

АНАЛІТИЧНІ ОГЛЯДИ

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PHARMACOGENETICS
OF ANESTHESIOLOGICAL SUPPORT*O. O. Skavinska¹, L. E. Fishchuk¹,
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(Kyiv, Ukraine)³**Summary.**

Pharmacogenetics studies the relationship between a person's individual genetic characteristics and the human body's response to the action of various drugs, particularly the occurrence of undesirable side effects. Thanks to the development of the latest technologies and methods, this branch of medical genetics and clinical pharmacology is developing very actively. Data are being accumulated, special databases are being created with the aim of creating individual genetic passports in the future, which will allow the selection of personalized treatment schemes.

Anesthesiology is a special area of pharmacogenetic research because, more than any other medical specialty, it is characterized by polypharmacy—the simultaneous or sequential administration of many drugs. The same dose of a drug may be inadequate for some patients and may be life-threatening or cause unwanted side effects for others. Today, information about genetic factors is being used by clinicians to prescribe drugs to tailor drug therapy to a patient's genome. In anesthesiology, the principles of pharmacogenetics have been explained for neuromuscular blocking agents, opioid metabolism, different types of anesthetics, and postoperative nausea and vomiting. On the other hand, a large number of anesthetics have a narrow therapeutic index.

This review summarizes the most recent data from the scientific literature on the pharmacogenetics of different types of anesthetics.

Inhalational anesthetics are halogenated derivatives of methyl ethyl ether, the exact mechanism of action of which is not yet fully understood. One of the rare but very serious side effects of all halogenated anesthetics is malignant hyperthermia, a genetically determined autosomal dominant disorder that manifests as a hypermetabolic response to drug administration. The dosage of intravenous anesthetics should also be carefully determined, taking into account the patient's age, cardiovascular, hepatic, and renal status, concomitant drug therapy, and genetic factors. Ontogeny and genetic variability of drug-metabolizing enzymes are interrelated because genetic variability in drug-metabolizing enzyme expression cannot be assessed until the required protein is sufficiently expressed. Pharmacogenetic variants may contribute to unpredictable drug exposure at the same weight-based drug dose.

There are a number of potentially clinically applicable pharmacogenetic data in newborns, but more research is needed to confirm these findings and understand how to incorporate them into clinical care.

The selection of drugs and dosing regimens based on a patient's pharmacogenomic profile may be an important part of the future of medicine. Personalized treatment based on the specific variants in the genome will ultimately reduce the incidence of side effects and length of hospital stay for patients and save healthcare costs. Although pharmacogenomics and its application in clinical practice are still in their infancy, different variants and their implications for many clinical areas, including anesthesiology, are emerging every day.

Key words: *Pharmacogenetics; Anesthetic Support; Inhalation Anesthetics; Propofol; Opiates; Neuromuscular Blockers; General Anesthesia in Children.*

Introduction

Genes are known to influence the pharmacokinetics and pharmacodynamics of the drug administered. The same dose of a drug may not be sufficient for some patients and may be life-threatening or cause adverse side effects for others. Today, information about genetic factors is used by clinicians to prescribe drugs in order to tailor drug therapy to the patient's genome. In anesthesiology, the principles of pharmacogenetics have been explained for neuromuscular blockers, opioid metabolism, different types of anesthetics, and postoperative nausea and vomiting. This review discusses the pharmacogenomics of inhaled and topical

anesthetics, opioids, and neuromuscular blocking agents currently used worldwide with a focus on the pediatric population.

Inhalation anesthetics

Inhalational anesthetics (IA) are halogenated derivatives of methyl ethyl ether and are classified according to their physicochemical properties (flammability, odor, volatility), minimum alveolar concentration, and solubility. The exact mechanism of their action is still not fully understood and has historically been explained by two main theories. The first theory, now largely abandoned, proposed a non-

specific interaction of the anesthetic with hydrophobic lipid components of the cell, while another theory proposed specific membrane proteins as sites for anesthetic binding [1]. Among these membrane proteins, neuronal ion channels are the most likely molecular targets. They are part of the complex of receptors for neurotransmitters such as nicotinic acetylcholine, GABA, and glutamate N-methyl-D-aspartate [2, 3]. The most commonly used inhalational anesthetics are isoflurane, desflurane, and sevoflurane.

Isoflurane causes concentration-dependent profound respiratory depression and hypotension due to a decrease in systemic vascular resistance. With rapid changes in concentration, it may cause transient tachycardia and hypertension as a result of sympathetic nervous system stimulation [4]. Nearly 99 % of the drug is eliminated unchanged through the lungs [1].

Desflurane has the lowest potency and solubility in blood and other tissues compared to other inhalational anesthetics. As a result, it provides rapid induction and recovery of the patient from anesthesia. In addition, it has the lowest blood solubility among inhaled anesthetics and is recommended for bariatric patients undergoing long-term surgery. It is almost completely metabolized unchanged in the lungs and carries no risk of hepatotoxicity or nephrotoxicity.

Nitrous oxide (N₂O) is the only gas with specific properties among the IAs. Although it does not provide the depth of anesthesia required, it is commonly used in combination with halogenated anesthetics. Nitrous oxide is the least soluble of all general anesthetics and therefore causes rapid onset and rapid recovery from anesthesia. It also has a significant analgesic effect by stimulating the central opioid and adrenergic systems [1]. N₂O stimulates the sympathetic nervous system and, when administered in combination with halogenated drugs, increases blood pressure, heart rate and cardiac output, while the opposite response is observed when administered concurrently with opioids. This can lead to certain risks such as pneumothorax, air embolism, middle ear obstruction [5].

N₂O oxidizes the cobalt in vitamin B₁₂, a cofactor for the enzyme methionine synthase, thereby reducing the remethylation of homocysteine for the synthesis of methionine and folic acid. This can lead to DNA hypomethylation, defective DNA synthesis, cell apoptosis, and signs of megaloblastic anemia and peripheral neuropathy [6]. The importance of MTHFR gene variants for these adverse effects of N₂O seems relevant, but further research is needed.

In general, the choice of medication depends on the duration and type of surgery, the clinical parameters of the patient, the personal preferences of the anesthesiologist, and sometimes the protocols of the health care institution. Removal of any anesthetic from the body occurs through metabolism and excretion. Metabolism includes Phase I catabolic reactions, i. e., hydrolysis, oxidation, and Phase II anabolic reactions, which involve the addition of a glucuronyl or methyl group to the metabolite. Excretion of the end product occurs through the kidneys, hepatobiliary system, or lungs. Excretion of IA occurs primarily through the alveoli [7]. Methoxyflurane is an exception as it is

also metabolized by enzymatic conversion followed by renal excretion. However, the use of this drug is currently minimized.

As mentioned above, the alveoli are the major route of elimination for inhalational anesthetics. Partial elimination by biotransformation (via CYP2E1) also occurs, but plays a minimal role in the elimination of the anesthetic. AIs that are metabolized more intensively (e. g., methoxyflurane) are more susceptible to enzymatic biotransformation [8]. Between 20 % and 50 % of halothane, 2 % of sevoflurane, less than 1 % of isoflurane, and 0.1 % of desflurane are metabolized by enzymes. Halothane is more soluble than sevoflurane, but is eliminated more rapidly due to more intense biotransformation [9].

Sevoflurane is known to affect GABAergic transmission [10]. In a recent experimental study by Mapelli J et al, sevoflurane altered neurotransmission by enhancing GABAergic inhibition while simultaneously inhibiting NMDA receptor activity [11].

Variants of the melanocortin-1 receptor (MC1R) gene have long been associated with an increased need for desflurane anesthesia [10]. Interestingly, the phenotype of all redheads can be traced back to different variants of the MC1R gene. It has been shown that women with red hair require almost 20 % more desflurane than women with dark hair and are also significantly more resistant to the effects of subcutaneously injected lidocaine [7].

One of the rare but very serious side effects of all potent halogenated anesthetics is malignant hyperthermia (MH) [12]. MH is a genetically determined autosomal dominant disorder that manifests as a hypermetabolic response to IA and is also observed with the use of the depolarizing muscle relaxant succinylcholine [6]. This disorder is characterized by hypermetabolism, hypoxia, hypercapnia, and hyperthermia due to impaired calcium homeostasis. Soon after exposure to the triggering drug, there is a rapid release of calcium ions from the sarcoplasmic reticulum, leading to an uncontrolled hypermetabolic state that can eventually cause cardiovascular collapse and even death if timely first aid measures are not taken [13]. For this reason, dantrolene, a skeletal muscle relaxant that inhibits the release of calcium from the sarcoplasmic reticulum, should now be stocked in operating and resuscitation rooms [13]. The frequency of malignant hyperthermia ranges from 1:10,000 to 1:250,000. Two genes whose variants are associated with the risk of MH are the RYR1 gene, which encodes the ryanodine receptor 1, and the CACNA1S gene, which encodes the α -1S subunit of the L-type calcium channel [14]. A thorough systematic review of the literature was conducted on the association between 48 pathogenic variants of the RYR1 gene, two variants of the CACNA1S gene, and MH. Therefore, based on a high level of evidence, the Clinical Pharmacogenetics Implementation Consortium (CPIC) issued therapeutic guidelines advising against the use of halogenated anesthetics in patients with an established genetic risk for MH based on RYR1 and CACNA1S gene variants [15]. Although the exact mechanism is unknown, these mutations may make the channels more sensitive to activation by depolarization or IA action [13].

Intravenous anesthetics

If necessary, taking into account the duration and type of surgery, as well as in patients with absolute or relative contraindications to IA, intravenous anesthetics may be used not only for induction but also for maintenance of general anesthesia. The dosage of intravenous anesthetics should be carefully determined, taking into account the patient's age, cardiovascular, hepatic and renal status, concomitant drug therapy, and genetic factors [1].

Propofol is the most commonly used parenteral anesthetic for induction and maintenance of anesthesia. Fospropofol is administered as an aqueous solution, unlike propofol, which is manufactured as a lipid emulsion, and is better tolerated. Propofol has sedative-hypnotic, anticonvulsant, anti-inflammatory, antiemetic, antioxidant, and possibly neuroprotective effects [16]. Adverse effects of propofol are well documented and the most common is post-injection pain, while others include bradycardia, hypotension, loss of airway reflexes, apnea, and hyperlipidemia [16, 17]. It has been repeatedly demonstrated that individual susceptibility to propofol and the risk of adverse effects vary widely and often cannot be estimated from the clinical characteristics and health status of the patient. It is possible that polymorphisms of genes encoding molecular targets or enzymes involved in drug clearance may influence the individual variability of propofol side effects, although clear evidence for the role of genes is still lacking.

Propofol activates GABA receptors, blocks NMDA glutamate receptors and prevents calcium from entering the cell [18]. One recent study analyzed genes possibly related to the pharmacological profile of propofol. It was established that carriers of the minor G allele of the *rs6313* variant of the *5HT2A* gene encoding the serotonin receptor required a lower dose of propofol and a shorter time for induction of anesthesia [19]. Associations between the *GABRA1* and *GABRB2* genes and sensitivity to propofol were also determined. It has been shown that variants of *GABRB2* *rs3816596* and *GABRA1* *rs4263535* are associated with sensitivity to the sedative effect of propofol, and variants of *GABRA1* *rs1157122* and *GABRB2* *rs76774144* are associated with a lower degree of decrease in blood pressure after administration of propofol [20]. In addition, the *CT/CC* genotypes of *GABRB1* *rs4694846* were associated with heart rate instability, and the *GG* *GABRB2* *rs1167768* genotype was associated with greater instability of mean blood pressure values [21].

The contribution of variants in the genes encoding the metabolic enzymes CYP2B6 and uridine-50-diphosphate (UDP) glucuronosyltransferase may also influence variability in response to propofol.

Propofol is mostly conjugated to the glucuronide (70 %), while 30 % of the drug is first hydroxylated by CYP2B6. As the *CYP2B6* gene is one of the most polymorphic *CYP* gene families, several recent clinical studies have investigated its importance for propofol dosing [22, 23]. Dosage modeling based on the *rs2279343* variant of the *CYP2B6* gene suggests a 50 % reduction in the infusion dose of propofol in patients with *AA* and *AG* genotypes during maintenance of general anesthesia.

Without dose adjustment, propofol exposure will increase by 250 % within 1 hour of the start of infusion, indicating the importance of this particular option for dose adjustment to ensure optimal anesthesia and avoid side effects [21].

Despite some positive correlation between specific genotypes and characteristics of propofol-induced anesthesia, the lack of reproducibility of the data limits the implementation of preoperative genetic screening to identify individuals requiring dose adjustment [20].

Etomidate is primarily used to induce anesthesia in patients at risk for arterial hypotension because of its minimal effects on the cardiovascular system [1]. This drug significantly suppresses the enzyme 11- β -hydroxylase and the synthesis of cortisol and aldosterone in the adrenal glands. Because this effect lasts for 6 to 8 hours after a bolus injection, etomidate may be harmful in critically ill patients. As a hydrophobic derivative of imidazole, etomidate is composed of propylene glycol, and injection of this solution causes severe irritation and is accompanied by severe pain. Unlike propofol, etomidate has simpler pharmacological properties: it mainly activates GABA receptors, and biotransformation involves hydrolysis by hepatic esterases to inactive metabolites that are excreted in the urine. The genetic contribution to the efficacy and safety profile of etomidate is still poorly understood. One study showed that *GABRA2* *rs279858*, *GABRB2* *rs2561*, *CYP2C9* *rs1559* and *UGT1A9* *rs11692021* variants were associated with individual differences during etomidate anesthesia, but this needs further study [18].

Another commonly used drug is ketamine. Due to its water solubility and extensive absorption, it can be administered by various routes: intramuscular, oral, rectal, and intranasal, which can be useful in patients with limited intravenous access [1]. It has a potent analgesic effect, inducing hypnosis and amnesia while allowing patients to breathe spontaneously. Ketamine is a non-competitive antagonist of glutamate NMDA receptors, thus preventing the influx of calcium ions into the cell, although it has other pharmacological targets with lower affinity [14]. In addition, ketamine reduces the need for opioid analgesics [15].

Unlike other anesthetics, ketamine increases heart rate, blood pressure, and cardiac output, has a broncholytic effect, and is therefore suitable for patients with hemodynamic instability such as hypovolemia, cardiogenic shock, constrictive heart disease, and severe asthma [1]. However, the use of ketamine can also lead to a unique set of side effects (e.g., behavioral changes, lacrimation, salivation, increased general muscle tone, spontaneous limb movements, as well as hallucinations, delusions, vivid dreams) that limit the use of this anesthetic [22].

Ketamine is actively metabolized in the liver. It is oxidized mainly by CYP3A4 and to a lesser extent by CYP2B6 to active norketamine, which is excreted by the kidneys in the form of glucuronide [23].

The relevance of different genotypes to the efficacy of ketamine has been investigated in several in vitro and clinical studies [20, 21, 23]. According to one of the clinical studies, the *CYP2B6**6 allele is associated with reduced clearance and, as a result, an increase in the concentration

of ketamine in the blood plasma, which leads to a higher frequency of side effects [24]. However, additional data on the potential clinical significance of *CYP2B6* gene genotypes are needed.

Thiopental is the only thiobarbiturate that is still used, albeit rarely, for anesthesia because of its potent sedative and hypnotic effects, rapid onset, and ultra-short duration of action due to its very high solubility in lipids [24]. Although the anesthetic effect lasts less than 10 minutes after a single bolus injection, the patient requires more than 24 hours to fully recover from anesthesia after a prolonged infusion. This is due to rapid redistribution of thiopental from the central nervous system and slow clearance from peripheral adipose tissue, where it accumulates. It is metabolized in the liver in several steps, including desulfurization and N-dealkylation to active pentobarbital, and is excreted in the urine.

As a positive allosteric modulator of GABA receptors, thiopental increases the time that GABA-associated chloride channels are open, while higher doses may directly activate channel opening. In addition, thiopental modulates the nACh receptor and the Ca²⁺-ATPase involved in calcium ion homeostasis [7]. Despite its long history of use, the potential influence of pharmacogenomics on its pharmacological properties, efficacy and safety is currently unknown.

Opioids

Opioids are the most widely used class of analgesics in anesthesia. They interact to varying degrees with mu, delta, and/or kappa receptors and produce a variety of effects, both desirable and undesirable [25].

Fentanyl and its parenteral analogs, sufentanil, remifentanil, and alfentanil, are synthetic opioids commonly used in anesthesia because of their rapid and potent analgesic effects. These anesthetics vary in potency, with alfentanil having approximately 1/4 to 1/10 the potency of fentanyl, while sufentanil is five to ten times more potent and is the most potent opioid analgesic. The choice of drug depends primarily on the duration of action. Fentanyl and sufentanil have a short time to achieve maximum analgesia, with rapid offset after small bolus doses – 30 and 20 minutes, respectively. Because remifentanil has a duration of action of <10 min and a low accumulation potential, it is suitable for short-term procedures [2]. In addition to the common side effects of opioids, remifentanil slows heart rate, lowers blood pressure, and increases the need for postoperative analgesia.

Fentanyl is metabolized by CYP3A4 and CYP3A5 enzymes. The presence of CYP3A5 (*CYP3A5*3*) and ABCB1 gene variants (1236C>T, 2677G>A/T and 3435C>T) leads to significant changes in plasma fentanyl concentration. Fentanyl levels were shown to be approximately twice as high in *CYP3A5*3* homozygotes compared to *CYP3A5*1* carriers. Response to fentanyl can be modified by opioid receptors and COMT gene variants [26]. Thus, OPRM1 (118A>G) and COMT (Val158Met, G>A) gene variants can lead to increased or decreased response to fentanyl depending on the genetic profile [1]. Despite the availability of data on these variants in

the literature, to date, no statistically significant results have been registered regarding the influence of a genetic determinant on the development of side effects associated with the use of fentanyl [27].

Remifentanil, like morphine and fentanyl, binds to the μ -opioid receptor, showing an analgesic effect. Moderate-quality evidence showed that variability in analgesic effect is influenced by genetic variants in the genes encoding OPRM1, P-glycoprotein (P-gp) and catechol-O-methyltransferase. One of the most studied genetic variants associated with OPRM1 and opioid analgesic action is the rs1799971 (118 A>G) variant of the OPRM1 gene of the same name. Convincing evidence in favor of this functional variant is given in a meta-analysis, where it was determined that the presence of the GG genotype is associated with a reduced analgesic effect and the need for higher doses of opioids. Further studies confirmed that this finding is also relevant for fentanyl, alfentanil and sufentanil [28]. Also, in Chinese women carriers of the OPRM1 rs9397685 variant with the AA genotype, a higher sensitivity to the analgesic effect of remifentanil was recorded [29].

It was shown that the rs5030977 variant of the CACNA2D2 gene was correlated with increased sensitivity to remifentanil, and the rs1045642 variant of the ABCB1 gene was associated with a higher risk of side effects when using this anesthetic [27]. In the literature, one can find conflicting results regarding the influence of variants of the ABCB1 gene, which encodes P-glycoprotein, on the dosage of anesthetics. Thus, the AA genotype with the rs1045642 variant seems to be associated with the efficacy of a lower dose of fentanyl [28]. However, further studies are needed to establish the clinical significance of this polymorphism.

Codeine is metabolized by CYP2D6 to morphine. Therefore, the response to codeine may vary depending on variants of the CYP2D6 gene [30]. It has been shown that there are both slow metabolizers (SM) and ultrametabolizers (UM) of codeine, which leads to an increase or decrease in the amount of its breakdown product in the blood [31]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines strongly recommend that UM and SM of CYP2D6 avoid codeine due to increased risk of toxicity and lack of analgesic effect, respectively [32]. In addition, the FDA cautions against using codeine in adolescents who are obese or in those with obstructive sleep apnea or severe lung disease due to problems with respiratory depression [1].

Morphine itself is a well-known, potent opioid that binds to the mu receptor OPRM1 and is metabolized by glucuronidation, specifically by the liver isoenzyme UGT2B7 [33]. Several genetic variants have been identified that may affect the ability of morphine to adequately treat pain and may be responsible for adverse effects such as respiratory depression. The P-glycoprotein transporter encoded by the ABCB1 gene transports morphine across the blood-brain barrier, and variants identified for this gene may be associated with the risk of respiratory depression with morphine [34].

Hydrocodone, like codeine, is extensively metabolized by CYP2D6. It is also metabolized by CYP3A4 to

norhydrocodone, which is further conjugated by UGT to water-soluble metabolites that are primarily excreted by the kidneys. CYP2D6 metabolizes hydrocodone to hydromorphone [35]. In one study, UM demonstrated an approximately 10-fold increase in hydromorphone plasma concentrations compared to SM [1].

Another genetic component that can significantly alter a patient's response to pain and the analgesic effect of hydrocodone are variants of the OPRM1 gene [36]. Hydromorphone has been shown to bind strongly to the mu receptor (encoded by the OPRM1 gene) and to exhibit variability in serum concentrations that correlates with OPRM1 gene variants [37]. Thus, a prospective study demonstrated that tapentadol and methadone may be more suitable than hydromorphone for G-allele carriers due to their dual mechanism of action and low sensitivity to the OPRM1 A118G polymorphism [38].

Methadone is commonly used to treat patients addicted to opioids. As with other opioids, studies have generally examined the relationship between variants in widely studied genes and methadone dose. CYP2D6, OPRM1, and ABCB1 gene variants have been associated with plasma methadone concentration or required dose [7].

According to the results of a genome-wide pharmacogenomic study, the therapeutic dose of methadone was significantly associated with the rs73568641 variant in African Americans, and patients with the C-allele of the rs73568641 variant required higher doses of opioid analgesics [39].

CYP2B6 alleles with impaired enzyme function, such as *4 (increased enzyme activity) and *6 (decreased enzyme activity), have a high prevalence [39]. CYP2B6*6 is the most studied variant and is a significant genetic determinant of methadone elimination variability, which has been repeatedly reported in various publications [39, 40]. Patients with CYP2B6*1/*6 and CYP2B6*6/*6 have been reported to have lower oral methadone clearance compared to CYP2B6*1/*1 carriers [39,41]. This is also confirmed by the results of the study by Packiasabapathy S. et al. [41], in which children – carriers of the variant CYP2B6*6/*6 with slow metabolism had half of the methadone clearance compared to normal/rapid metabolizers.

Tramadol is metabolized by CYP2D6 to its major active metabolite O-desmethyltramadol, which has a higher affinity for opioid receptors than tramadol [42]. O-desmethyltramadol binds the mu-opioid receptor, while (+) and (-) tramadol inhibit the reuptake of serotonin and norepinephrine, resulting in a wide range of clinical effects [43]. CYP2D6 SM has been shown to protect against adverse side effects such as seizures and serotonin syndrome. UM, on the other hand, can have life-threatening adverse reactions and higher peak concentrations of O-desmethyltramadol in the blood plasma and show stronger analgesia and a higher frequency of nausea [43, 44].

CYP2D6 polymorphism is a key factor affecting tramadol metabolism in vivo [22]. The recommendations of the US FDA and the Working Group on Pharmacogenetics of the Royal Netherlands Association of Pharmacists (Koninklijke Nederlandse Maatschappij ter bevordering

der Pharmacie, KNMP) focus on diverse effects in different CYP2D6 metabolizers [5, 43]. In general, UM should either reduce the dose of tramadol by 30 % or choose an alternative drug, SM should be warned about the reduced efficacy of tramadol and should choose an alternative drug or watch for symptoms of insufficient analgesia [5].

In addition to CYP2D6, other genes may also affect the pharmacokinetics or pharmacodynamics of tramadol. For example, the TT CYP2B6 G516T genotype has been reported to correlate with higher tramadol plasma levels [42]. However, these results require further confirmation and should be interpreted with caution given the small sample size.

Oxycodone is often substituted for other opioids when they are ineffective [16], so pharmacogenetic testing allows for optimization of therapy [17].

Most oxycodone is metabolized by CYP3A4 to its inactive metabolite, noroxycodone, and a smaller proportion of oxycodone is metabolized by CYP2D6 to its active metabolite, oxymorphone [5]. Evidence for the effect of genetic variants on oxycodone is mixed. There is convincing evidence for the correlation of CYP2D6 and CYP3A variants on its pharmacogenomics and pharmacokinetics [45]. The CPIC recommendations are based on conflicting data and are similar to the recommendations for tramadol and codeine, so an alternative drug should not contain tramadol or codein, which are metabolized by CYP2D6 [32].

Other genes and their variants, including OPRM1 (rs1799971), OPRK1 (rs7016778), ABCB1 (rs1045642), and COMT (rs4680) were also studied for effects on oxycodone dosing/side effects, but ABCB1 and COMT did not show a significant difference in dose requirements for all options [3, 4].

Neuromuscular blockers

Neuromuscular blocking agents are an integral part of general anesthesia. Although there are two types of neuromuscular blocking agents (depolarizing neuromuscular blocking agents and nondepolarizing neuromuscular blocking agents), most muscle relaxants used in anesthesia are nondepolarizing [5].

Succinylcholine is a widely used depolarizing neuromuscular blocking agent. As a substrate of butyrylcholinesterase (BChE), succinylcholine is hydrolyzed by BChE in plasma [5]. Studies have shown, that variants of the *BCHE* gene play a critical role in succinylcholine-induced long-term neuromuscular blockade [7]. In the European population, the most common are the A-variant (atypical, *Asp70Gly*) and the K-variant (*Kalow, Ala539Thr*) of the *BCHE* gene. Patients with heterozygous genotypes for A- and K-variants are more sensitive to the action of succinylcholine (ie, have longer muscle relaxation) than phenotypically normal patients. One of the most serious and rare variants is the S-variant (*Leu335Pro*) of the *BCHE* gene – patients homozygous for the substitution may experience paralysis for up to 8 hours with a single induction dose of succinylcholine [46]. Other significant variants *BCHE*FS126*, *BCHE*I3E4-14C* and *BCHE*328D* were identified in patients with prolonged duration of action

of succinylcholine [7]. The *BCHE*FS126* and *BCHE*328D* variants were associated with reduced enzyme function and prolonged duration of neuromuscular blockade. Recently discovered seven new variants in the *BCHE* gene – *I373T*, *G467S*, *W518R*, *L184S*, *V421A*, *M462I* and *R577H* – were associated with a prolonged effect of succinylcholine or mivacurium [5]. In addition, 4 new variants were associated with prolonged apnea: *p.Trp205Cys*, *p.Leu22His*, *p.Glu469Gln* and *p.Lys276Ter*[47], but only 58 patients were included in this study.

Rocuronium is a non-depolarizing neuromuscular blocking agent and is commonly used in anesthesia for endotracheal intubation. The main metabolic pathway of rocuronium is biliary excretion, which depends on hepatocellular uptake via OATP1A2 [5]. Pharmacogenetic studies of rocuronium have mainly focused on transporters in the liver. A recent study showed that the *-189_-188InsA* variant of the *SLCO1A2* gene is associated with rocuronium clearance [48]. More precisely, patients with the *A* allele (in the hetero- or homozygous state) had a lower overall clearance of rocuronium.

A recent GWAS study of 918 individuals identified one genome-wide significant locus on chromosome 12. Single nucleotide variants with the most significant associations were located in or near the *SLCO1A2* gene. In particular, it was shown that two intronic variants *rs7967354* and *rs11045995* of the *SLCO1A2* gene, as well as clinical characteristics accounted for 41 % of the variability of the rocuronium dose [4]. In general, genetic variants of the *SLCO1A2* gene encoding the OATP1A2 transporter account for 4 % of the variability in rocuronium intake [4].

In addition to rocuronium, atracurium and vecuronium are also widely used as muscle relaxants. Theoretically, the effects of both drugs may be influenced by nicotinic acetylcholine receptors and, accordingly, variants of the genes encoding them [5].

Data on the pediatric population

Attention to CYP2D6 phenotypes has increased after the reported cases of death with the use of usual doses of codeine in carriers of the UM genotype of the *CYP2D6* gene [49]. In the carrier of the UM phenotype, codeine is converted to morphine in a dangerously high concentration. Fatalities have been reported in infants breastfed by mothers taking codeine, in children following adenotonsillectomy and other surgeries, particularly in the presence of apnea and obesity [49]. A review of adverse effects in children taking codeine-containing products found cases of severe respiratory depression and death [50]. This has led to the development of guidelines and clinical practice guidelines for the use of codeine by the World Health Organization, the FDA, the European Medicines Agency (EMA), and Health Canada, as well as the Medicines and Healthcare products Regulatory Agency Great Britain [50]. Restrictions have been established for the use of codeine in children under 12 years of age after adenotonsillectomy procedures [51].

The CPIC guidelines suggest the use of alternative analgesics for patients with SM and UM phenotypes based on the *CYP2D6* gene for safety reasons [49].

Similar cautions have also been expressed about tramadol after a report of tramadol-induced respiratory

depression in a child who was UM. In addition, oxycodone is also O-demethylated by CYP2D6 to oxymorphone and noroxymorphone, which are 14- and 10-fold more potent than the parent compound [52]. However, data on the effect of *CYP2D6* on oxycodone are currently not sufficient. Hydrocodone is 12 times more potent at opioid receptors than codeine and is metabolized by CYP2D6 and CYP3A4 to hydromorphone and norhydrocodone, respectively [53]. Thus, UM by *CYP2D6* can have up to eightfold higher hydromorphone plasma concentrations, while SM receives minimal analgesia [52-53]. In response to more than 400 cases of side effects linked to the use of hydrocodone, the FDA has banned the sale of more than 200 drugs because hydrocodone is a common ingredient in cough suppressants. .

As already noted, pharmacokinetic variations in response to opioids can be caused by changes in transport proteins such as P-glycoproteins. These include members of the ATP-binding cassette family ABCB1 and ABCC3 and organic cation transporter protein 1 (OCT1). The *ABCB1* gene is located on chromosome 7. A number of SNPs with low mean allelic frequencies have been reported, the most frequent variants were *3435C>T*, *1236C>T*, and *2677G>T/A* [49]. They are often inherited together, and the response, mediated by one variant, is often influenced by others [47]. The ABCC3 protein in hepatocytes serves as an efflux transporter for morphine metabolites into the bloodstream. The *rs4793665 (211C>T)* variant of the *ABCC3* gene leads to a decrease in protein expression, in particular, the *211CT* and *211TT* genotypes are associated with lower levels of morphine metabolites in plasma [47]. The *A*-allele of *ABCC3 rs4148412* and the *G*-allele of *ABCC3 rs729923* were reported to increase the odds of respiratory depression in children [54].

Ontogeny and genetic variability of drug-metabolizing enzymes are interrelated because genetic variability in drug-metabolizing enzyme expression cannot be assessed until the required protein is sufficiently expressed. Pharmacogenetic variants may contribute to unpredictable drug exposure at the same weight-based drug dose [45].

There are a number of potentially clinically applicable pharmacogenetic data in neonates, but more research is needed to confirm these findings and understand how to incorporate them into clinical care. Thus, in newborns, the effect of genetic variability of *CYP2D6* is evident even for premature babies. In critically ill newborns, genetic variation of the liver organic cation transporter (OCT1) is associated with morphine metabolism [55-57]. There have already been successful attempts to create a physiologically based model that takes into account the ontogenesis of OCT1 and the effect of morphine pharmacogenetics in newborns [58].

In neonates, the combined carrier of genetic risk alleles of the *OPRM1* and *COMT* genes was associated with a higher need for emergency morphine during mechanical ventilation [54, 57]. It may be possible to predict, based on genotype, which infants are most likely to require opiates for pain relief during intubation [55].

Further studies should also take into account recent data suggesting that individual drug-metabolizing isoenzymes belong to three classes [56]. The first group of enzymes

(e.g., CYP3A7, SULT1A3/1A4) is expressed at the highest level during fetal development, and their activity decreases and gradually disappears during the first 2 years of life. The second group consists of enzymes (e.g., CYP3A5, CYP2C19, SULT1A1) that show only modest increases after birth and become more active during adulthood. Levels of the third group of enzymes (e.g., CYP2D6, CYP3A4, CYP2C9, CYP1A2) increase slightly during the second and third trimesters of pregnancy and continue to increase during childhood.

Conclusions

Although pharmacogenomics is a relatively young field, it has already been shown that a better understanding

of an individual's genome can improve drug therapy outcomes.

The selection of drugs and dosing regimens based on a patient's pharmacogenomic profile may be an important part of the future of medicine. Personalized treatment based on the specific variant(s) in the genome will ultimately reduce the incidence of side effects and length of hospital stay for patients and save healthcare costs [60, 61]. Although pharmacogenomics and its application in clinical practice are still in their infancy, different variants and their implications for many clinical areas, including anesthesiology, are emerging daily. However, the evidence in most pharmacogenetic studies is still inconclusive, and more large-scale prospective studies are needed.

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ФАРМАКОГЕНЕТИКА АНЕСТЕЗІОЛОГІЧНОЇ ПІДТРИМКИ

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Резюме.

Фармакогенетика вивчає взаємозв'язок між індивідуальною генетичною характеристикою людини та реакцією організму людини на дію різних лікарських засобів, зокрема, виникнення небажаних побічних ефектів. Завдяки розвитку новітніх технологій та методик цей розділ медичної генетики та клінічної фармакології дуже активно розвивається. Накопичуються дані, створюються спеціальні бази з метою створення в майбутньому індивідуальних генетичних паспортів з можливістю підбору персоналізованих схем лікування.

Анестезіологія є особливою областю вивчення фармакогенетики, адже вона більше ніж будь-яка інша медична спеціальність характеризується поліфармацевтикою – одночасним або послідовним введенням багатьох лікарських засобів. Однакова доза препарату може бути недостатньою для деяких пацієнтів, і становити загрозу для життя або призводити до небажаних побічних ефектів для інших. Сьогодні інформація про генетичні фактори використовуються клініцистами для призначення ліків, щоб належним чином адаптувати медикаментозну терапію до геному пацієнта. В анестезіології були пояснені принципи фармакогенетики нервово-м'язових блокаторів, метаболізму опіоїдів, різних видів анестетиків, післяопераційної нудоти та блювання. З іншої сторони, велика кількість анестезіологічних препаратів мають вузький терапевтичний індекс.

В цьому огляді ми узагальнюємо останні дані наукової літератури щодо фармакогенетики анестезіологічних препаратів різних видів.

Інгаляційні анестетики є галогенпохідними метилетилового ефіру, точний механізм їх дії на даний момент повністю не з'ясований. Одним із рідкісних, але дуже серйозних побічних ефектів усіх галогеновмісних анестетиків є злоякісна гіпертермія – генетично обумовлений аутосомно-домінантний розлад, що проявляється як гіперметаболічна відповідь на введення препарату.

Дозування внутрішньовенних анестетиків теж слід ретельно визначати з урахуванням віку пацієнта, стану серцево-судинної системи, печінки та нирок, супутньої медикаментозної терапії, а також генетичних факторів. Онтогенез і генетична мінливість ферментів, що метаболізують ліки, взаємопов'язані, оскільки неможливо оцінити генетичну мінливість у експресії ферменту, що метаболізує ліки, доки необхідний білок не буде достатньо експресований. Фармакогенетичні варіанти можуть сприяти непередбачуваним експозиції препарату при однаковій дозі препарату, розрахованій на вагу.

Існує ряд потенційно придатних для клінічного застосування фармакогенетичних даних у новонароджених, але необхідні додаткові дослідження, щоб підтвердити ці висновки та зрозуміти, як включити їх у клінічну допомогу.

Вибір ліків і схем дозування виходячи з фармакогеномного профілю пацієнта може бути значною частиною майбутнього медицини. Індивідуалізоване лікування, засноване на певному варіанті(ах) в геномі, зрештою зменшить частоту побічних ефектів і тривалість перебування пацієнтів в лікарні і заощадить витрати на охорону здоров'я. Хоча фармакогеноміка та її застосування в клінічній практиці все ще знаходяться в зародковому стані, різні варіанти та їх значення для багатьох клінічних галузей виявляються щодня, в тому числі для анестезіології.

Ключові слова: фармакогенетика; анестезіологічна підтримка; інгаляційні анестетики; пропофол; опіати; міорелаксанти; загальна анестезія у дітей.

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