PERIOPERATIVE OUTCOME: GENETICS, ENVIRONMENT OR BOTH?

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Abstract

In some individuals, response to stress of surgery, anaesthesia or intensive care treatment, may differ of predicted outcome. While pharmacogenetics studies inherited variation in drug metabolism and differences in response to drugs, pharmacogenomics means wide population genomic testing for genetic variation. Toxicogenomics and ecogenomics investigate genomic changes as results of, or the effects of drugs, either environmental pollutants, respectively.

Different responses to drugs used in anaesthesia represent consequence of genetic background an individual patient brings, as well as environmental influences he/she has been exposed to, psychological state, or different patient's habits. Gene products interact with, and their expression and function is affected by a variety of environmental factors (nutrition, alcohol, smoking, environmental xenobiotics, pathogens, chronic disease, other medications and stressful life events).

This gene- environment interaction is reflected by individual differences in all aspects of health and disease, including responses to drugs and stress related to anaesthesia.

Key words: anaesthesia: outcome, genetics, environment

Introduction

Pharmacogenetics investigates inherited variation in drug metabolism and differrences in response to drugs, especially safety and efficacy, *pharmacogenomics***,** refers to the study of the many different genes that determine drug behaviour. *Toxicogenomics* and *ecogenomics***,** study genomic changes as results of the effects of drugs and environmental pollutants, respectively [16]. According to toxicogenomic principles, every adverse drug reaction is accompanied by an abnormality of gene expression, and that change in gene programming occurs far earlier than the clinical manifestation of reaction. With micro robotic techniques, analyzing large numbers of genes, it is possible to find out association of a drug with an adverse reaction, and the related genes and transcribed proteins [15].

It has been shown that both, adverse drug reactions (ADRs) and variable drug response, may often be polygenic caused, not only by one isolated gene action [7]. Completion of the «Human genome project» encourages in certain changes in the choice of safer drugs and therapy for the patient [18].

One cannot expect that pharmacogenetic testing could eliminate ADRs, as many of them are the result of environmental, rather than heritable factors only. For example, alcohol consumption and smoking, are both implicated in the expression of the metabolic enzyme CYP2E1, thereby affecting the pharmacokinetics of certain drugs [8]. However, emerging knowledge of genotype/phenotype correlations of drug response could guide clinicians in choosing optimal treatment options. This is most obvious for choices concerned with reducing ADRs risks and maximizing drug efficacy, when choosing between various therapies, in particular when a drug has a narrow therapeutic index.

We are witness that drugs are still being prescribed on the manner of «protocolized medicine», or as «one drug fits all», neglecting new concept of «personalized-individualized» prescription, which imply «the right drug, at the right dose, in the right patient». Dose adjustment according to patient-specific phenotypic or genotypic laboratory tests is uncommon.

Anesthesiologists in their everyday practice often meet patients whose individual response to stress of surgery, anaesthesia or intensive care treatment, may change perioperative outcomes (such as respiratory distress syndrome, myocardial infarction, haemodynamic instability, coagulopathies, inflammatory response or intense pain). They are all variable response to stress, and pharmacodynamic differences. Common classification of patients into risk classes, based on difficult airway, general condition ("ASA class"), and the indices of cardiac risks, does not mean perfect prediction. The main problem is confrontation

with the patients that don't respond in a predictable way - "outliers", to which anaesthesiologists have to be prepared to deal. More information about genetic background of the patients might help them in better prediction [2].

Unpredictable perioperative reactions represent consequence of genetic background an individual patient brings, as well as environmental influences he/she has been exposed to (in immediate and distant past), psychological state, or different patient's habits. Gene products interact with, and their expression and function is affected by a variety of environmental factors, such as nutrition, alcohol, smoking, environmental xenobiotics, pathogens, chronic disease, other medications and stressful life events. This interaction between gene and environment is reflected by individual differences in all aspects of health and disease, as well as by responses to drugs and stress. This is the raison why it might be unwise to personalize pharmacotherapy on the basis of genetic information only [5, 12].

Basic pharmacogenetics and anaesthesia

Now are well documented differences in allele distributions for many genes, including those relevant for pharmacogenetic testing. Pharmacogenetic variability may influence drug disposition, drug transport, receptor structure and function, cell signaling and numerous responses, which produce a therapeutic effect or adverse reaction.

Enzymes

Enzymes phase I: N-acetyl transferase

Of historical significance for genetic variation in anaesthesia was development of atypical enzyme butyrilcholinesteraze- BchE, which metabolizes depolarizing myorelaxans succinylcholine and mivacurium. Its variability, found in 1:3.500 Caucasians, means the prolonged respiratory paralysis and emergence from anaesthesia and surgery.

Drugs used in anaesthesia are mostly metabolized by enzymes of system *cytochrome P-450 (CYP450)* in the liver. CYP2D6, from CYP450 super family, has more than 75 allele variations, among them some are inactive, but the others have enhanced activity. Multiple gene copies could have about 29% of east-African population, with unusual response to following drugs: analgesics (codeine, tramadol, metaraminol), or antiemetics (ondansetrone, granisetrone). Poor metabolize through CYP2D6 have also lower pain threshold. [6]. Local anaesthetics, midazolam and antiepileptic drugs, but also the most used opioid analgesics in anesthesia- fentanil, alfentanil and sufentanil, are metabolized by CYP3A4. Clinically significant difference in alfentanil duration of action, which clearance ranges widely, could be explained by wide variability of CYP3A3/4 [9].

Drug transport proteins

Homozygote for alleles connected with low P-glycoprotein activity occurs in about 25% Caucasian population. P-glycoprotein, if blocked, enhances entry of morphine into the central nervous system with possible adverse drug reactions.

Receptors

- Malignant hyperthermia syndrome (MHS) was the first discovered interaction between drug and mutating receptor. If persons with mutation on Ryanodin receptor (RYR1) gene were exposed to inhalational anaesthetic-halothane, or depolarizing myorelaxans succynilcholine, uncontrolled calcium ion release from skeleton muscles would have occur, with hyperpyrexia, muscle destruction and multi-organ dysfunction (MODS). More than 50 mutation RYR1 gene at chromosome 19 has been discovered; such persons are known as MHS phenotype, due to predisposition to malignant hyperthermia in contact with trigger-drug [10].

- Mu-opioid receptor (MOR) is another example of various receptor expressions, which causes different level of analgesia with morphine agonistic action; genetic polymerphism in gene transcription/regulation could explain higher or lower pain threshold. [3]

- GABRE genes are important for the new class of receptors in humans- epsilon (gene map locus Xq28). Changes in this gene cause significant susceptibility to diazepam, barbiturates or propofol, as well as alcohol addiction [4].

Environment, heredity and perioperative outcome

Besides genetics, it is of great importance that causes of interindividual variability in perioperative period include age, concomitant disease, environment (diet, smoking, alcohol

consumption), and interaction with drugs and herbals, too.

Smoking pharmacogenetics

Smoking, including passive tobacco smoke inhalation, still exists as an important factor of morbidity. Considerable interest exists in the metabolism of nicotine, and its role in initiation and maintenance of nicotine addiction. Liver enzyme induction by nicotine is well known, with its effects on anaesthesia outcome. Thus, the hepatic enzyme CYP2A6 (or coumarin 7-hydroxylase) catalyses nicotine, and inactivate it to cotinine, by C-oxidation [11]. Furthermore, functional variants of this enzyme might be connected to different levels of addiction between individuals [13]. In a tobacco-dependent population there is a lower incidence of two null (inactive) alleles of CYP2A6, namely CYP2A6*2 and CYP2A6*3. Nicotine addicts adjust their smoking to maintain constant nicotine levels, and therefore individuals with impaired metabolism need to smoke fewer cigarettes, and even smokers who are heterozygous for the CYP2A6 null- allele need significantly fewer cigarettes. Ethnic differences in nicotine metabolism have also been found that are related to different activities of CYPA26. It has been recognized that Chinese Americans absorb less nicotine per cigarette and metabolized nicotine more slowly than whites or Latinos, and have lower incidence of lung cancers [1]. Numerous different alleles of CYP2A6 have been identified, and correlation of the incidence of these genetic variants with both smoking and lung cancer rates has been approved. It was found that smokers whose nicotine metabolism was impaired using the enzyme blockers tranylcypromine and methoxalen required fewer cigarettes and had a longer latent period between cigarettes [14].

Ecogenetic, cancer and anaesthesia outcome

Identification of gene expression levels and profiles for various xenobiotics enables studies of the possible deleterious effects of environmental substances and pollutants. Carcinogenic potential of cigarette smoke is well known. The effect on liver enzyme induction is also well documented and has been suggested as the mechanism for altering outcome from anaesthesia [17]. The effect of any foreign substance will be determined by a number of factors that include the total dose and the duration of exposure, as well as host conditions, that increase the potential for previously mentioned gene-environment interactions. A genetic predisposition to some cancers, such as breast cancer, is recognized. Genetically determined polymorphisms of CYP enzymes involved in the degradation and/or activation of toxins may also result in a higher probability of cancer.

Conclusion

Some genetic, as well as environmental factors could alter specific patient disease during the perioperative period, which have to be considered if patients don't respond in predictable way. Individual patient's response to different environmental conditions, like drug administration, inflammatory response to stress of anaesthesia and surgery or hemodynamic changes, may influence perioperative outcomes. New disciplines, like proteomics, bioinformatics, genomics, and for clinicians important toxicogenomics, pharmacogenomics and ecogenomics give possibilities to predict perioperative outcome more precisely than it was fifty years ago.

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