ADVRSE EFFECTS THAT DEPEND ON GENETIC POLYMORPHISM

For today, it has been described a number of hereditary metabolic defects that lead to drug idiosyncrasy (abnormal reactions to drugs that are genetically determined). We are talking about congenital deficiency of certain enzymes: glucose-6-phosphate dehydrogenase, butyrylcholinesterase, catalase, etc.

Genetic polymorphism of glucose-6-phosphate dehydrogenase (G-6-PDG). Changes in the pharmacodynamics of drugs can be caused by gene mutations of enzymes responsible for protection against oxidation of sulfhydryl groups of cell membrane proteins under the action of some drugs, in particular glucose-6-phosphate dehydrogenase (G-6-PDG). At the same time, in carriers of such mutations, hemolysis of erythrocytes occurs in connection with the deficiency of G-6-PDG when using a number of medicinal products, in particular derivatives of sulfonamides, nitrofurans. Under certain conditions, hemolysis of erythrocytes can also occur when aspirin, chloroquine, unitiol, etc. are prescribed. G-6-PDG takes in the transformation of oxidized glutathione into a reduced form. Reduced glutathione is an active antioxidant that protects cell membrane proteins from oxidation. The prevalence of G-6-PDG deficiency is 1-15%; it is extremely rare among the inhabitants of Europe. G-6-PDG enzyme deficiency affects over 400 million people worldwide, and the World Health Organization has categorized G-6-PDG activity into five classes (Table 1). The majority of polymorphic G-6-PDG -deficient genotypes are associated with class II for severe deficiency (< 10% enzyme activity) and class III for moderate deficiency (10–60% enzyme activity). Most individuals with reduced function alleles of G-6-PDG have ancestries in geographical areas of the world corresponding to areas with high malaria prevalence. Polymorphic alleles gained in frequency over time as they offered some benefit against death from malaria. The estimated frequency of G-6-PDG deficiency is approximately 8% in malaria endemic countries, with the milder *G-6-PDG -A(–)* allele prevalent in Africa, and the more severe G-6-PDG –Mediterranean allele widespread across western Asia (Saudi Arabia and Turkey

to India). There is a much more heterogeneous distribution of variant alleles in East Asia and Asia Pacific, which complicates G-6-PDG risk predictions; however, the most frequently identified forms in Asia include the more severe class II alleles.

Table 1. Classification of G6PD deficiency (WHO Working Group, 1989)

World Health Organization Class	Level of Deficiency	Enzyme Activity	Clinical phenotype
I	Severe	<10%	Chronic (nonspherocytic) hemolytic

			anemia
II	Severe	<10%	Risk of acute hemolytic anemia; intermittent hemolysis
III	Moderate	10–60%	Risk of acute hemolytic anemia; hemolysis with stressors
IV	None	60–150%	Normal
V	None	>150%	Enhanced activity

Butyrylcholinesterase. The physiological function of butyrylcholinesterase is the hydrolysis of acetylcholine. In addition, butyrylcholinesterase catalyzes the hydrolysis reaction of the depolarizing muscle relaxant *succinylcholine* (dithyline, suxamethonium). Succinylcholine is widely used in anesthesiology. Since the beginning of the 50s, there have been reports of increased sensitivity to succinylcholine, which is due to reduced activity of butyrylcholinesterase and was accompanied by prolonged respiratory arrest (apnea) - two or more hours instead of 5 minutes. Genetic studies have revealed a number of mutations in the *butyrylcholinesterase (BCHE)* gene. Increased sensitivity to succinylcholine is observed only in homozygotes ("*slow metabolizers*"). The prevalence of homozygotes among European countries is 1:3000; the frequency of heterozygotes and homozygotes together is 1:2500. Neuromuscular blockade produced by succinylcholine can be prolonged in patients with an abnormal genetic variant of plasma cholinesterase. The dibucaine number is a measure of the ability of a patient to metabolize succinylcholine and can be used to identify at-risk patients. Under standardized test conditions, dibucaine inhibits the normal enzyme by 80% and the abnormal enzyme by only 20%. Many genetic variants of plasma cholinesterase have been identified, although the dibucaine-related variants are the most important. Given the rarity of these genetic variants, plasma cholinesterase testing is not a routine clinical procedure but may be indicated for patients with a family history of plasma cholinesterase deficiency. Another reasonable strategy is to avoid the use of succinylcholine where practical in patients with a possible family history of plasma cholinesterase deficiency.

The introduction of butyrylcholinesterase genotyping into clinical practice will allow more accurate identification of individuals with increased sensitivity and will ensure high safety of succinylcholine use. The FDA recommends avoiding the use of succinylcholine in "*poor metabolizers*" or administering a test dose first to assess sensitivity to succinylcholine.

A similar pattern is shown for another muscle relaxant, mivacurium. "I*ntermediate*" and "*poor metabolizers*" (*BCHE*) have higher concentrations of mivacurium and a higher risk of side effects (prolonged neuromuscular blockade), so mivacurium should not be used in "*poor metabolizers*."

Antagonists of mivacurium - anticholinesterase agents such as galantamine and donepezil - are metabolized in the liver by the CYP2D6 enzyme. The presence of the genotype of "*slow metabolizers*" and "*ultra-rapid metabolizers*" (*CYP2D6*) may be accompanied by a change in the concentration of the drug in the blood and require individual selection of the dose.

Porphyria is a disorder associated with a impairment of the synthesis of porphyrin, which is a component of heme hemoglobin. This disorder is associated with excess content in liver cells of such an enzyme as aminolevulenic acid synthetase. The disease is manifested by attacks of intestinal colic, polyneuritis, muscle paralysis, mental disorders, epileptic attacks, etc. Aggravation of the disease is provoked by barbiturates, as well as *sulfonamide drugs, estrogens* (including those contained in contraceptives), *calcium channel blockers, diclofenac, ACE inhibitors, tricyclic antidepressants* and some tranquilizers. These drugs enhance the formation of α-aminolevulenic acid. The probability of using barbiturates and tranquilizers in the case of patients with porphyrias is quite high, because mental disorders and epileptic seizures are quite often observed in these people.