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THE SIGNIFICANCE OF PHARMACOGENETIC TESTING FOR BETTER ANAESTHETIC OUTCOME AND LESS SURGICAL STRESS. LITERATURE REVIEW

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Kristina Tatzhikova, Bela Kantemirova✉, Aleksei Zhidovinov, Irakliy Kitiashvili, Ekaterina Orlova

Astrakhan State Medical University, Astrakhan, Russia

✉ *belakantemirova@rambler.ru*

ABSTRACT — The review is devoted to the problem of optimizing the anesthetic manual based on pharmacogenetic data in order to achieve an adequate depth of anesthesia and stress protection and reduce the number of adverse drug reactions. We analyzed the data of Pub Med and Web of Science databases to investigate the influence of genetic polymorphism on the body's response to the main groups of drugs used for anesthesia, and changes in the effects of drug interaction. Specifically, we have reported that the use of preoperative genetic screening for a set of markers (polymorphic alleles of a number of cytochromes) is a promising tool in the anesthesiologist's practice.

KEYWORDS — pharmacogenetics, anaesthetic manual, surgical stress, genetic polymorphism.

INTRODUCTION

The main objective of the anaesthetic manual is to achieve an optimal level of sedation, analgesia and neurovegetative protection in order to reduce surgical stress and associated perioperative complications. Surgical stress response is a complex of neurometabolic, neuroendocrine, and inflammatory disorders that develops as a result of surgical trauma [5]. If it is not prevented by its own stress-limiting systems (GABA, opioid peptides, antioxidant system, and others), it leads to perioperative dysfunction of organs and systems [5, 10]. This condition is regarded as *insufficient anesthesia*. However, complete blockage of all reactions to trauma, the so-called *stress-free anesthesia*, is accompanied by a lot of complications, significant respiratory depression, and requires prolonged artificial ventilation. That is, the question of in what casesthe extent to which suppression of the response to chemical stress is desirable remains unresolved [12]. The modern anaesthetic manual is based on the principle of multimodality (multi-component), since no component of anesthesia is able to provide the necessary level of anti-stress protection. The variability of the patient's response to the components of anesthesia and, accordingly, its adequacy in 20–95% of cases is determined by the genetic polymorphism of the substrates of their pharmacokinetics and / or pharmacodynamics (metabolic enzymes, receptors, transport systems, etc.), which naturally affects the effects of drug interaction. Projected the specialist anesthesia for the patient in this case, it often may not provide a sufficient level of depth of anesthesia or accompanied by manifestations of undesirable, toxic drug reactions, or to increase the frequency of their manifestation and severity. From these positions, it is necessary to search for new ways to optimize the anesthetic manual, personalize the selection of components and dosages of drugs used [9, 3]. The use of a personalized approach using *omix* technologies and advances in pharmacogenetics in the future will allow using the most effective drug in a sufficient dose and safe from the point of view of undesirable drug reactions (NLR) [13].

METHODS

The analysis of published data, including in the Pub Med and Web of Science databases, on the influence of genetic polymorphism on the body's response to the main groups of drugs used for anesthesia, and changes in the effects of drug interaction. 118 sources were analyzed from 2005 to 2018, and 22 sources are included in the article.

PHARMACOGENETICS: RELEVANCE FOR THE ANAESTHETIST

Neuroendocrine changes are the basis of complex reactions of the body to surgical trauma. From the perspective of a comprehensive and preventive effect on surgical stress, it is relevant to assess the genetically determined changes in the pharmacodynamics of the most significant groups of drugs in the anesthesiological support for the development and limitation of this process. This is especially important due to the peculiarities of anesthesiological practice and the need to use a wide range of highly active drugs from different

pharmacological groups in high doses as part of a single manual. Taking into account the pharmacogenetic features of the kinetics and mechanism of action of drugs and their altered interaction with each other will help to ensure the sufficiency and safety of anesthesia components [1, 15]

In accordance with the pathogenesis of surgical stress, the most significant components of an anesthetic aid are sleep, analgesia, and correction of autonomic disorders, which are provided by the use of such groups of drugs as General anesthetics, hypnotics, opioid analgesics, neuroleptics, and others.

Currently, volatile liquids (fluorotane, enflurane, sevofluan, influrane) and gaseous substances (nitrous oxide, xenon) are used from the group of inhaled General anesthetics. The pharmacokinetics of gaseous agents practically excludes the effect on their metabolism (xenon does not undergo biotransformation, nitrous oxide is only 0.01% metabolized in the gastrointestinal tract). In this case, xenon has an effect on the inflammatory component of the surgical stress response.

According to some data, from 20 to 45% of fluorotane undergoes hepatic metabolism with the participation of cytochrome P450 CYP2E1, being oxidized to trifluoroacetic acid (TRIFLUOROACETYL chloride binds to liver proteins and triggers an autoimmune response), chlorine and bromine ions, and under hypoxia is restored with the formation of hepatotoxic products. However, there are no data on common mutations of the CYP2E1 gene that are accompanied by changes in metabolism and contribute to the development of halothane-induced hepatitis. the activity of the enzyme depends more on the properties of the phenotype and dietary characteristics [4]. Repeated contact with halothane increases the risk of necrosis and increases the associated mortality. An inhibitor of the CYP2E1 isoenzyme is disulfiram, which reduces the formation of the metabolite and may reduce the risk of halothane hepatitis. There are experimental data on the ability of benzodiazepines, a number of which are used as premedication components (diazepam, nitrazepam, midazolam), to also have an inhibitory effect on the activity of the CYP2E1 enzyme in micromolar concentrations. Their effect on the development of adverse drug reactions (NLR) of halothane in the form of hepatitis has not been studied.

In addition, halothane itself can act as an inducer of the metabolism of phenobarbital and other barbiturates and thus reduce the effectiveness of sodium thiopental used as a hypnotic.

Hepatic metabolism and the risk of hepatitis in other volatile anesthetics is significantly lower (isoflurane 0.17%, desflurane 0.01%, sevoflurane 1–5%, enflurane 2.4% is metabolized in the liver). Sevoflurane does not produce acylated protein compounds; the main product of sevoflurane degradation under the action of bases is nephrotoxic vinyl ether (compound A) [11].

The leading role in the metabolism of the intravenous anesthetic ketamine (calypsol), its conversion to norketamine is played by the enzymes CYP2B6, CYP3A4, and CYP2C9 (the latter two are auxiliary). The genetic polymorphism of these enzymes has no convincing evidence of influence on the drug's action. But the parallel use of ketamine with inducers or inhibitors of cytochromes significantly affects its metabolism. Inhibitors of CYP3A4, CYP3A6, SUR2C19, SUR2B6, SUR2C9, antibodies to these cytochromes and their common inhibitor aminobezotriazole block the metabolism of calypsol and reduce the rate of its D-methylation. In connection with the above, the ability of pharmacological components of anesthesia to influence the activity of processing processes of this intravenous anesthetic has prospects for study [8].

Hypnotics are drugs that promote sleep, but their effect is not accompanied by analgesia. These are barbiturates (sodium thiopental, hexenal), benzodiazepines (diazepam, midazolam) and propofol.

Barbiturates are currently used as part of drugs for the induction of anesthesia. Compounds of pharmacologically inert barbituric acid with oxygen make up the group of oxybarbiturates (hexobarbital), compounds with sulfur — thiobarbiturates (sodium thiopental). The metabolism of the former occurs only in the endoplasmic reticulum of hepatocytes, the latter also have extrahepatic metabolism (CNS, kidneys) [12]. Transformation of barbiturates occurs in several stages: hydroxylation in the liver with the participation of NADH and P450 with the formation of oxyceto- and carboxybarbituric compounds, dealkylation, destruction (hydrolysis opening) of the barbituric ring, in thiopental — desulfurization with the formation of phenobarbital, pentobarbital. The P450 isoforms CYP2C19 and CYP2C9 have the highest value in the transformation. Not only barbiturates are metabolized by CYP2C19 (S-mephenytoin hydroxylase), but also many other widely used drugs (benzodiazepines, beta-blockers,proton pump inhibitors, and others), about 8% of all registered drugs. Today, 17 variants of CYP2C19 alleles are known, which are more or less associated with a decrease in protein expression, a decrease or lack of functional activity of the enzyme, and a different distribution of polymorphic variants in different ethnic groups [6, 7]. This multisubstrate metabolism contributes to the inter-drug interaction. Barbiturates have the property of self-induction against CYP2C19. The significance of the polymorphism of this gene in the practice of using barbiturates

as part of an anesthetic aid and the effect on drug interaction requires further study. The situation is similar for CYP2C9 substrates [12].

Benzodiazepines are mainly used for premedication, anxiolysis, amnesia, and sedation. Currently, in most countries of Europe and the United States, three benzodiazepine receptor stimulators of this structure are used in anesthesiology — midazolam, diazepam and lorazepam. Most benzodiazepine derivatives are metabolized by liver enzymes of the cytochrome P-450 system to polar compounds and are excreted in the urine and bile [4]. The metabolism of benzodiazepines is an example of how each substrate can be processed by several enzymes. According to the results of numerous studies, the isoenzymes CYP3A4, CYP3A5, and CYP2C19 are involved in the biotransformation of these substances. There are also indications of a possible role for CYP2D6 and CYP2C9. Polymorphisms of the CYP2C19 and CYP2C9 genes are significantly associated with the risk of adverse events (NLR) when using benzodiazepines as tranquilizers [8].

Diazepam is converted to temazepam by hydroxylation with the participation of CYP3A4 (nonlinear dependence), and then to N-dimethyldiazepam by dealkylation under the action of CYP2C19 (according to the Mikhail-Menkes system). The ratio of metabolites is 4/1. The kinetics of diazepam is influenced by the patient's gender, age and weight, and functional safety of the liver, but a significant effect of the CYP2C19 gene polymorphism has also been reliably established. The half-life of diazepam in *fast metabolizers*, homozygotes for the A-allele G681A polymorphism of this cytochrome is 4 times higher than in most *slow metabolizers*. In individuals who are heterozygous for the A-allele, the half-life varies between these two values [4, 8]. *Slow* genetic variants or the use of CYP2C19 inhibitor drugs (proton pump inhibitors, paroxetine, and others) may be clinically manifested by prolongation or deepening of sedation after diazepam administration. Since diazepam has a dose-dependent respiratory depression, there may be an increase in cases of apnea on the introduction of an induction dose [8].

At the same time, genetically determined accelerated metabolism or the use of inducer drugs (carbamazepine, barbiturates) can theoretically be accompanied by insufficient effectiveness of diazepam as a hypnotic for induction anesthesia. Benzodiazepines have a greater value as the stress-limiting preparations, compared to inhaled anesthetics and barbiturates. Their use significantly limits the increase in cortisol concentration, since their mechanism of action affects not only the hypothalamic-pituitary system, but also direct suppression of the synthesis of glucocorticoids is not excluded. Accelerated metabolism may affect the amnesic effect of the drug and contribute to the preservation of unpleasant memories in the postoperative period [8].

Unlike diazepam, the clinical response to midazolam is poorly associated with genetic factors. CYP3A4 and CYP3A5 polymorphisms are associated with a decrease in midazolam clearance, but these associations are not sufficiently pronounced to indicate a clinical difference due to the existence of alternative pathways of metabolism and excretion [8].

Based on clinical observations of the reactions of patients of the same ethnic origin, significant individual susceptibility to the intravenous anesthetic propofol was determined, and this variability is reflected in the different dose requirements and time required for recovery. Based only on the traditional algorithm for calculating the dose of propofol, it is very difficult for patients to get adequate anesthesia. Deep sedation with propofol, which suppresses the stress response, is accompanied by hypotension. Sedation-related complications or even brain trauma can subsequently worsen the outcome of surgery in patients. Similarly, insufficient propofol sedation, defined as inadequate anesthesia, would cause hypertension, tachycardia, or movement of the patient and lead to intraoperative consciousness. The etiology of individual variability of the response to propofol may be influenced by genetic polymorphisms of its metabolic enzymes or structures involved in the implementation of the pharmacological effect. The effect of the CYP2B6 polymorphism on propofol pharmacodynamics and General anesthesia has not been sufficiently studied [8].

Studies evaluating propofol sensitivity have only targeted the CYP450 genes that are involved in propofol metabolism. Murana and co-authors found that a polymorphism in the CYP2B6 gene (rs3745274) affects sensitivity to propofol anesthesia. Studies by Lian and others have demonstrated that the influence of CYP2C9 polymorphism also contributed to changes in susceptibility to propofol. These observations6 have shown that the enzymes involved in the metabolism of this hypnotic affect the susceptibility to it and that the total consumption of propofol can be disrupted by other substances, inducers or inhibitors of these enzymes used during surgery [23].

The pharmacodynamics of propofol also changes under the influence of receptor polymorphism. Researchers from China, using the Sequenom MassARRAY single-nucleotide polymorphism (SNP) genotyping method, identified a mutation (rs6313) in the 5HT2A receptor gene that correlated with individual propofol sensitivity, concentration, and induction start time. Carriers of the minor allele (G) 5ht2a rs6313

required less propofol (20% reduction in concentration) and less time (40% reduction in start time) to induce anesthesia, and they show stronger activation of sleep-stimulating neurons in the ventrolateral preoptic region (VLPO), which contribute to anesthetic hypnosis. This result may significantly contribute to elucidating the role of 5HT2A receptors in sensitivity to propofol anesthesia.

Binding to agonistic GABA sites is thought to contribute to the hypnotic effect of propofol. GABA receptors and M2 cholinergic receptors contribute to cardiovascular susceptibility to propofol anesthesia. A g-to-A mutation in the rs2279020 gene in the GABA receptor can alter its pharmacological properties by changing the composition and location of subunits. When anesthetized with propofol, the minor a allele can cause a stronger inhibition in the brain in the carrier, which is manifested by higher BIS rates in these patients after loss of consciousness [23].

Dominant mutations in the genes GOMKA1 rs2279020, GABKA2 rs11503014, and the M2 holinoreceptor gene rs1824024 may presumably be associated with a predisposition to cardiovascular complications during propofol anesthesia. Propofol significantly reduced heart rate against the background of loss of consciousness in patients who were carriers of the minor g allele rs11503014 in GABA-2, compared with patients without the g allele. Variation of the C-To-a rs2283265 polymorphism in HRM2 resulted in lower heart rate values. Changes from G to a rs2279020 in GABAA1 are accompanied by a lower BP curve after propofol anesthesia [23].

Clinically significant concentrations of propofol alter the functions of potential-dependent sodium channels, thereby inhibiting the release of glutamate from presynaptic endings. The SCN9A gene, which encodes the Nav1.7 sodium channel, is associated with various pathophysiological conditions, such as human sensitivity to pain [34]. A Chinese study confirmed the significant role of SCN9A in propofol sensitivity. Patients who were heterozygous or homozygous for the minor allele (a) rs6746030 in SCN9A recorded significantly lower BIS values . Changing rs6746030 in SCN9A from G to A can change the function of the sodium channel; changes in glutamate release and intrinsic ionic conductivity resulted in greater susceptibility to propofol, which is shown by significantly lower BIS values after propofol-induced unconsciousness. This result may help clarify the role of SCN9A in propofol sensitivity [23].

Thus, if only the traditional propofol dose calculation algorithm is used, patients with the minor allele (G) rs6313 in 5HT2A, homozygous carriers of the main allele (GG) rs2279020 in GABA1, and carriers of the minor allele (A) rs6746030 in SCN9A are highly likely to suffer from drug overdose. This result is a prerequisite for the introduction of preoperative genetic screening to identify individuals with a high risk of excessive sedation and vascular complications during propofol anesthesia [23].

Numerous data indicate the ability of opioid analgesics to limit the severity of endocrine-metabolic changes in the stress response. Endogenous opioids are an essential part of the antinociceptive system, but the genes of opioid receptors are characterized by polymorphism [20].

Strong opioids, complete opioid receptor agonists, are represented by morphine, hydromorphone, oxycodone, Oxymorphone, fentanyl, and methadone. Fentanyl-a synthetic opioid often used during surgical procedures, causes a rapid analgesic effect when administered intravenously, easily penetrates the blood-brain barrier and demonstrates 200 times greater effectiveness than morphine. Intravenously administered fentanyl is also relatively short-acting, as it is rapidly metabolized by CYP3A4 to norfentanyl [2]

Genetic differences in patients can significantly change the pharmacokinetics of painkillers, an example of which is the mixed-action analgesic tramadol. It, like codeine and hydrocodone, is essentially a *prodrug* that requires transformation to produce a more active metabolite. In the first phase of tramadol biotransformation reactions, demethylation occurs with the participation of the P-450 CYP2D6 isoenzyme [2]. As a result, most of the drug forms O-desmethyltramadol, which has a much higher analgesic activity, the remainder is converted to inactive N-desmethyltramadol via CYP2B6 and CYP3A4. Polymorphisms of the CYP2D6 gene can significantly change the rate of biotransformation and affect the effectiveness of tramadol use, which has been convincingly demonstrated in studies of postoperative pain management in gynecology [16, 21]. Four CYP2D6 phenotypes were identified: slow metabolizers (activity score 0), intermediate metabolizers (activity score 0.5), extensive metabolizers (activity score 1.0–2.0), and ultra-lipid metabolizers (activity score >2.0). Carriers with two null alleles in the CYP2D6 gene or a combination of one null allele with a second allele with reduced function are characterized by reduced or completely absent enzymatic activity of the 2D6 isoenzyme (5–10% of Europeans). These patients are characterized by rapid accumulation of narcotic analgesic, and they need to prescribe lower doses [17].

The frequency of polymorphisms C100T and G1846A of the CYP2D6 gene of the cytochrome P-450 isoenzyme, which significantly reduce the effectiveness of analgesia and contribute to severe

sympathicotonia, can reach 30 % in different races and populations [2, 30, 29, 26]. Ultrafast metabolizers of CYP2D6 substrates are potentially susceptible to life-threatening levels of the active metabolite O-desmethyltramadol, which cause respiratory depression and neurotoxicity [2, 21].

The CYP3A4 enzyme is responsible for N-demethylation of opioids such as tramadol, fentanyl, and oxycodone to the inactive metabolites N-desmethyltramadol, norfentanyl, and noroxicodone, respectively. CYP3A4 is relatively non-polymorphic with 41 allelic variants described, of which nine have insignificant enzymatic activity in in vitro studies. Many of these variants are extremely rare, making it difficult to evaluate them in a clinical context. However, several in vitro and in vivo studies have shown that the CYP3A4*1G variant is associated with a lower fentanyl metabolic rate and significantly lower consumption compared to patients with wild-type alleles, which should be taken into account when selecting a dose for adequate pain management [16].

The metabolism of narcotic analgesics with the participation of cytochrome P450 determines the risk of drug interactions with substrates that are inducers or inhibitors of this liver enzyme system, which must be taken into account during anesthesia. All drugs that are metabolized with the participation of the 2D6 isoenzyme are potential substrate inhibitors. The inhibitory effect of substances such as grapefruit juice bergamot, ondansetron, captopril, carvedilol, tamoxifen, tamsulosin, metoprolol, nifedipine, amitriptyll and others, as well as the presence of true CYP2D6 inhibitors that are not substrates and are not metabolized with the participation of the 2D6 isoenzyme [22], such as amiodarone, celecoxib, metoclopramide, paroxetine, sertraline, ticlopidine, venlafaxine, fluoxetine and others [2]

The opioid response is mediated by corresponding receptors (μ, κ, and δ) in the Central nervous system, which interact with endogenous and exogenous opioids via G-proteins, resulting in reduced transmission of nerve impulses and inhibition of neurotransmitter release. The OPRM1 gene encoding the mu-opioid receptor may contain more than one hundred single-nucleotide polymorphisms that change the structure of the extracellular part of the receptor. A number of patients carrying the OPRM1 118AvG variant, with wild-type aspartate replacement, reduced mRNA and protein expression, and reduced signal transmission efficiency, have a reduced response to the narcotic analgesics fentanyl and Alfentanil. According to research results, they require higher doses of drugs for pain relief in the early postoperative period and, accordingly, they can have the same effect intraoperatively [16].

Some authors describe an increase in cortisol and ACTH levels in the first hour and a half after naloxone administration in individuals with genotypes 118G/G and 118A/G, as well as they were more likely to experience early postoperative complications in the form of nausea and vomiting.

DISCUSSION AND CONCLUSION

The results of current research linking polymorphisms to differences in opioid response are promising. It is hoped that future research involving a large number of SNPs in genes that determine both pharmacokinetic and pharmacodynamic parameters will one day lead to the personalization of opioid therapy in order to maximize the analgesic effect while minimizing the risk of adverse events [2].

The use of drugs in anesthesiology has significant differences from other types of pharmacotherapy, consisting primarily in the need to often simultaneously use combinations of several substances without a previous history of their appointment. The effectiveness and safety of drugs, their ability to create adequate anesthesia that reduces the severity of surgical stress and, consequently, associated perioperative complications, is determined by the features of their pharmacokinetics and pharmacodynamics, as well as various types of drug interactions. However, these factors are subject to significant variability due to genetic polymorphism of metabolic enzymes and targets in specific individuals. The above-mentioned features of anesthesiological practice do not allow applying the recommended criteria for determining the need for genetic tests in the routine practice of an anesthesiologist in the surgical Department. This problem does not have the necessary level of illumination in the published results of domestic and foreign studies. There is no conclusive evidence of the clinical utility and ability to evaluate the effectiveness of pharmacogenetic tests in perioperative practice. Further research is needed, including evaluating pharmacogenomics data and correlations with treatment outcomes. An analysis of the available literature leads to the conclusion that preoperative genetic screening for a set of markers that are significant in altered sensitivity to the most popular drugs and their combinations (such as CYP2D6, CYP3A4, CYP2B6, CYP2E1, CYP2C9, CYP2C19) may have clinical and economic effectiveness. This approach will optimize the clinical decision-making tool and individualize the dosage of drugs used to achieve an adequate depth of anesthesia and analgesia, and reduce the number of functional and biochemical tests for monitoring and timely correction of surgical stress reactions, which will have a positive impact on the duration of the recovery postoperative period.

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