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Research Article,

Polymorphisms That Affect Propofol Metabolism and Their Clinical Effects
Short title: Polymorphisms that affect propofol

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Polymorphisms that affect propofol metabolism and their clinical effects

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Abstract:

The purpose of this study was to determine the polymorphisms of UGT1A9 and CYP2B6 the effects of these polymorphisms on propofol consumptions and hemodynamic datas and recovery times.This study included 100 pediatric patients (Group I–II; 2–8 years of age), 100 young-median age adults (Group III–IV; 18–60years of age), and 100 elderly patients (Group V–VI; 60years of age and older). Hemodynamic situations, propofol consumption and recovery timesof the patients were recorded. The genotypes UGT1A9 (rs72551330, rs17868320, and rs6714486) and CYP2B6 (rs3745274, rs2279343) were determined by real-time PCR.A remarkable decrease (p=0.043) in heart rate (HR) and blood pressure (BP) was observed following induction in the female children with the polymorphism UGT1A9 (rs72551330). The HR dropped significantly (p=0.044) following induction in the male pediatric group with the polymorphism CYP2B6 (rs3745274). A significant decrease (p=0.004) in BP was observed only in elderly women with the CYP2B6 (rs2279343) polymorphism. Propofol consumption was significantly low in female children. Recovery periods were the same in all groups. Hemodynamic changes were mostly observed in pediatric patients. Propofol consumption was significantly low in female children. Recovery times were similar.

Keywords: propofol, polymorphism, UGT1A9, CYP2B6, sedation

Introduction:

Propofol is an intravenous anesthetic agent that has been used extensively for many years for both general anesthesia and sedation. Some of the favorable features of propofol are the following: it acts quickly; its action time is controllable; it has bronchodilator and antiemetic effects; short recovery period; and provides a clear awaking from the anesthesia. Tachypnea depression and causing hypertension are some of the undesirable effects [1].

The dose and response relationship of propofol may be changeable. Accordingly, hemodynamics and recovery periods change. It is thought that these changes are rooted in changes in the metabolism of the medicine. Genetic polymorphisms play a large role in metabolic differences between individuals. Therefore, defining enzyme polymorphisms associated with propofol could eliminate its adverse effects. Imperfect or excessive responses can be estimated and a reliable anesthesia method can be provided as well [2]. Propofol is a short-acting agent that can be easily removed from the body; its elimination is accomplished by glucuronidation (UGT1A9) in the liver. Almost 70 % of the administered dose undergoes biotransformation by conjugation with glucuronic acid. The majority of the remaining propofol is metabolized by cytochrome P450 enzymes (CYP2B6). Enzymes that cause propofol biotransformation are considerable polymorphic enzymes as they can differ between individuals and ethnicities in terms of reactions to the medicine (e.g., medication requirements and adverse effects) [3].

The primary goal of this study was to determine the polymorphic variables in the genes UGT1A9 and CYP2B6 in a population. A secondary goal was to evaluate the hemodynamic effects of these polymorphisms clinically.

Materials and methods:

The research was actualized by the financial support of Erciyes University Research Project Department after receiving ethics committee approval (No: 2013/215) of the Erciyes University Medical Faculty (Project no: TSA-2013-4597) (Clinical Trial Number: NCT 02271542). We obtained written informed consent from patients and their guardians for pediatric patients. The study included100 pediatric patients (Group I–II; 2–8 years of age), 100 young-median age adults (Group III–IV; 18–60years of age), and 100 elderly adults (Group V–VI; 60years of age and older). The gender ratios were equal in each of the groups. As a result of data loss or problems with DNA isolation, eight patients in the elderly group were excluded from the study.

Pediatric patients had a tooth pulled. Anesthesia induction was provided by 2 mg/kgpropofol and continued by 100 mcgr/kg/min, 1mg/kg propofol was added if the child felt unwell (extremity or body movement).

Women in groups III and V were curetted and applied dilatation because of abnormal uterine bleeding. Anesthesia induction was provided by the administration of 2 mg/kg propofol and continued by 100 mcgr/kg/min;0.5mg/kg propofol was added if the patient felt unwell (extremity or body movement).

Since there was no planned procedural implementation for propofol administration for male patients in both the young and elderly groups, only hemodynamic responses that occurred during general anesthesia induction were evaluated. Propofol dose requirement and recovery periods were not evaluated in these groups.

Blood samples were obtained after induction of anesthesia. Rates of incidence of UGT1A9 (rs72551330, p.M33T; rs17868320, -2152C>T; and rs6714486, -275 T>A) and CYP2B6 (rs3745274, c.516G>T and rs2279343, c.785A>G) polymorphisms were determined in each of the subgroups. Clinical situations affecting these polymorphisms in each of the subgroups as well as the hemodynamic response, propofol dose requirement, and recovery period following administration of propofol were evaluated. Since the working design was not planned for the same situation in Groups IV and VI, propofol dose requirement and recovery period were not considered.

DNA extraction and genotyping:

Peripheral blood (2 ml) was collected from all of the participants in EDTA. Genomic DNA was extracted from peripheral blood mononuclear cells with a High Pure PCR Template Preparation Kit (Roche, Germany). The final DNA concentration was determined using a BioSpec-Nano Spectrophotometer. DNA was stored at−80°C until use. All patients were screened for fivesingle nucleotide polymorphisms in UGT1A9 (rs17868320, rs72551330, and rs6714486) and CYP2B6 (rs3745274 and rs2279343). Genotyping was carried out using the LightSNiP assay on a LightCycler 480 Real-Time PCRsystem (Roche Applied Science, Germany) according to the manufacturer's instructions.

Statistical analysis:

Mutation ratios for each of the groups were tested using the Pearson Chi-Square test. Relationships between each of the polymorphisms and smoking, alcohol consumption, anesthesia history, diabetes mellitus, antihypertensive use, and coronary artery disease were also reviewed by the Pearson Chi-Square test. Comparison of hemodynamic data for each of the groups was performed using the Wilcoxon test.

Relationships between each of the polymorphisms and the hemodynamic situation was tested using the Mann–Whitney U test.

Results:

Table 1 shows weight, smoking, alcohol consumption, anesthesia history, and comorbidities in each of the groups. Table 2 shows the genotypes for UGT1A9 (rs17868320, rs72551330, and rs6714486) and CYP2B6 (rs3745274 and rs2279343).

Table 1: Weights, ages, smoking, alcohol drinking, anesthesia exposure and comorbidities in the groups.

	Children(n=100)		**YoungAdults (n=100)**		**ElderAdults (n=92)**	
	GroupI (female, n=50) Median (IR)	Group II (male, n=50) Median (IR)	Group III (Female, n=50) Median (IR)	Group IV (Male, n=50) Median (IR)	Group V (Female, n=45) Median (IR)	Group VI (Male, n=47) Median (IR)
Age (year)	5(2)	5.5(3)	41.5(16.75)	37.5(19.75)	68(8)	67(7)
Weight (kg)	19(4)	20(8.5)	75.5(22)	80(14.25)	80(11)	76(13)
Smoking						
No	50(100%)	50(100%)	48(96%)	47(94%)	45(100%)	29(92%)
Yes	0	0	1(2%)	0	0	14(29.8%)
Used to smoke	0	0	1(2%)	3(6%)	0	4(2.7%)
Alcohol	0	0	1(2%)	0	0	0
Anesthesia exposure						
No	47(94%)	39(78%)	21(42%)	34(68%)	25(55.6%)	22(46.8%)
1 time	3(6%)	11(22%)	22(44%)	13(26%)	12(26.7%)	18(38.3%)
2 andmore	0	0	7(14%)	3(6%)	8(17.8)	7(14.9)
Comorbidities						
D.Mellitus	0	0	4(8%)	0	10(22%)	5(10.6%)
Coronery artery disease	0	0	2(4%)	0	2(4.4%)	5(10.6%)
Hypertansion treatment	0	0	6(12%)	0	17(38%)	11(23%)
Diabetes Mellitus treatment	0	0	2(4%)	0	4(9%)	1(2%)

There was no mutant genotype of the UGT1A9 rs72551330 polymorphism in elderly patients. There were polymorphisms present at varying rates in all of the other groups (Table 2). The UGT1A9 (rs6714486) homozygote genotype (AA) had a significantly higher incidence rate in pediatric patients compared with the other groups.

Table 1: Weights, ages, smoking, alcohol drinking, anesthesia exposure and comorbidities in the groups.

	Children(n=100)		**YoungAdults (n=100)**		**ElderAdults (n=92)**	
	GroupI (female, n=50) Median (IR)	Group II (male, n=50) Median (IR)	Group III (Female, n=50) Median (IR)	Group IV (Male, n=50) Median (IR)	Group V (Female, n=45) Median (IR)	Group VI (Male, n=47) Median (IR)
Age (year)	5(2)	5.5(3)	41.5(16.75)	37.5(19.75)	68(8)	67(7)
Weight (kg)	19(4)	20(8.5)	75.5(22)	80(14.25)	80(11)	76(13)
Smoking						
No	50(100%)	50(100%)	48(96%)	47(94%)	45(100%)	29(92%)
Yes	0	0	1(2%)	0	0	14(29.8%)
Used to smoke	0	0	1(2%)	3(6%)	0	4(2.7%)
Alcohol	0	0	1(2%)	0	0	0
Anesthesia exposure						
No	47(94%)	39(78%)	21(42%)	34(68%)	25(55.6%)	22(46.8%)
1 time	3(6%)	11(22%)	22(44%)	13(26%)	12(26.7%)	18(38.3%)
2 andmore	0	0	7(14%)	3(6%)	8(17.8)	7(14.9)
Comorbidities						
D.Mellitus	0	0	4(8%)	0	10(22%)	5(10.6%)
Coronery artery disease	0	0	2(4%)	0	2(4.4%)	5(10.6%)
Hypertansion treatment	0	0	6(12%)	0	17(38%)	11(23%)
Diabetes Mellitus treatment	0	0	2(4%)	0	4(9%)	1(2%)

Each of the subgroups was evaluated for polymorphisms in terms of their relationships with anesthesia history, diabetes mellitus, smoking, coronary artery disease, alcohol consumption. There was a significant relationship between the rs17868320 and rs6714486 UGT1A9 polymorphisms ($p = 0.008$ and $p = 0.008$, respectively) and receiving anesthesia two or more than two times in elderly women. There was also a significant relationship between the rs17868320 and rs6714486 UGT1A9 polymorphism ($p = 0.045$ and $p = 0.070$, respectively) and diabetes mellitus in elderly women.

There was no significant relationship between UGT1A9 (rs17868320) and UGT1A9 (rs6714486) polymorphisms and hemodynamic variables in any of the subgroups when each of the subgroups was evaluated in terms of the effects of polymorphisms on the hemodynamic data. A significant decrease in HR

(p = 0.043) and BP (p = 0.009) was observed following induction in female children when subgroups were evaluated in terms of the UGT1A9 (rs72551330) polymorphism. There was also a significant difference in HR and blood pressure change. When the groups were evaluated in terms of the CYP2B6 rs3745274 polymorphism, the change in HR was significantly decreased (p=0.044) in male children. The change in HR was significant (p=0.035) in young women for this mutation; again, with a tendency to decrease. BP changes were significant for the same polymorphism in elderly women; these changes also had a tendency to decrease (p=0.09; Table 3). When the groups were evaluated in terms of the CYP2B6 rs2279343 polymorphism, there was a significant decrease in elderly women (p=0.004) only.

Administration of propofol was significantly low (240mcg/kg/min; 44mcg/kg/dk; p=0.014) in female children with the UGT1A9 rs6714486 polymorphism compared with propofoladministration for patients with or without polymorphisms in each of the subgroups. There was no significant difference between individuals with and without polymorphisms in terms of propofol consumption (Table 3).

There was no significant difference in the recovery period with the different polymorphisms in any of the groups evaluated (Table 3).

Table 3: Heart rates, blood pressures, recovery times, propofol consumptions and duration of procedures

	Children(n=100)		**YoungAdults (n=100)**		**ElderAdults (n=92)**	
	GroupI (female, n=50) Median (IR)	Group II (male, n=50) Median (IR)	Group III (Female, n=50) Median (IR)	Group IV (Male, n=50) Median (IR)	Group V (Female, n=45) Median (IR)	Group VI (Male, n=47) Median (IR)
MAP O.min (mmHg)	80(13)	84(17)	105(18)	96(18)	111(28)	102(21)
MAP 3.min(mmHg)	77(15)	81(21)	97(17)	85(17)	98(21)	92(25)
MAP end (mmHg)	72(17)	78(18)	98(15)	-	100(28)	-
HR O.min (mmHg)	106(19)	99(16)	96(21)	84(21)	89(13)	80(21)
HR 3.min (mmHg)	107(23)	100(17)	83(22)	80(18)	78(13)	77(18)
HR end (mmHg)	110(18)	98(24)	80(18)	-	80(19)	-
Recovery time (min)	10(4.5)	10(2)	10(5)	-	10(4.5)	-
Propofol consumption (mcg/kg/min)	219(256)	363(222)	39(120)	-	31(44)	-
Pocedure duration (min)	7(5)	7.5(5)	6(1.25)	-	6(1)	-

MAP: Mean arterial pressure
HR: Heart rate

Discussion:

In this study we analyzed UGT1A9 (rs72551330, rs17868320, and rs6714486) and CYP2B6 (rs3745274 and rs2279343) gene polymorphism ratios and propofol consumption in patients with these genes. The effects of these genes on the hemodynamic data of patients were analyzed at the same time. In this study population, genetic polymorphisms were present in each of the groups which affected propofol metabolism, although the

UGT1A9 rs72551330 polymorphism was not present in elderly patients. The UGT1A9 (rs6714486) homozygote polymorphism (AA) was significantly higher in the pediatric patient group compared with other groups. Age, receiving anesthesia several times, and diabetes mellitus affected the polymorphism.

A previous study actualized target-controlled propofol sedation in pediatric oncology patients and showed a relationship between propofol consumption and the American Society of Anesthesiologist (ASA) status of the patient. It has also been noted in the same study that patients in the ASA I–II group require 43 % more propofol compared with patients in the ASA III–IV group [4]. Moura et al. determined that age and weight affect the propofol dose requirement under general anesthesia; propofol metabolism decreases in patients who have the c.516 G>T polymorphism [5]. Kanaya et al. [6] observed that UGT1A9, CYP2B6, gender, and hemodynamic changes do not affect propofol pharmacokinetics. However, body mass index (BMI) is effective as an independent factor. According to Tachibana et al. [7], BMI (body mass index) effects propofol plasma concentration and can cause patient overdose. In our study, age and UGT1A9 rs6714486 polimorphism affected propofol metabolism. Propofol consumption was significantly low in elderly patients compared with children. Propofol consumption was also low (240mcg/kg/min; 44mcg/kg/dk; p=0.014) in female children with the UGT1A9 rs6714486 polymorphism.

It has been noted that individuals with the D256N mutation in the UGT1A9 gene are at higher risk in terms of propofol-related adverse effects; thus, extra caution must be used with these patients (5). A previous study indicated that the presence of the CYP2B6 G516T and UGT1A9 1399 C>T polymorphisms and advanced age increased the negative effects of propofol. Propofol metabolism decreased in patients with the c.516 G>T polymorphism; thus, the adverse effects of propofol must be reviewed carefully (5). Also, we observed significant changes in KAH and blood pressure in male children, and young and elderly women with the c.516 G>T polymorphism.

With reference to Mikstacki et al. [3], BMI and c.516G>T polymorphisms affected propofol metabolism when UGT19, CYP2B6, and CYP2C9 genes are worked in propofol metabolism. CYP2B6 expression was high in individuals who smoke and consume alcohol. The amount of propofol amount required to induce sensory loss and anesthesia in individuals who smoke and consume alcohol is increased [8,9]. According to our findings, receiving anesthesia more than two times and the presence of diabetes mellitus affect the incidence rates of polymorphisms.

A study was conducted with 240 children who underwent tonsillectomy surgery under propofol-remifentanil infusion to review the effects of the 1236C>T, 2677G>T/A, and 3435C>T gene polymorphisms. The study showed a shortening in induction time, normalizing the respiratory, eye-opening, and extubation time for patients with 1236C>T CC genotypes. Higher VAS scores at hours 1, 2, 4, and 8 in patients with CT+TT genotypes were observed compared with patients with the 1236C>T CC genotype [10]. Choong et al. [8] observed that women could metabolize propofol faster and also wake up from propofol anesthesia earlier. Recovery periods in male patients were not evaluated in our survey. Moreover, significant differences were not found between the other groups. The reason for this may be that we added propofol for each group when there was a need and the required propofol doses were different.

The greatest hemodynamic changes were observed in patients with the CYP2B6 (rs3745274; C516G>T) polymorphism. While HR decreased in male children and young women with this mutation, blood pressure has a tendency to decrease more in elderly women.There was no difference in terms of the recovery period in any of the groups.

In conclusion, in all groups polymorphisms were observed for all of the genes evaluated, except for the UGT1A9 (rs72551330) polymorphism in elderly patients. Homozygote genotypes were high in pediatric patients; propofol consumption was significantly low in female children. Recovery periods were similar in all groups. Hemodynamic changes were mostly observed in pediatric patients and individuals who had a CYP2B6 polymorphism.

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Conflict of interest: The author have no conflict of interest

Author Contributions: A.Ü and EFŞ; conceived and design the study, **AÜ;** wrote the manuscript, **DGC and AÇ;** Provision of patients,, **SSP;** Conducting a research and investigation process, **YÖ**; planning and execution, including mentorship external to the core team.

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