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Pharmacogenomic Considerations In Propofol: A Review

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Abstract

Pharmacogenomics is one of the pivotal fields of science in the era of precision medicine. It helps provide an understanding of what causes the differences in terms of pharmacokinetics and pharmacodynamics of a particular drug in patients. Hence, this leads to better efficacy. This branch of medicine also applies to sedative drugs in the anesthesia field, one of which is propofol. Changes in propofol pharmacokinetics and pharmacodynamics properties might lead to toxicity and inadequate sedation. This review wishes to better understand how pharmacogenomics is applied in anesthesia, especially in propofol, one of its most commonly used medications.

Keywords: Pharmacogenomics, Anesthesia, Sedative, Propofol

Introduction

Pharmacogenomics is significant in current practice since it explains how genes affect how our body responds to certain medications.1 Pharmacogenomics will help identify which drug and dose will work better for individuals. The field of genetics, including pharmacogenomics, has improved significantly after the human genome.[2] A genome is all of the genes in an organism, and genomics is the branch of medicine that studies the genome related to hereditary. Pharmacogenomics is the branch of medicine focusing on how the genome affects how the body responds to the medication.[3]

The pharmacology of a drug can be observed in its pharmacodynamics (the impact of medication on the body) and pharmacokinetics (the body's reaction to drugs). Changes in hereditary material can make significant changes in pharmacodynamics and pharmacokinetics.[3] One of the leading issues in pharmacogenomics is the incidence of adverse events and the differences in drug responses that signal heterogeneity in pharmacology. This phenomenon also applies to anesthesia, with various adverse events and differences in drug efficacy between patients. The contributing factors to this diversity were age, sex, race, body weight, comorbidities, simultaneous medication use, and individual genetic makeup.[2]

In anesthesia, pharmacogenomics plays a part during the preoperative assessment by the anesthesiologist since it offers the chance for a customized sedative arrangement.[4]

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Patients can be grouped into phenotypic types based on the level of enzymatic activity: broad metabolizers (typical action), super quick metabolizers (expanded action), average metabolizers (decreased action), and low metabolizers (almost no enzymatic movement).[5] General anesthetics are commonly conducted in anesthesia, with many considerations, including consciousness, sensory system, blood pressure, respiratory, and pain.[6] As pharmacogenomics researches emerge, hereditary condition and genetic factors are now being considered when choosing anesthetic agents, based on the trials to improve drug distribution.[4,7] This literature review wishes to briefly explain pharmacogenomics consideration in propofol.

Propofol

Propofol as an Intravenous Anesthetics

Propofol is quite possibly regularly utilized intravenous anesthesia drugs. It works using the GABA-A receptor, that no inclination in a certain subunit. CYP2B6 protein hydroxylates Propofol and further O-glucuronidation by UGT1A9. In the auxiliary course, 4-hydroxypropofolis is created by CYP2C9 which is additionally used by the proteins DT-diaphorase (NQ01) and sulphotransferase or formed. Propofol infusion disorder, asystole, and Bradycardia are unfavorable impacts of propofol; however, it isn't clear if they are possibly portioned subordinate or, on the other hand, assuming hereditary variables influencing propofol attitude and impacts assume a part.[8]

Propofol as an Intravenous Induction Drug

Propofol is the enlistment of general sedation that might include the assistance of inhibitory neurotransmission interceded by GABA-A receptor restriction. Propofol allosterically builds restricting liking of GABA for the GABA receptor. This receptor, as recently noted, is coupled to a chloride channel, and the actuation of the receptor prompts hyperpolarization of the nerve layer.[9]

Propofol isn't water-soluble, but a fluid arrangement is accessible for intravenous administration as an oil-in-water emulsion. This mixing will frequently cause pain during infusion that can be diminished by earlier infusion of lidocaine or less really by blending lidocaine 9 There is a significant individual vulnerability to propofol. Its cause can be connected with hereditary polymorphism. There is a change in our gene related to propofol use, specifically a change in the 5HT2A gene.[8] Because of propofol's quick beginning and fast recuperation, it is a generally expected sedative medication for acceptance and upkeep. In any case, propofol administration isn't suggested for basically sick youngsters. As of late, the calming impact of propofol has been thought of.[8]

Ongoing investigations and research has zeroed in on the differential impacts on the proteome of intravenous versus inhalational specialists. Distributions have shown that propofol and unstable sedatives produce proteomic changes that are discoverable in the research facility.[3] Higher propofol openness will occur within 1 hour from the beginning of the mixture without dose change in these patients hence showing the meaning of this specific polymorphism for portion change to get ideal sedation and avoid unfriendly impacts.[6]

The Use of Pharmacogenomics in Perioperative Medication

Perioperative medications and sedation-related circumstances can be ordered, given information acquired from hereditary arrangements and variations. Malignant Hyperthermia (MH) is an autosomal predominant condition. Strange calcium homeostasis causes hypermetabolism,

hypoxia, hypercapnia, and hyperthermia in this condition. One potential explanation for changes in the ryanodine receptor quality (RYR1) in 70% of cases and transformations in the CACNA1S quality in 1% of the populace is recommended. Unstable sedatives or suxamethonium trigger MH; so thus, dantrolene (a skeletal muscle relaxant that lessens the arrival of calcium from the sarcoplasmic reticulum) is kept in the working room and recuperation area.[8]

For patients associated with having encountered MH, a muscle biopsy is prescribed to test the contracture condition. In this test, constriction is a positive outcome. Patients with positive or obscure effects ought to get MH-safe sedation for example, intravenous sedation. Powerful testing diminishes the MH death rate. Propofol infusion disorder (PRIS) is a model that could be an objective for pharmacogenomic research. PRIS starts with the presence of metabolic acidosis, rhabdomyolysis, and arrhythmias. Arrhythmias brought about by long haul (>48 hours) and high portion (>4 mg/kg/hour) of propofol. In patients who have had PRIS, a comprehension of the specific etiology of the genotype is vital. Screening given this pharmacogenomic information can successfully lessen the occurrence of PRIS. Individual hereditary profiles permit deciding treatment regimens for them in light of their pharmacokinetic genotype.[8]

Pharmacokinetics (PK) of Propofol

Absorption

Propofol is more appropriate to use intravenously and is not good enough to be taken orally because of its taste. The low oral metabolism caused by the first entry of metabolism impact and the high liver extraction rate of about 90% makes it unsuitable for use by routes other than intravenous. Several researchers have tried to expand propofol's oral bioavailability, one of which is by using nanoparticle assay.[10]

Distribution

Propofol is broadly engaged with the proteins in the plasma, for example, albumin, and red blood cells, after intravenous organization. The free division is, as it were 1.2–1.7%. Almost 50% of propofol is bound to the erythrocytes, and numerous clinical Pharmacokinetic examiners degree entirety concentrations instead of plasma propofol concentrations.[10,11] When propofol causes rapid loss of consciousness in one cycle, it can cross the blood-brain barrier.

Cardiac output is very important in patient induction, especially in the speed of induction and implantation. The proportion of free propofol in CSF is about 31%, of which 1% goes into plasma. The balance between brain and blood concentrations occurred after 30 minutes, with the proportion of propofol as much as 0.01 – 0.02. Propofol is safe to use in cesarean section because the placenta exchange is relatively fast and extensive, in neonates, the concentration will be removed, so there is no need to worry about its effects because it will not last long in neonates. The proportion of mother to fetus is about 0.7 to 0.8.[10]

In a rapid initial distribution, the clinical effect will also be shorter because the time given is relatively short after a single bolus administration. The volume distribution of propofol into the large-capacity compartment will be slow due to its high lipid solubility. Therefore, a large volume of distribution of 3-4 times the total body volume is produced, although there is no obesity factor. The redistribution of this drug is slow due to an imbalance between metabolism and excretion. However, clinically the effect is still above other hypnotic intravenous medicines.[10]

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In some cases, reducing this drug's dose is quite beneficial compared to other types of hypnotics. An infusion of about three hours can decrease by nearly eighty percent for fifty minutes; on the other hand, an infusion of a long duration of almost half a day can increase by about three hours.[10,12]

Metabolism

Conjugated propofol will become propofol glucuronide, almost seventy percent, which is facilitated by UDP glucuronosyltransferase. 4 - hydroxypropyl is the hydroxylation product of nearly thirty percent of propofol. Various isoforms of cytochrome P450 interact in propofol metabolism, with CYP2C9 first and CYP2B6 being the lowest. The result of this conjugation of propofol can provide a hypnotic effect compared to its main metabolite.[10]

Hepatic perfusion and hepatic blood flow will affect propofol levels; the lower the flow, the lower the metabolism. The efficiency of this drug metabolism is almost Ninety percent in the liver. The clearance process is higher than the blood flow to the liver, which is 2.2 liters per minute. Reductions that occur outside the hepatic process are up to forty percent, for example, in the kidneys, with a ratio of sixty to seventy percent, or equivalent to one-third of the total metabolism. If it enters the small intestine, the extraction reaches twenty-five percent. On the other hand, lung involvement is still temporary, releasing propofol from returning to circulation.[10]

Elimination and Excretion

The process of elimination of propofol can be found in the urine after five days almost 90%. Only a small part (<1%) was found intact, the metabolites would be found in a green color change in the urine. On inhalation, propofol is also excreted in minimal amounts. However, there was no difference in concentration between the plasma and the expired concentration. Measurement of concentration in the breath can use a spectrometer from exhaled air.[10]

Pharmacodynamic (PD) of Propofol

Central Nervous System

The hypnotic effect of this drug is the result of the potentiation of the neurotransmitter GABA inhibitors. Postsynaptic hyperpolarization and inhibition of neuronal depolarization result from binding to the b-subunit of postsynaptic GABAA but also influence this effect. If given a high concentration, it will directly open the activation channel; if the concentration is low, there will be chloride potentiation by the influence of GABA.[10,13]

Cardiovascular System

The main effect on the cardiovascular system is decreased cardiac output and a systemic down in blood pressure. However, this happens depending on the dose, and even in the sedative dose can still occur. In geriatrics, this is partly mediated by a critical diminish in sympathetic tone with changes in vascular resistance while being decreased. Cardiovascular depressant effects may occur, inhibiting the bare reflection of the physiological response.[14]

Hepatorenal System

Liver function is not affected much by this drug, although its metabolism and excretion are very extensive in the liver. High hepatic arteries and the presence of portal venous flow affect hepatic perfusion. Therefore we must maintain cardiac output to maintain liver and kidney perfusion. This is done so that there is no impaired function of the kidneys and liver. Cloudy urine is slightly greenish is the effect of the phenol green chromophore, after which uric acid excretion will occur in the urine, resulting in cloudy urine.[11]

Pharmacogenomics can influence the use of anesthetic drugs, which can result in adverse

drug events, overdose, and even death. In the use of anesthetic drugs, two types of events are the main focus of the adverse drug event, namely prolonged apnea and malignant hyperthermia.[15]

Propofol is often used as an induction and maintenance agent in anesthesia. Propofol is metabolized by CYP2B6 by extrahepatic cytochrome, CYP2C9, and UGT1A9. However, the CYP2B6 enzyme has been the most studied of the metabolic processes of propofol in several pharmacogenomic studies. CYP2B6*4 showed a significant difference in the process of elimination of propofol. In patients with CYP2B6*6, the T allele represents the need for a lower dose when undergoing general anesthesia. In the UGT1A9 gene, polymorphism also affects glucuronidase (propofol metabolism) and increases the risk of adverse reactions.[16]

The use of propofol in deep sedation inhibits the stress response, resulting in hypotension, sometimes brain tissue damage, complications due to sedation, and even worsening for the patient. If used under light sedation, or inadequate anesthesia, it can lead to tachycardia, hypertension, or worse; the patient is conscious during the operation. Propofol is also influenced pharmacodynamically by gene variants at the gamma-aminobutyric acid (GABAA) receptor target (GABRE).[17]

The effect of propofol on each individual generally has the same response, but in certain individuals, its use causes different symptoms or ADEs. This is partly influenced by the genetic composition of the individual. According to Awad et al., 2019[7] in patients with the CYP2B6*4 allele, it describes a decrease in drug clearance so it is suspected that there will be an increase in drug toxicity even with the usual dose. In a study by Luzon et al., 2018 in assessing nitric oxide synthase (NOS3), it was found that an increase and a decrease in average blood pressure and nitrite level occurred in patients with the CT + TT and ba + aa genotypes. A significant decrease in heart rate occurred in carriers of the ba + aa genotype. In carriers, the TT genotype resulted in a higher nitrate level increase than the GT and GG genotypes.[18]

Pavlovic et al., 2020, conducted a study on polymorphisms of the genes UGT1A9, CYP2B6, and CYP2C9 with propofol pharmacokinetics in children. As a result of metabolism by UGT1A9, the TT genotype required a higher dose of propofol than the CT genotype. The same data are shown from the metabolic process of CYP2B6, the dose required for patients with the GG genotype is greater than in patients with the GT+TT genotype.[16,20]

According to Zhang et al., 2017, who examined the propofol-remifentanil combination with MDR1 gene polymorphism in pediatric tonsillectomy surgery, the results of MDR1 1236C>T genotype CT+TT required a longer time than children with the CC genotype, at induction, recovery time. exhalation, eye-opening, and extubation. the same thing showed that patients with genotype TT require large doses of propofol and remifentanil because decreased of transport function by P-GP patients with TT genotype, which made propofol and remifentanil accumulate in the liver.[21]

Conclusion

Individuals will have different responses on medication, and it also happens in anesthesia medication, such as propofol. The number of doses, cleaning time, and side effects of propofol is determined by each individual's genetics.

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References

1. Pharmacogenomics: What does it mean for your health? | CDC. Cdc.gov. (2022). Retrieved 9 February 2022, from https://*www.cdc.gov/genomics/disease/pharma.htm.*
2. P, D., S, T., S, D., Awad, H., & JP, K. Pharmacogenomics applications in perioperative medicine. *Journal Of Translational Science*. 2018;4(5). https://doi.org/10.15761/jts.1000228
3. Walton, Thomas.. Omic and anesthesia: pharmacogenomics, proteomics, and metabolomics. *Anesthesia and intensive care medicine,* 2019, 1-6. https://doi.org/10.1016/j.mpaic.2019.01.019.
4. Jhun, Ellie. 2019. Pharmacogenomic considerations for medications in the perioperative setting. *Pharmacogenomics* (2019) 20(11), 813–827.
5. Dib P, Tung SR. 2018. Pharmacogenomics applications in perioperative medicine. *Journal of Translational Science* (2018) Volume 4(5): 1-6. DOI: 10.15761/JTS.1000228
6. Bach-Rojecky, Lidija. Challenges in anesthesia personalization: resolving the pharmacogenomic puzzle. *Future Medicine*.2019;16;6. doi: 10.2217/pme-2019-0056
7. Awad, Hamdy. Potential role of pharmacogenomics testing in the setting of enhanced recovery pathways after surgery. *Pharmacogenomics and Personalized Medicine.* 2019:12 145–154. http://doi.org/10.2147/PGPM.S198224.
8. Dabbagh, Ali. 2021. *Personalized Medicine in Anesthesia, Pain and Perioperative Medicine.* Switzerland; Springer.
9. Butterworth, J., Mackey, D., & Wasnick, J.. Morgan & Mikhail's. *Clinical Anesthesiology*, 2018; 8e (6th ed., pp. 303-304). McGraw-Hill Education LLC.
10. Sahinovic, MM; Michel M. R. F. Struys; Anthony R. Absalom. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clinical Pharmacokinetics*. 2018;57:1539–1558.
11. Sahinovic MM. I*ntravenous drug dose optimization and drug effect monitoring in anesthesia*. Groningen: Rijksuniversiteit Groningen; 2017.
12. Colin P, Eleveld DJ, van den Berg JP, Vereecke HEM, Struys MMRF, Schelling G, et al. Propofol breath monitoring as a potential tool to improve the prediction of intraoperative plasma concentrations. *Clinical Pharmacokinetics*. 2016;55:849–59.
13. Adapa RM. Consciousness and anesthesia. In: Absalom AR, Mason KP, editors. *Total intravenous anesthesia and target-controlled infusions*. Cham: Springer International Publishing; 2017. p. 63–78.
14. Hara M, Masui K, Eleveld DJ, Struys MMRF, Uchida O. Predictive performance of eleven pharmacokinetic models for propofol infusion in children for long-duration anesthesia. *British Journal of Anaesthesia*. 2017;118:415–23.
15. Dinis-Oliveira, R. Metabolic Profiles of Propofol and Fospropofol: Clinical and Forensic Interpretative Aspects. *Biomed Research International,* 2018, 1-16. https://doi.org/10.1155/2018/6852857
16. Pavlovic, D., Budic, I., Jevtovic Stoimenov, T., Stokanovic, D., Marjanovic, V., Stevic, M., Slavkovic, M., & Simic, D. The effect of ugt1a9, cyp2b6, and cyp2c9 genes polymorphism

on propofol pharmacokinetics in children. *Pharmacogenomics and Personalized Medicine,* 2020;Volume 13, 13–27. https://doi.org/10.2147/pgpm.s231329

17. Xie, S., Ma, W., Guo, Q., Liu, J., Li, W., McLeod, H., & He, Y. The pharmacogenetics of medications used in general anesthesia. *Pharmacogenomic*s, 2018;19(3), 285-298. https://doi.org/10.2217/pgs-2017-0168 (5
18. Luizon, M., Pereira, D., & Tanus-Santos, J. Pharmacogenetic relevance of endothelial nitric oxide synthase polymorphisms and gene interactions. *Pharmacogenomics,* 2018;19(18), 1423-1435. https://doi.org/10.2217/pgs-2018-0098
19. Zhang, L., Zheng, Z., Ma, W., Zhang, S., Xue, F., & Wang, H. et al. The Effects of Gene Variations of GABRA2, GABRB1, GABRG2, GAD1, and SLC1A3 on Patients with Propofol During Anesthesia Induction. *Pharmacogenomics And Personalized Medicine*, 2021;Volume 14, 1185-1192. https://doi.org/10.2147/pgpm.s326885
20. Eugene, AR. CYP2B6 Genotype Guided Dosing of Propofol Anesthesia in the Elderly Based on Nonparametric Population Pharmacokinetic Modeling and Simulations. *International Journal Of Clinical Pharmacology & Toxicology,* 2017; 242-249. https://doi.org/10.19070/2167-910x-1700041
21. Zhang, Y., Li, Y., Wang, H., Cai, F., Shen, S., & Luo, X. Correlation of MDR1 gene polymorphism with propofol combined with remifentanil anesthesia in pediatric tonsillectomy. *Oncotarget,* 2017;9 (29), 20294 - 20303. https://doi.org/10.18632/oncotarget.23168