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Pharmacogenetic Aspects of Anesthesia and Postoperative Anesthetization

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Abstract: ***Surgery is the most common and predictable source of severe pain. Untreated postoperative pain may result in adverse psychological and physiological effects that increase morbidity and mortality, thereby compromising the quality of recovery. The general analgesic effect is not unilateral, but is influenced by a number of genes affecting different pathways of drug metabolism. This is why its successful management requires the provision of anesthesia and analgesia without adverse side effects. Pharmacogenetics in anesthesiology has the potential to improve pain management by predicting the individual response to a particular drug prior to starting therapy and is therefore able to improve the therapeutic course of anesthesia and subsequent treatment.***

Keywords: Pharmacogenetics, pharmacogenomics, analgesia, anesthesia

1. Introduction

In essence, pharmacogenetics is a science which studies the impact of genetic factors (mutations in various genes) in the change in the pharmacological response (efficacy and safety) of drugs. (1), (2), (3), (4)

The first mentioning of pharmacogenetics in anesthesiology dates back to the mid-1950s, when observations emerged which proved that a patient's genetic characteristics could alter the pharmacological effect of drugs. The first work in this sphere was demonstrated by the association of prolonged postoperative muscle relaxation with the administration of Succinylcholine and the inherited decrease in the activity of the pseudocholinesterase. (5)

In essence, pharmacogenetics refers to the manner in which genetic differences between individuals affect the drug reactions of the patients.

It is proven that at conventional drug dosing toxicity develops in some patients, while other patients do not get adequate analgesia despite receiving the same dose of the drug. Differences in the effectiveness of medications may vary from 2 to 10 times or 100 times even amongst members of the same family. (6), (7), (8)

Currently, pharmacogenetic methods are used to study the efficacy and safety of pharmacological agents, inclusive of drugs used in anesthesiology (opioid analgesics, non-steroidal anti-inflammatory drugs, inhalation anesthetics, benzodiazepines).

It is established that there is a number of pharmacodynamic factors based on variations in target drug receptors and pharmacokinetic factors which exert impact over drug metabolism and/or elimination by altering the relationship between drug dose and serum drug concentrations in a stationary state. The development of tolerance, which may occur through both dynamic and kinetic mechanisms, results in variations in the response.

Genetic variability is one of the factors that plays a role in the manner in which drugs exert impact over the physiology. Undoubtedly, the rate at which anesthetic drugs are metabolized turns out to be of significance as well.

The rate of the drug metabolism is assessed by the so-called metabolic clearance, i.e. by its hypothetical plasma volume.

Depending on the activity of the enzyme, patients are divided into three groups:

First group: Extensive metabolizers - these are people with a "normal" rate of drug metabolism (the majority of the population refers to this group).

Second group: Slow metabolizers - this refers to individuals with a reduced rate of drug metabolism. They synthesize a "defective enzyme" or no enzyme synthesis at all, resulting in frequently reduced or absent enzyme activity. In such people, medications may accumulate in the body and result in intoxication, so their dose should be carefully selected.

Third group: Hyperactive or fast metabolizers - this refers to people with an increased rate of drug metabolism. In such individuals, the concentration of the drug in the blood is not sufficient to achieve a therapeutic effect. For overactive metabolisers, the dose of the drug should be higher. (9), (10)

Metabolism of some groups of drugs used during anesthesia

Metabolism of benzodiazepines: Metabolism of benzodiazepines: It is established in a research conducted by Inomata S. et al. that the pharmacokinetics of Diazepam is significantly dependent on the CYP2C19 polymorphism. Its half-life in "fast" CYP2C19 metabolites (H-allele homozygotes) is 4 times higher than in "slow" metabolizers. In A-allele heterozygotes, the individual half-life period varies between these two values. (10), (11)

In another research conducted by Ogawa R. et al. a conclusion is drawn that with slow CYP2C19 metabolisers adverse reactions more frequently developed at use of

tricyclic antidepressants, and no clinically significant change in the pharmacodynamics of Diazepam was simultaneously observed. (10), (12)

Unlike Diazepam, the clinical response to Midazolam is weakly associated with genetic factors.

Propofol is a commonly used intravenous anesthetic. It is characterized by its metabolism by conjugation with UDF-glucuronic acid with the participation of phosphate-glucuronyltransferase and the oxidation with the participation of CYP2B6 and CYP2C19. It is established that CYP2C9 has low affinity for Propofol. (10), (13)

Opioid analgesics: Regardless of the growing volume of pharmacogenetic studies, there are very few researches on the clinical study of such an approach to postoperative analgesia.

Clinical practice shows individual, difficult to predict reactions of patients to opioid analgesics, which complicates the conduct of postoperative analgesia in each of them and raises the question of the relationship between analgesia and genetic factors. (14), (15)

The genetically determined features in the pharmacokinetics of drugs may also exert impact over the effectiveness of postoperative analgesia.

At present, the choice of drugs for postoperative analgesia is still not conformed to the genetic variability of the individual.
The information accumulated so far, however, allows us to talk about the prospect of pharmacogenetic research in anesthesiology.

There is considerable variability with regard to the results obtained from postoperative analgesia. (16), (17), (18)

Due to the limitations which exist pertaining to the determination of the intensity of postoperative pain, the so-called pharmacogenetic approach is used for facilitation. (19)

According to a number of authors, this model proves that patients' sensitivity to opioid analgesics is influenced by a number of genetic factors which are able to alter both their pharmacodynamics and their pharmacokinetics. (15), (19), (20), (21), (22), (23)

As a whole, the genes that affect the results of treatment with opioid analgesics may be divided into two major groups:
First group: Genes influencing pharmacokinetics;

Second group: Genes influencing pharmacodynamics. (24)

Genes encoding cyclooxygenase enzymes, opioid receptors, and the enzyme catecholamine methyltransferase (COMT) may also exert impact over the pharmacodynamics of drugs. (24), (25)

Sensitivity to opioid analgesics may depend on genetically determined variability to μ-opioid receptors (encoded by the MOR-1 gene). In the absence of the MOR-1 gene, morphine reduces its effect. Some studies reported an increased need for opioid analgesics in patient-controlled analgesia in carriers of the alternative form of MOR-1, namely OPRM. (10), (26)

Neuromuscular blockers: Neuromuscular blockers are some of the most commonly used medications during anesthesia. Their effectiveness (especially in Succinylcholine) largely depends on the variations in the plasma cholinesterase gene which hydrolyzes them and which is associated with the appearance of serious differences with regard to its duration of effect between individuals. It is shown that people who are heterozygous pertaining to the expression of Asp70Gly pseudocholinesterase need a 3-8 times higher dose of muscle relaxant. In homozygotes, the neuromuscular block is up to 60 times longer than that associated with the normal allele. (27)

Inhalation anesthetics: The biotransformation of inhalation anesthetics is realized through the enzyme CYP2E1. The particular interest in the pharmacogenetics of inhalation anesthetics is due to the risk which their use poses to the occurrence of malignant hyperthermia when used in combination with Succinylcholine.

In a research conducted by Liem E. et al. and Benton I. et al. on healthy ginger-haired females who are allele-bearing (MC1R), a link between the availability of allele and the concentration of Desflurane needed to suppress the electrical pain stimulus response was demonstrated. (28)

Compared to females with black hair, those with ginger hair showed a need for a 20% higher dose of Desflurane. It is also established that it is namely in the subpopulation of ginger-haired females who have the MC1R genetic polymorphism that there is marked resistance to subcutaneously administered Lidocaine. (29)

Pharmacogenomics of local anesthetics: There are basically two types of local anesthetics in terms of chemical structure - ester and amide type. The metabolism of the amide anesthetics lidocaine and bupivacaine is associated with CYP3A4 and that of Ropivacaine is associated with CYP1A2. (27). The effect of lidocaine is also associated with the 395N> K mutation of the SCN9A sodium channel encoding gene, resulting in increased resistance. (30)

2. Conclusion

In recent years, anesthesiology has developed to the extent that it managed to create maximum safety for the patients and achieve excellent end results.

Irrespective of that, quite a few clinical cases were described that prove that these results are unsatisfactory in some of these patients due to the existing genetic polymorphism to certain anesthetic drugs.

Thanks to the validation and the use of pharmacogenomics and pharmacogenetics in anesthesiology, possibility was provided to apply the so-called approach to personalized medicine, through which each patient is approached individually according to his needs and characteristics, which makes it possible to reduce side effects of the applied medications and at the same time to achieve high quality of the medical service offered.

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