UDK: 618.14-089.87-089.5:577.2

ORIGINAL ARTICLE

PHARMACODYNAMICS OF PROPOFOL INFLUENCE OF GABRE AND ABCB1 GENES

Ivanov E[1], Karadjova D[1], Sivevski A[1], Kokareva A[2], Pop-Stefanija Corbeva V[1], Gjorgjevic A[1]

[1]*University Clinic of Gynecology and Obstetrics – Skopje, Republic of North Macedonia*
[2]*University Clinic for TOARILUC – Skopje, Republic of North Macedonia*

Abstract

We live in a world where the pharmaceutical industry is experiencing its rise and attention, and every day we face different reactions, different response to different drugs in different people. On the other hand, we are witnessing a wave of encouraging new drugs, especially in the field of oncology, which are based on the concept of individualized therapy. The aim of our study was to investigate the influence of the cytochrome, γ -aminobutyric acid type A (GABAA) receptor γ1 subunit *GABRA1* (rs2279020) and ATP-binding cassette sub-family B member 1 *ABCB1* (rs1045642) gene polymorphisms on propofol therapeutic outcomes in the patients undergoing abdominal hysterectomy. Ninety patients aged 29-74 years, with different ethnicities were included in this study. The presence of polymorphisms was analyzed using TaqMan SNP genotype analysis on Stratagene MxPro 3005P real-time polymerase chain reaction (qPCR). Our study did not detect a statistically significant influence of the *GABRA1* (c.1059+15G>A) and *ABCB1* (c.3435T>C) variants on the variability of clinical parameters (doses for induction in anesthesia, additional doses, induction time and wake time after anesthesia and side effects of propofol). The observed trend on the possible influence of the *GABRA1* (c.1059+15G>A) and A*BCB1* (c.3435T>C) variants warrant an extension of these studies in a larger number of patients.

Key Words: *ABCB1 gene; GABRA1 gene; Pharmacogenetic; Propofol.*

Introduction

We live in a world where the pharmaceutical industry is experiencing its rise and attention, and every day we face different reactions, different response to different drugs in different people. On the other hand, we are witnessing a wave of encouraging new drugs, especially in the field of oncology, which are based on the concept of individualized therapy. The response to the same drug varies among different individuals, and this is often due primarily to variations in genes that determine drug disposition.

Pharmacogenomics is defined as the search for genetic variations that can be observed in how a drug works, and the possibility of improving the efficacy and safety of the drug through a personalized approach. On the other hand, pharmacogenetics is concerned with linking genetic variation and inter-individual variation.

Propofol (2,6-diisopropylphenol) is the most popular intravenous anesthetic used in modern medicine. The main cardiovascular effect is the reduction of arterial blood pressure. It acts on the respiratory system as a respiratory depressive agent, possibly causing apnea after the induction dose. The majority of propofol (about 70%) is metabolized to propofol glucuronide, for which UDP-glucuronosyltransferase enzyme encoded by the UGT1A9 genome (UDP-glucuronosyltransferase family 1, polypeptide A9, MIM 606434) is responsible. Alternative pathways for biotransformation of propofol (approximately 29%) are under the action of enzymes encoded by genes CYP2B6 (MIM 123930) and CYP2C9 (MIM 601130), as well as SULT1A (MIM 171150) and NQO1 (MIM 125860) (12,53).
The GABRE gene is responsible for the synthesis of proteins that modulate inhibitory neurotransmission through the $GABA_A$ receptor in various regions of the central nervous system, while the ABCB1 gene encodes transmembrane proteins that play an important role in maintaining the barrier and protecting the brain from accumulation of toxic components.
A study was conducted to determine the variability in response to propofol as a result of the genetic information of each organism separately.
The aim of this research is to determine whether the single nucleotide polymorphisms (SNP) of the genes GABRE and ABCB1, that is, whether their established variations (homozygous and heterozygous) affect induction time, propofol dose and awakening time, as well as the side effects of the anesthesia in patients undergoing abdominal hysterectomy during general anesthesia.
Through this set of tested genes, we tried to answer the question whether patients with different genotypes show a difference in the response to the dose of propofol, which will be manifested in the difference in certain parameters such as: induction time, entropy time, time under anesthesia, time of awakening and the presence of certain side effects of propofol (nausea, vomiting and prolonged sedation).

Material and Methods

This is a cohort, prospective, longitudinal study performed at the University Clinic for Gynecology and Obstetrics and at the Center for Biomolecular Analysis at the Faculty of Pharmacy, in Skopje, R. N. Macedonia.
The study was approved by the Ethic Committee for Human Research of the Medical Faculty, “Ss. Cyril and Methodius” University in Skopje, Republic of Macedonia, no. 03-242/1, Ethics Committee of the Faculty of Medicine in Niš, Republic of Serbia, no. 12-3182-2/7 and from the Professional Collegium of the University “Ss Cyril and Methodius” - Faculty of Pharmacy, Skopje no. 03-51/1.
Ninety (90) female patients scheduled for abdominal hysterectomy were included in this study. All patients signed an informed consent before entering the study. Inclusion criteria were age between 25 and 75 years, body weight within 20% above and below ideal, ASA classification 1-2-3.
Propofol was administered according to a standard protocol based on the status and individual characteristics of the study group, as well as empirical medical data obtained from the

instructions for use (0.1–0.15 mg/kg/min. IV for 3–5 minutes). This was a non-interventional study that involved the use of propofol according to a standard dosing protocol and monitoring the clinical response of the patients under general anesthesia. The patients were not divided into groups and there was no deviation from the usual plan of administration of anesthesia. All data were recorded in the anesthesia card as an integral part of medical documentation, and they were subsequently analyzed.

After adequate preoperative preparation, a peripheral 16G or 18G intravenous line was placed. Non-invasive monitoring - blood pressure (BP), electrocardiogram (ECG), heart rate (HR), saturation with O_2 ($SatO_2$) and capnography was used to monitor vital functions, and entropy was used to monitor depth of anesthesia. All patients received general endotracheal anesthesia. For induction: midazolam 0.1mg/kg, fentanyl 2mcg/kg, propofol 1% given at a rate of 400ml/hour until values of SE entropy of 40 to 60 were achieved with loss of eyelash reflex (dose of 1.5 to 2.5 mg/kg) and rocuronium bromide (0.4–0.6 mg/kg). For maintenance: propofol 50–150 mcg/kg/min, boluses of rocuronium bromide of 0.3mg/kg, fentanyl 2mcg/kg, lung ventilation with oxygen and nitrous oxide in a ratio of 50:50%. At the end of the intervention, neuromuscular block reversal was achieved with 2.5mg of neostigmine and 1mg of atropine, after which the patient was extubated and transferred to a recovery room.

During maintenance of anesthesia, propofol was dosed based on hemodynamic parameters: heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure, which were measured every 5 minutes, as well as continuous entropy readings with the goal of maintaining values between 40 and 60.

Entropy parameters are the following: Response Entropy (RE) are values in the range from 0 to 100, and State Entropy (SE) are values in the range from 0 to 91. RE reacts faster, starting with facial muscle activation, while SE is a stable parameter which monitors the hypnotic effect of the anesthetic used. SE values are always identical or slightly lower than RE.

In the study we also analyzed opioid side effects: nausea, vomiting and level of sedation. Adverse effects were observed 24 hours after the operation. We assessed the presence of nausea with a nausea score: (0 – no nausea, 1 – mild nausea, 2 – moderate degree of nausea, 3 – severe nausea). Sedation was assessed according to the Ramsey sedation score (0 – awake, 1 – anxious, 2 – cooperative, oriented, 3 – reacts to command, 4 – reacts to tactile stimuli, 5 – weakly and slowly reacts to verbal and tactile stimuli, 6 – no reacts to strong and painful stimuli).

Genetic Analysis

Before the start of anesthesia, 4ml of blood sample was taken from a total of 90 patients who underwent abdominal hysterectomy under total intravenous propofol anesthesia at the Gynecology and Obstetrics Clinics in Skopje. Genomic DNA (deoxyribonucleic acid) was extracted from the sample. As a source of DNA, the patient's whole blood was used, which was previously sampled with EDTA as an anticoagulant and kept at -20°C until the moment of DNA isolation. An automatic extractor Mag CoreHF16 Plus (RBC Bioscience, Taiwan) was used for DNA isolation. Amplification of DNA was performed using chain reaction DNA amplification and analysis of restriction fragment length polymorphism - Real-time PCR system. Real time PCR method of chain amplification DNA, tested by analysis of polymorphism length of

restriction fragments, consisting of a Taq Man probe molecule, which consists of a nucleotide, the sequence of which is complementary to specific alleles in the desired amplification region. A fluorophore is attached to the 5' end of the sequence, and a so-called "quencher" is found at the 3' end. The presence or absence of characteristic alleles is defined by baseline Ct values characteristic of an allele-specific sample.

Statistical Analysis

Statistical data processing was performed in the software statistical program SPSS 21 for Windows. Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to test the normality of data distribution. Descriptive data processing included absolute and percentage frequency values. Continuous variables are represented by mean value and standard deviation. Chi square test, Fisher's exact probability test, Student's T test, ANOVA (post-hoc Bonferroni test) were used to rank three genotypes in relation to the analyzed variable. Correlation between the consumption of propofol in relation to the age of the patients and the duration of the operation was analyzed based on the Pearson correlation coefficient. A value of $p<0.05$ was taken for statistical significance.

Results

The study included 90 female patients from the Clinic of Gynecology and Obstetrics in Skopje, who underwent abdominal hysterectomy. The patients were aged between 29 and 74 years, with an average age of 51.5 ± 8.8 years. The patients' body weight ranged from 48 to 131 kg, with an average of 77.7 ± 16.6 kg. The largest ethnic group of participants consisted of Macedonian women, accounting for 73.3% (66).

Table 1. Patient characteristics.

Demographic characteristics	
Age (mean χ±SD) / years	51.5 ± 8.8
Weight (mean±SD) / kg	77,6 ± 16,6
Ethnicity (n/%)	
Macedonian	66 (73.3)
Albanian	23 (25.6)
Turkish	1 (1.1)

In three genotype groups of GABRA1, women of Macedonian ethnicity were predominantly homozygous with the genotype GG - 79.4% (27), while women of Albanian nationality were predominantly heterozygous with the genotype AG - 28.95% (11). The patient of Turkish nationality was homozygous with the genotype AA. There was a statistically insignificant difference in the expression of the three genotypes of the GABRA1 gene concerning the ethnic structure of the patients (Table 2).

Table 2. Demographic characteristics of patients with GABRA1 genotypes – ethnicity.

Ethnicity n (%)	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Macedonian	12 (66.67)	27 (71.05)	27 (79.41)	p = 0.41 ns
Albanian	5 (27.78)	11 (28.95)	7 (20.59)	
Turkish	1 (5.56)	0		

p (Fisher exact)
AA – homozygotes with two normal alleles
AG – heterozygotes with one normal allele and one mutated allele
GG – homozygotes with two mutated alleles

The genetic polymorphism of GABRA1 did not exhibit a significant influence on various parameters, including the duration of induction (p=0.53), the time required to reach entropy values of 40–60 (p=0.52), the duration of anesthesia (p=0.78), the time to awakening (p=0.78), and the overall duration of anesthesia from commencement to completion (p=0.7). Similar median induction and entropy times were observed across all three genotype groups (median = 60 seconds and 30 seconds, respectively). Among patients, those homozygous for the normal AA genotype showed marginally shorter mean anesthesia durations compared to individuals with other genotypes (median = 88.5 minutes vs 100 minutes vs 101 minutes). Similarly, the mean time to awakening was slightly shorter in the AA genotype group compared to AG and GG genotypes (median = 13 minutes vs 15 minutes vs 15 minutes). Additionally, patients homozygous for the normal AA genotype also exhibited slightly shorter total anesthesia durations compared to those with pathological genotypes, AG heterozygotes, and GG homozygotes (median = 102 minutes vs 114 minutes to 117 minutes).

Table 3. The correlation between GABRA1 genotypes and the following parameters was examined: induction time, time to achieve entropy values of 40–60, duration of anesthesia, time to awakening, and overall duration of anesthesia from commencement to completion.

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Induction time (seconds)				
mean ± SD	64.2 ± 30.2	91.7 ± 150.5	93.5 ± 86.6	P = 0.53 ns
median (IQR)	60 (35–75)	60 (60–60)	60 (60–120)	
Time to achieve entropy of 40-60 (seconds)				
mean ± SD	32.8 ± 13	28.4 ± 10.1	32.7 ± 22.9	p = 0.52 ns
median (IQR)	30 (20–45)	30 (20-35)	30 (20-35)	

Duration of anesthesia (minutes)				
mean ± SD	92.6 ± 31.6	104 ± 55.25	104.1 ± 42.1	p = 0.78 ns
median (IQR)	88.5 (75–125)	100 (80–110)	101 (75–125)	
Awakening time (minutes)				
mean ± SD	13.1 ± 5.1	14.3 ± 6.8	14 ± 8.2	p = 0.78 ns
median (IQR)	13 (10–15)	15 (10–20)	15 (10–15)	
Total duration from the beginning to the end of anesthesia (minutes)				
mean ± SD	105.7 ± 33.1	118.3 ± 55.2	118.1 ± 41.4	p = 0.7 ns
median (IQR)	102 (88–130)	114 (90–130)	117 (86–135)	

p (Kruskal-Wallis)
AA – homozygotes with two normal alleles
AG – heterozygotes with one normal allele and one mutated allele
GG – homozygotes with two mutated alleles

Analysis of the impact of GABRA1 gene polymorphism on the occurrence of adverse effects showed that the three genotype groups had insignificantly different frequencies of nausea (p=0.54), vomiting (p=0.33), and sedation (p=0.96).

Table 4. Adverse effects in patients across three genotype groups of the GABRA1 gene.

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Nausea – number n (%)				
0	18 (100)	36 (94.74)	32 (94.12)	p = 0.54 ns
1	0	1 (2.63)	0	
2	0	0	2 (5.88)	
3	0	1 (2.63)	0	
Vomiting – n (%)				
0	18 (100)	37 (97.37)	32 (94.12)	p = 0.33 ns
1	0	0	2 (5.88)	
2	0	1 (2.63)	0	
Sedation – n (%)				
0	18 (100)	34 (89.47)	31 (91.18)	p = 0.96 ns
1	0	1 (2.63)	0	
2	0	1 (2.63)	2 (5.88)	
3	0	1 (2.63)	1 (2.94)	
4	0	1 (2.63)	0	

AA – homozygotes with two normal alleles
AG – heterozygotes with one normal allele and one mutated allele
GG – homozygotes with two mutated alleles

Propofol consumption, both initial, additional, and total, did not significantly depend on the genotype of the GABRA1 gene (p=0.78, p=0.33, p=0.22). The mean initial propofol

consumption across all three genotype groups was 150mg; the mean supplementation was slightly higher in the homozygous GG group compared to homozygous AA and heterozygous AG groups (150 vs 115 vs 100mg); the overall mean intraoperative propofol consumption was slightly lower in the group with the pathological AG genotype, i.e. in patients with one normal and one mutated allele, compared to groups with two normal and two mutated alleles (median = 250 vs 300 vs 300) (Table 5).

Table 5. The correlation between propofol consumption and GABRA1 genotypes.

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
propofol for induction of anesthesia / mg				
mean ± SD	156.1 ± 39.7	146.8 ± 43.3	152.1 ± 41.5	p = 0.78 ns
median (IQR)	150 (120–200)	150 (100–200)	150 (120–200)	
additional dose of propofol for maintenance of anesthesia / mg				
mean±SD	136.12 ± 51.2	122.92 ± 46.7	140.9 ± 4.6	p = 0.33 ns
median (IQR)	115 (100–200)	100 (100–150)	150 (100–200)	
total intraoperative propofol consumption / mg				
mean±SD	292.2 ± 70.3	269.7 ± 77	292.9 ± 66.1	p = 0.22 ns
median (IQR)	300 (250–350)	250 (200–300)	300 (250–350)	

p (Kruskal-Wallis)
AA – homozygotes with two normal alleles
AG – heterozygotes with one normal allele and one mutated allele
GG – homozygotes with two mutated alleles

From women of Macedonian ethnicity, 81.8% (18) had the CC genotype for the ABCB1 gene, 71.1% (32) had the CT genotype, and 73.9% (17) had the TT genotype. Albanian women accounted for 18.2% (4), with 28.9% (13) having the CC genotype, 21.7% (5) having the CT genotype, and 21.7% (5) having the TT genotype. The patient of Turkish nationality was a carrier of the TT genotype for this gene. No significant difference in the expression of the three ABCB1 genotypes was found concerning the ethnic structure of the patients (p = 0.43) (Table 6).

Table 6. Demographic characteristics of patients with ABCB1 genotypes – ethnicity.

ethnicity n (%)	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Macedonian	18 (81.82)	32 (71.11)	17 (73.91)	p = 0.43 ns
Albanian	4 (18.18)	13 (28.89)	5 (21.74)	
Turkish	0	0	1 (4.35)	

p (Fisher exact)
C – homozygotes with two normal alleles
CT – heterozygotes with one normal allele and one mutated allele

TT – homozygotes with two mutated alleles

No significant difference was found among patients with CC, CT and TT genotypes for the ABCB1 gene regarding the duration of induction (p=0.15), time to achieve adequate entropy values (p=0.93), duration of anesthesia (p=0.51), awakening time (p=0.94), and total anesthesia time (p=0.53). The same median induction time and entropy time were observed in all three genotype groups (median = 60 seconds and 30 seconds, respectively). Patients with the TT genotype had slightly shorter mean anesthesia durations than the other two genotype groups (median = 85 vs 101 vs 100 minutes); the mean awakening time was slightly shorter in the TT genotype group compared to CC and CT (median = 13 vs 15 vs 15 minutes). The total mean duration from start to finish of anesthesia was also slightly shorter in the TT genotype group for the ABCB1 gene (median = 100 vs 116 vs 115 minutes).

Table 7. The correlation between ABCB1 genotypes and the following parameters was examined: induction time, time to achieve adequate entropy values, duration of anesthesia, awakening time, and total duration from the beginning to the end of anesthesia.

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Induction time				
mean ± SD	90.9 ± 94,1	98.7 ± 141.5	60.1 ± 31.2	p = 0.15 ns
median (IQR)	60 (60–120)	60 (60–120)	60 (30–60)	
Time to achieve entropy values of 40-60				
mean ± SD	30.2 ± 10.2	29.1 ± 9.4	35.2 ± 28.3	p = 0.93 ns
median (IQR)	30 (25–40)	30 (20–35)	30 (20–48)	
Duration of anesthesia				
mean ± SD	104.6 ± 38,6	106 ± 54	90.8 ± 8.2	p = 0,51 ns
median (IQR)	101 (90–120)	100 (75–130)	85 (75–110)	
Awakening time				
mean ± SD	13.8 ± 6.6	14.1 ± 8.1	13.7 ± 5.1	p = 0.94 ns
median (IQR)	15 (10–20)	15 (10–15)	13 (10–15)	
Total duration from the beginning to the end of anesthesia				
mean ± SD	118.5 ± 38,9	120.1 ± 53.8	104.5 ± 34.9	p = 0.53 ns
median (IQR)	116 (95–130)	115 (88–150)	100 (86–130)	

p (Kruskal-Wallis)
C – homozygotes with two normal alleles
CT – heterozygotes with one normal allele and one mutated allele
TT – homozygotes with two mutated alleles
Analysis of the impact of ABCB1 gene genotypes on the occurrence of adverse effects showed that the three groups had insignificantly different frequencies of nausea (p = 0.68), vomiting (p = 0.43), and sedation (p = 1.0).

Table 8. Adverse effects in patients across three genotype groups of the ABCB1 gene.

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Nausea – number n (%)				
0	21 (95.45)	42 (93.33)	23 (100)	p = 0.52 ns
1	1 (4.55)	0	0	
2	0	2 (4.44)	0	
3		1 (2.22)	0	
Vomiting – n (%)				
0	22 (100)	42 (93.33)	23 (100)	p = 0.75 ns
1	0	2 (4.44)	0	
2		1 (2.22)		
Sedation – n (%)				
0	21 (95.45)	41 (91.11)	21 (91.30)	p = 0.88 ns
1	0	1 (2.22)	0	
2	0	2 (4.44)	1 (4.35)	
3	1 (4.55)	0	1 (4.35)	
4	0	1 (2.22)	0	

p (Fisher's Exact Test)
CC – homozygotes with two normal alleles
CT – heterozygotes with one normal allele and one mutated allele
TT – homozygotes with two mutated alleles
The initial dose of propofol was insignificantly correlated with the age of patients with the CC genotype (p=0.18), but significantly correlated with the age of patients with CT and TT genotypes of the ABCB1 gene (p=0.001, p=0.047). These two correlations were negative, suggesting that with increasing age of patients carrying two combined alleles and two mutated alleles for the ABCB1 gene, the administered propofol dose was lower (ro = -0.462, ro = -0.417, respectively). The additional dose of propofol was insignificantly correlated with the age of patients with CC and CT genotypes (p=0.56, p=0.26, respectively), but significantly correlated with the age of patients with the TT genotype for the ABCB1 gene (ro= -0.552, p=0.006). The additional dose of propofol was lower in older patients with the pathological TT genotype, and vice versa.

Table 9. Consumption of ABCB1 genotypes.

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Propofol for induction of anesthesia / mg				
mean ± SD	161.4 ± 36	149.3 ± 42	143 ± 45.6	p = 0.4 ns
median (IQR)	150 (120–200)	150 (120–200)	150 (120–200)	
Additional dose of propofol for maintenance of anesthesia / mg				
mean ± SD	1382 ± 51	132.2 ± 50.3	126.9 ± 45.5	p = 0.78 ns

median (IQR)	100 (100–200)	100 (100–200)	100 (100–150)	
Total intraoperative propofol consumption / mg				
mean ± SD	299.5 ± 62.4	281.6 ± 73.8	270 ± 76,3	p = 0.35 ns
median (IQR)	300 (250-350)	270 (230-330)	250 (230-300)	

p (Kruskal-Wallis)
CC – homozygotes with two normal alleles
CT – heterozygotes with one normal allele and one mutated allele
TT – homozygotes with two mutated alleles

Discussion

Preceding scientific investigations have suggested a correlation between diverse patients' responses to propofol in general anesthesia and polymorphisms of genes involved in its metabolism (1).
The aim of this research was to determine whether individual single nucleotide polymorphisms (SNPs) of the GABRE and ABCB1 genes, and their identified variations (homozygous and heterozygous), influence the induction time, propofol doses, awakening time, as well as the adverse effects of anesthesia.
The study was conducted to ascertain the response variability to propofol as a consequence of the genetic information of each individual organism separately. The GABRE gene is responsible for synthesizing proteins that modulate inhibitory neurotransmission via $GABA_A$ receptors in various regions of the central nervous system, while the ABCB1 gene encodes transmembrane proteins that play a crucial role in maintaining the blood-brain barrier and protecting the brain from the accumulation of toxic components. Through this set of tested genes, we attempted to answer whether patients with different genotypes would demonstrate differences in response to the administered dose of propofol, which would manifest in variations in certain parameters such as induction time, entropy time, duration of anesthesia, awakening time, and the presence of certain undesirable propofol effects (nausea, vomiting, and prolonged sedation). However, in the obtained results, we did not find a correlation for any of the tested genotypes of the mentioned genes with the clinical parameters we investigated. This could be due to the small sample size, study design, but also the fact that propofol metabolism, and thus its clinical effects and adverse effects, are much more complex and depend on many other factors that are not genetic based(patient condition, age, comorbidities, gender, etc.).
The only significant difference observed in our study was the correlation between the age of the patients and the requirement for propofol. Older patients required a lower dose of the medication to achieve adequate anesthesia (2,3). This observation has been noted by other authors as well. Schüttler and Ihmsen demonstrated that blood concentrations of propofol were significantly higher in older individuals compared to younger ones due to reduced minute volume and hepatic blood flow in the older population (4). However, minute volume and hepatic blood flow are not reduced in all older patients and vary individually. Furthermore, no other factor influencing propofol pharmacokinetics can be attributed solely to the fact that patients are older (5).

It was concluded that anesthesia doses required to achieve the same anesthetic state in older patients can be up to half lower than those needed for younger patients (2) The authors believe that the lower anesthesia requirements of older individuals are a consequence of changes in cardiovascular, respiratory, hepatic and renal functions that occur with aging. However, according to these authors, the primary cause of different anesthetic effects lies in the central nervous system. This is supported by the fact that the incidence of delirium and postoperative cognitive dysfunction after general anesthesia and sedation increases in older patients who exhibit typical aging, defined by anatomical and physiological changes that occur in the brain over the years. Therefore, more attention should be paid to the brain and how typical brain aging affects anesthesia requirements and increased susceptibility to cognitive impairment. These findings have important implications for clinical monitoring and management of general anesthesia in older patients.

The induction dose of propofol in healthy adult patients: Participants ranged from 2–2.5mg/kg, but varied due to various factors in each patient, such as age, gender, body mass index, but primarily from preoperative levels of albumin in the blood, as well as concurrently administered medications (6). Ethnicity also influenced the concentrations of doses required for propofol induction.

Gender differences in metabolite elimination could also contribute to the overall observed differences. Gender differences were discovered in the formation of propofol metabolites, which manifested as significantly higher levels of these metabolites in the plasma of female patients. Therefore, the results indicate a significant contribution of gender to the degree of glucuronidation and hydroxylation of this drug during anesthesia. Further research is necessary to clarify the clinical impact of these findings (7).

The GABRE gene has four polymorphic variations. Literature data relating to the influence of the GABRE gene on induction time in anesthesia, time to BIS <70, and time to response to stimulation are available, but they did not show a statistically significant correlation between the four polymorphic variations of the GABRE gene and these parameters. However, the influence of this gene on propofol anesthesia cannot be ruled out (1,8). The data obtained in this study also indicate that there is no significant correlation between GABRE genotypes and the parameters examined.

Our results indicate that the frequency of these polymorphisms in our patients is similar to that in other population studies. In our study, we found differences in the doses of propofol administered to patients with different genotypes studied. Our results show that the ABCB1 (c.3435C>T) variant does not influence the clinical parameters in our patients undergoing propofol anesthesia. Although there is limited information on the impact of this variant on propofol anesthesia, our findings are consistent with those reported by Zakerska-Banaszak and colleagues, who did not find a significant statistical difference in the effect of propofol among ABCB1 genetic variants (9,10).

Conclusion

The potential impact of GABRA1 and ABCB1 gene variants on the pharmacodynamics of propofol in abdominal hysterectomies suggests that pharmacogenetic studies on larger number of

genes are necessary in the form of prospective clinical trials involving large number of patients to determine the benefit and cost-effectiveness of genotyping in therapy individualization in anesthesiology.

References

1. Mikstacki, A., Skrzypczak-Zielinska, M., Tamowicz, B., Zakerska-Banaszak, O., Szalata, M., Slomski, R., The impact of genetic factors on response to anaesthetics. Advances in Medical Sciences. 2013; 58(1):9-14.
2. P. L. Purdon, K. J. Pavone, O. Akeju, et al.. The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. BJA: British Journal of Anaesthesia. 2015; 115(1):46-57.
3. R. Searle, P. M. Hopkins. Pharmacogenomic variability and anaesthesia. BJA: British Journal of Anaesthesia. 2009; 103(1):14-25.
4. Jürgen Schüttler, Harald Ihmsen. Population Pharmacokinetics of Propofol: A Multicenter Study. Anesthesiology. 2000; 92:727–738. doi: https://doi.org/10.1097/00000542-200003000-00017
5. Kanaya A, Sato T, Fuse N, Yamaguchi H, Mano N, Yamauchi M. Impact of clinical factors and UGT1A9 and CYP2B6 genotype on inter-individual differences in propofol pharmacokinetics, J Anesth. 2018; 32(2):236-243. doi: 10.1007/s00540-018-2470-3. Epub 2018 Feb 21.
6. Vasanth Sukumar, Arathi Radhakrishnan, Venkatesh H Keshavan. Effect site concentration of propofol at induction and recovery of anaesthesia - A correlative dose-response study. Indian J Anaesth. 2018; 62:263-8.
7. Choong, E., Loryan, I., Lindqvist, M., et al, M. Sex Difference in Formation of Propofol Metabolites: A Replication Study. Basic Clin Pharmacol Toxicol. 2013; 113:126-131. https://doi.org/10.1111/bcpt.12070.
8. Iohom G, Ni Chonghaile M, O'Brien JK, Cunningham AJ, Fitzgerald DF, Shields DC ;An investigation of potential genetic determinants of propofol requirements and recovery from anaesthesia, Eur J Anaesthesiol. 2007; 24(11):912-9. Epub 2007 Jun 7, PMID:17555608 DOI: 10.1017/S0265021507000476.
9. Zakerska-Banaszak O, Skrzypczak-Zielinska M, Tamowicz B, et al. Longrange PCR-based next-generation sequencing in pharmacokinetics and pharmacodynamics study of propofol among patients under general anaesthesia. Sci Rep. 2017; 7(1):15399.
10. Zhong Q, Chen X, Zhao Y, Liu R, Yao S. Association Of Polymorphisms In Pharmacogenetic Candidate Genes With Propofol Susceptibility. Sci Rep. 2017 Jun 13;7(1):3343. doi: 10.1038/s41598-017-03229-3.