolism involving succinylcholine and serum cholinesterases. Broad differences in duration of apnea due to succinylcholine administration (as now generally understood by most anesthesiologists) is secondary to well-described polymorphisms in metabolism.

The level and quality of plasma cholinesterase activity (pseudocholinesterase, butyrylcholinesterase [BCHE]) is now understood to determine the clinical effects of several pharmacologic agents. Of the neuromuscular blocking agents, succinylcholine and mivacurium are well-described to be metabolized by these cholinesterases.[6]

Currently, all inherited causes of clinically relevant BCHE deficiency are secondary to point mutations located on chromosome 3.[7] Genetic variations in the BChE have expanded from only 4 known forms to more than 20 identifiable variants in the last several years. This has greatly increased the complexity of diagnosis and interpretation of these genetic traits.[4] More than 96% of the population is homozygous for the normal pseudocholinesterase genotype (U, representing the usual variant) with 3% to 4% heterozygous for the atypical genes. It is estimated that 1 in 2800 people are homozygous for the autosomal-recessive genes of an atypical enzyme.[8,9]

The 2 most common mutations are the A-variant (atypical, or dibucaine resistant; Asp70Gly) and the K-variant (Ala539Thr), which are both common among whites.[10,11] Those who are heterozygous for the K- or A-variant can have prolonged muscle relaxation for up to an hour (3–8 times longer) after 1 to 1.5 mg/kg administration of succinylcholine. Homozygous expression of these alleles can prolong neuromuscular block for up to 60 times longer compared with the normal allele.[3] One of the most serious and rare variants is known as the S-variant. A person homozygous for the S genotype will have no pseudocholinesterase activity and may experience paralysis for up to 8 hours with a single induction dose of succinylcholine.[12,13] Other well-described variants include the fluoride-resistant (F)-variant (with altered hydrolyzing activity) and 2 quantitative variants with decreased enzyme concentration (H, J) (**Table 1**).

Unlike succinylcholine, mivacurium is a benzylisoquinolinium nondepolarizing neuromuscular blocker that has an onset of action of 2 to 3 minutes and a duration of action of 12 to 20 minutes. This duration of action is approximately twice that of succinylcholine and less than half of intermediate-acting nondepolarizing neuromuscular blockers.[13] Because it is also metabolized by pseudocholinesterase, it is not surprising that longer durations of action are seen in many of the described variants. When used for neuromuscular blockade, mivacurium is found to be 4 to 5 times more potent in patients homozygous for atypical or silent genes compared with normal plasma cholinesterase.[14] Of note, mivacurium is currently not being marketed in the United States.