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The impact of genetic factors on response to anaesthetics

Mikstacki A[1], Skrzypczak-Zielinska M[2], Tamowicz B[1], Zakerska-Banaszak O[3,4], Szalata M[2,3], Slomski R[2,3,*]

1 Department of Anaesthesiology and Intensive Therapy, Regional Hospital, Poznan, Poland
2 Institute of Human Genetics, Polish Academy of Sciences in Poznan, Poznan, Poland
3 Department of Biochemistry and Biotechnology, University of Life Sciences, Poznan, Poland
4 The NanoBioMedical Centre, Adam Mickiewicz University, Poznan, Poland

* CORRESPONDING AUTHOR:
Institute of Human Genetics,
Polish Academy of Sciences,
Strzeszynska 32,
60-479 Poznan, Poland
Tel.: +48 61 657 92 10
Fax: +48 61 848 72 11
E-mail: slomski@up.poznan.pl (Ryszard Slomski)

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ABSTRACT

In recent years, exceptional progress has been observed in pharmacogenetics, i.e. investigations of inherited conditioning of the organism's response to drugs or xenobiotics. On the other hand, modern molecular biology techniques have been implemented, making it possible to perform studies determining the involvement of genetic factors in differing responses to agents employed in general anaesthesia. Unexpected and incorrect response of the organism to the administration of specific anaesthetics is most commonly associated with a genetic defect of the metabolic pathway of a given agent or its receptor.

The majority of agents used in anaesthesia are metabolised in the liver by the cytochrome P450 superfamily enzymes (CYPs) and phase II drug-metabolising enzymes: glutathione S-transferases (GSTs), sulphotransferases (SULTs), UDP-glucuronosyltransferases (UGTs) and NAD(P)H:quinone oxidoreductase (NQO1). Propofol is presently widely used for gastrointestinal (GI) and several other procedures. Among genes associated with metabolism of the most commonly applied anaesthetics such as propofol and sevoflurane, the following ones can be mentioned: *CYP2E1, CYP2B6, CYP2C9, GSTP1, UGT1A9, SULT1A1* and *NQO1*. Moreover, the basic mechanism of propofol action involves its interaction with an ionotropic receptor GABAA inhibiting transfer of nerve impulses. Molecular studies have shown that polymorphic changes in *GABRG2* receptor gene turn out to be important in the propofol anaesthesia.

Planning of optimal anaesthesia can be considerably assisted by the determination of genetic factors of prognostic value taking advantage of genotyping and making it possible to select anaesthetics and reduce risk of side effects as well as undesirable actions.

Key words: anaesthesia, pharmacogenetics, propofol, sevoflurane, genes

INTRODUCTION

First discoveries combining pharmacology, anaesthesiology and genetics appeared shortly after 1959 when a German researcher F. Vogel proposed and defined the concept of pharmacogenetics as a science of genetically conditioned responses to drugs or xenobiotics. At the beginning of 1960s, Simpson and Kalow [1] in their studies on a local anaesthetic – procaine, and on a muscle relaxing drug – succinylcholine, discovered polymorphism of hydrolysis associated with plasma pseudocholinesterase which fails to guarantee appropriately fast metabolism of the agent. In patients suffering from cholinesterase enzymopathy, an appropriate dose of succinylcholine can lead to undesirable side effects due to excessively long biotransformation [2].

A consecutive breakthrough in the investigations regarding genetic diversity in anaesthetics metabolism was the discovery of the role of drugs and xenobiotics oxidation processes. Oxidised substances become inactive and can be eliminated from the body in the form of hydrophilic products [3]. Detailed identification of metabolic pathways made it possible to determine genes coding enzymes involved in drug metabolism.

The above discoveries were accompanied by the development of nucleic acid analysis methods with its peak at the turn of the 21st century crowned by sequencing of the human genome in 2003 and characterization of over 3.1 million human single nucleotide polymorphisms (SNP) [4-5]. Automation of genetic material amplification techniques, special equipment for genotype determination and mass reading of nucleic acid sequences (microarrays, new generation sequencers), as well as, bioinformatics advancement, all show new possibilities for the application of research results in anaesthesiology. They are based on the determination of alleles closely associated with poor, intermediate, ultra rapid or efficient metabolism of agents currently applied in general anaesthesia. Both, this knowledge and the advancement, aim at the development of a genetic diagnostic test, which will help to individualize anaesthesia for each patient.

REVIEW

General anaesthesia

An ideal anaesthetic agent should be characterised by both anaesthetic and analgesic actions, without any adverse effect on the respiratory and circulatory system, lack of irritating influence on the skin and mucous membrane, wide therapeutic range, lack of transformation to toxic metabolites and easy management of the course of anaesthesia. None of the currently available anaesthetic agents meet the above-mentioned requirements completely.

Therefore, apart from exclusively inhaled or intravenous anaesthesia TIVA (total intravenous anaesthesia), mixed anaesthesia is also frequently employed, combining several agents according to the type of surgery and associated requirements, but also depending on the health condition and age of the patient.

From among inhaled anaesthetic agents, halogen ethers such as: isoflurane, sevoflurane and desflurane introduced in 1990s are applied most commonly [6].

Currently employed halogen ethers contain fluorine (e.g. sevoflurane and desflurane) or chlorine atoms (in the case of isoflurane molecule) in their structure. Chemical composition of halogen ethers does not differ from the old generation agents, except that they possess a higher number of halogen atoms and greater molecular weight.

Sevoflurane (1,1,1,3,3,3-hexa-fluoro-2-(fluorometoxy)-propane, $C_4H_3F_7O$) is believed to be an agent of the most advantageous anaesthetic properties in comparison with the remaining halogen ethers and, therefore, it is applied most frequently in practice [6]. It is absorbed by air vesicles and is characterised by rapid induction time. Anaesthetic action, depending on the concentration of the inhaled sevoflurane, occurs after 1-2 minutes and it also shows a weak analgetic action.

In the case of intravenous general anaesthesia, one of the most commonly applied agents is propofol (2,6-di-isopropylphenol, $C_{12}H_{18}O$) [7]. It was introduced into the clinical practice in 1970s. An important advantage of these anaesthetics is its short time of introduction into deep anaesthesia (about 30 to 50 seconds) with a possibility of quick waking of the patient (about 4 to 6 minutes).

However, in general anaesthesia, the application of potentially most advantageous anaesthetic agents at recommended doses, sometimes turns out to be impossible because side effects such as: bradycardia, hypotension, motoric disorders are observed or even potentially fatal Propofol Infusion Syndrome (PRIS) may occur [8, 9]. The patient's clinical condition exerts an essential influence on the occurence of undesirable side effects, in particular, serious concomitant diseases may interfere with the course of anaesthesia. However, at present, special attention is focused on the individual metabolic variability that is more and more often reported in literature. It is maintained, on the basis of current research, that the metabolism of the applied substances depends on genetic polymorphisms of enzymes taking part in the biotransformation of the anaesthetic agent or mediating its action, such as receptor proteins [10, 11].

Metabolism of anaesthetics and genetic variants

Sevoflurane. Majority of drugs (about 70-80%) is metabolised in the liver by enzymes from the group of cytochromes P450 (CYPs) and this refers also to anaesthetic agents. CYP genes mutations can cause cancellation, decrease, change or increase of enzyme activity [10] and they belong to the first phase of response. In the case of sevoflurane and isoflurane, enzyme coded by *CYP2E1* gene (cytochrome P450, family 2, subfamily E, polypeptide 1, MIM 124040) take part in their metabolism. Under the influence of CYP2E1, approximately 5% of sevoflurane undergoes biotransformation to hexafluoroisopropanol and fluorides [8, 12]. It is suspected that the fluorides may exhibit nephrotoxic action. A toxic effect is also caused by vinyl ether fluoromethyl-2,2-difluoro-1-[trifluoromethyl], a product of sevoflurane degradation following interaction with carbon dioxide absorbents [13]. The remaining 95% of sevoflurane is secreted from the organism in unchanged form (Figure 1).

Thirteen variants of *CYP2E1* gene (Human Cytochrome P450 Allele Nomenclature Committee, www.cypalleles.ki.se/cyp2e1.htm) have been described in literature and the ones occurring most frequently include: *CYP2E1*5* (-1293G>C; -1053C>T) leading to enhanced transcription

Figure 1. **Scheme of sevoflurane metabolism [8].**

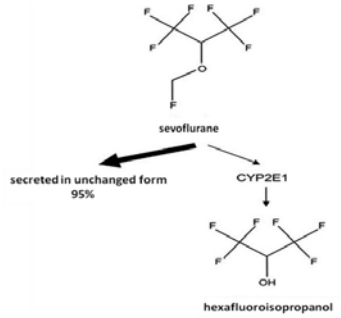
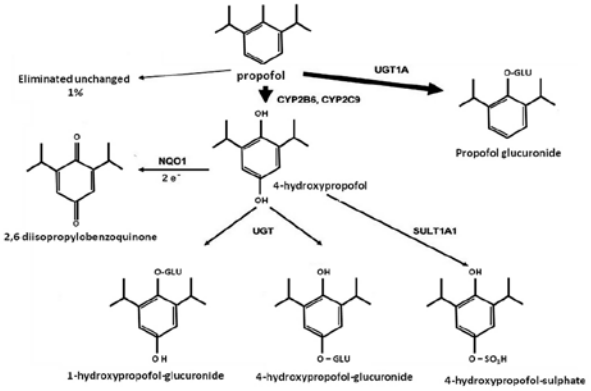


Figure 2. **Scheme of propofol metabolism [8].**



and *CYPE1*2* (R144C) reducing enzyme activity [8, 14, 15] (Table 1). Moreover, based on a comprehensive database SuperCYP described by Preissner et al., products of *CYP2A6, CYP2B6* and *CYP3A4* genes are also involved in sevoflurane metabolism. [16]. Sevoflurane serves as a substrate for these three cytochrome P450 enzymes [17].

In studies involving the application of inhalatory anaesthetics for general anaesthesia, a close correlation of I105V polymorphism in the glutathione S-transferase gene (*GSTP1,* MIM 134660) with a hepatotoxic effect of these agents was suggested [18]. One of the causes of the toxic action on hepatocytes is the reduction of the liver blood flow. Another mechanism implies biotransformation to toxic metabolites. Measurement of GST enzyme concentration in the serum is one of the most sensitive indicators of the liver function and the level of enzyme expression, according to principles of molecular biology, is conditioned by the coding gene genotype, in this case - *GSTP1* [18].

Propofol. Sevoflurane undergoes only slight biotransformation (about 5%) in the organism, whereas propofol is metabolised in the liver in over 90% into a number of products which are secreted with urine. The above biotransformation may run in different ways. Majority of propofol (about 70%) is metabolised into propofol glucuronide, for which UDP-glucuronosyltransferase coded by *UGT1A9* (UDP glucuronosyltransferase 1 family, polypeptide A9, MIM 606434) gene is responsible [19]. An alternative pathway of propofol biotransformation

Table 1. **List of most frequent genetic variants associated with sevoflurane and propofol metabolism.**

Agent	Gene	Genetic variant	Name of allele	Literature
Sevoflurane/ Isofluran	*CYP2E1*	R76H	*CYP2E1*2*	[8, 14, 15]
		-1293G>C; -1053C>T	*CYP2E1*5*	
Sevoflurane	*GSTP1*	I105V	---	[18]
Propofol	*GABRG2*	Y444W	---	[28]
	UGT1A9	M33T	*UGT1A9*3*	[8, 35, 36, 37, 38, 39]
		Y242X	*UGT1A9*4*	
		D256N	*UGT1A9*5*	
		IVS1+399C/T	---	
	CYP2B6	K262R (rs2279343)	*CYP2B6*4*	[8, 39, 40, 41]
		R487C (rs3211371)	*CYP2B6*5*	
		Q172H (rs3745274)	*CYP2B6*9*	
		I328T (rs28399299)	*CYP2B6*18*	
		Q172H + K262R	*CYP2B6*6*	
		K262R + I328T	*CYP2B6*16*	
	CYP2C9	R144C I359L	*CYP2C9*2* *CYP2C9*3*	
	SULT1A1	R213H (rs9282861)	*SULT1A1*2*	[42]
	NQO1	P187S (rs1800566)	*NQO1*2*	[43]
		IVS4-3C/T	---	

(approximately 29%) is performed by the enzymes coded by *CYP2B6* (MIM 123930) and *CYP2C9* (MIM 601130) genes as well as by *SULT1A* (MIM 171150) and *NQO1* (MIM 125860) genes (Figure 2). So far experiments indicate a relationship between patients' response to propofol in general anaesthesia and polymorphism of these genes (Table 1). In addition, there are suggestions in the literature about other polymorphisms located in the promoter region, which may play an important role in the enzyme activity and propofol biotransformation, for example -118(dT)9>10, -275(T>A)/-2152(C>T) in the *UGT1A9* gene [20, 21]. Following the action of CYP2B6 and CYP2C9 enzymes, a 4-hydroxypropofol develops and the end-products include: 2,6-diisopropyl-1,4-benzoquinone with the NQO1 participation, 1- and 4-hydroxypropofol 1-O-β-D-glucuronide with the UGT participation as well as 4-hydroxypropofol sulphate as a result of the action of the SULT1A enzyme [19, 22].

It is well known that the basic mechanism of propofol action is based on its interaction with an ionotropic receptor $GABA_A$ inhibiting the transfer of nerve impulses between neurons in the central nervous system [23]. The $GABA_A$ (gamma-aminobutyric acid type A) receptor involved in propofol action is a protein of complex structure. The α, β, γ, δ, ε, θ, ρ, π subunits have been discovered which, in various combinations, may participate in the composition of the receptor and, hence, determine its sensitivity to GABA [24]. The dominant receptor isoform in the central nervous system consists of α1, β2 and γ2 subunits. The activity of the receptor is regulated by the binding of a specific ligand – γ-aminobutyric acid (in particular, presence of γ2S, γ2L, β2 and α2 subunits enhances affinity) but it also contains domains recognizing anaesthetics. In the case of propofol, these include mainly β3 and β2 subunits but also β1 [25]. Receptor activation, which results in the hyperpolarisation of the neuron membrane and, hence, prevents the development of an action potential, takes place as a result of the intensification of the influence of the γ-aminobutyric acid on $GABA_A$ or by way of a direct induction caused by the anaesthetic agent [26]. The performed investigations proved that the activation of the receptor as a result of propofol action (3 μg/ml) was the strongest after 2 minutes and the hyperpolarisation of the neuron membrane lasted up to 10 seconds.

Genes coding $GABA_A$ receptor subunits are situated in cluster forms on: 5q34, Xq28, 4p12 and 15 chromosomes. So far, 19 genes have been discovered including, among others: *GABRB2* coding subunit β2 as well as *GABRA1*, *GABRA3*, *GABRG1*, *GABRG3*, *GABRB3* genes [27]. In literature, polymorphism of selected genes is particularly stressed in the action of propofol but the current knowledge in this area is superficial. Investigations indicate that the course of general anaesthesia is also affected by *GABRG2* (gamma-aminobutyric acid, MIM 137164) gene polymorphism and, in particular, by the change of amino acid tyrosine to tryptophan at codon 444 (Y444W) [28] (*Tab. 1*). The four polymorphic variations (358G/T, 20118C/T, 20326C/T and 20502 A/T) in the GABRE gene showed no statistically significant correlation with the anaesthesia induction time, but the impact of this gene on propofol anaesthesia cannot be excluded [29].

Symptoms of undesirable action of propofol include: short-term apnoea changing into hyperventilation, muscular tremors, drop of blood pressure as well as vision disturbances and hallucinations [9].

Perspectives of development and application of pharmacogenetics in anaesthesiology

Population genetic variability has already been described many times using as examples various disorders as well as differences in drug metabolism [30]. Such information is extremely useful and frequently makes it possible to narrow the scope of search in molecular-genetic diagnosis. However, when analysing response to treatment, it is necessary to remember not only about differences at the level of populations but also of each organism. This principle also refers to the administration of agents for general anaesthesia where it is important to individualise the use of anaesthetics in order to ensure optimal effect for each anaesthetised patient [31]. A significant support in this field can be provided by precise indication of genetic factors taking part in the metabolism of anaesthetics as well as analgetic agents.

Scientists have already determined genes taking part in metabolism of individual substances which was also shown in this study taking as examples the most frequently administered anaesthetics – sevoflurane and propofol. In addition, appropriate tools have also been developed such as the haplotype map (HapMap) intended, in particular, for investigations in the fields of pharmacogenetics and pharmacogenomics [32]. The above-mentioned achievements, in association with further clinical studies of genetic factors in anaesthesiology may result, in near future, in the development of a diagnostic tool for precise and individualised anaesthetics adjusted to patients' genotypes. In close perspective, the next challenge will be combining a genetically conditioned response to an agent with the impact of environment, i.e. moving research into the field of pharmacoepigenomics [33, 34].

CONCLUSION

In recent years, pharmacogenetics has been the object of intensive study for many branches of medicine. It may be the basis of personalized anesthesiology in the near future. Determination of genetic factors of prognostic value for a target anaesthetic agent choice and dosing, before the start of surgery, would improve the safety of patients especially with cardiac or renal dysfunction. Anaesthetics biotransformation in the organism as well as genes encoding

proteins of metabolic pathways are known. Scientists have already done research on the impact of single genotypes on the pharmacokinetics and pharmacodynamics of propofol and on a hepatotoxic effect of sevolfurane in the patients under surgical anaesthesia. However, now it is important to carry out further comprehensive clinical studies in different populations, and hopefully, it will be possible to introduce dosing recommendation for anaesthetics in clinical practice based on individual genotype of patients.

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