Effects of Genetic Polymorphism of CYP2B6 and UGT1A9 and Sex Differences on Pharmacokinetics of Propofol

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Abstract

Background: Genetic polymorphisms of metabolic enzymes, as well as a patient’s sex, age, and individual susceptibility, affect the pharmacokinetics of propofol. Several reports show that polymorphisms of metabolic enzymes of propofol affect loss of consciousness during propofol anesthesia. We investigated whether genetic polymorphisms of the liver cytochrome P450 2B6 (CYP2B6), the main metabolic enzyme for propofol, and UDP-glucuronosyltransferase 1A9 (UGT1A9), as well as sex differences, affect the pharmacokinetics of propofol.

Methods: Between June 2009 and May 2011, 94 patients (51 males, 43 females) who underwent respiratory surgery with total intravenous anesthesia were examined. Arterial blood samples were collected immediately or 5, 10, 20, 30 and 60 min after the termination of propofol infusion for the determination of the propofol blood concentrations and genetic polymorphisms of CYP2B6 and UGT1A9. We analyzed blood pharmacokinetics of propofol and assessed the association between genetic polymorphisms, sex differences, and blood pharmacokinetics. Stepwise multiple linear regression analysis was used to detect important factors of pharmacokinetics of propofol.

Results: Although $C_0$ (the blood concentrations of propofol immediately after the termination of propofol infusion) rose for the T/T mutation in CYP2B6, there were no significant differences in changes of blood propofol concentrations after the termination of drug infusion and in waking times for both genetic polymorphisms. $C_0$ was significantly higher in females than in males (1.7: 1.4 μg/mL, female: male, $P=0.015$) and the rate of decline in the blood propofol concentration from $C_0$ to $C_5$ was faster in females than in males (67: 60%, $P=0.015$). Stepwise multiple regression analysis revealed that sex ($B = 0.32, P = 0.01$) was a contributor to $C_0$ ($R = 0.27, P = 0.01$).

Conclusions: We suggest that differences between females and males for $C_0$ and the rate of decline in the blood propofol concentration may cause individual differences in both sensitivity and recovery of consciousness from propofol anesthesia. We conclude that polymorphisms of CYP2B6, but not UGT1A, and sex differences affect the pharmacokinetics of propofol.

Key words

genetic polymorphism, blood pharmacokinetics, sex differences, propofol

Introduction

Propofol is widely used as an intravenous anesthetic. Propofol has several advantages, such as easy control of the depth of anesthesia, a rapid recovery of consciousness, and less postoperative nausea and
vomiting after anesthesia\(^1\). However, it is well known that individual differences exist in propofol’s anesthetic effects. For example, anesthetic effect site concentrations can vary between 2.78–4.34 μg/mL\(^2\). Iwakiri et al. and Ueta et al. demonstrated that effect site concentrations of propofol for the loss of consciousness differed according to age and between individuals\(^3\)\(^4\). Furthermore, a few reports also exist showing that emergence from anesthesia is significantly delayed after propofol with fentanyl infusion\(^5\)\(^6\). Major factors in waking times for intravenous anesthetics include liver metabolism and renal excretion of anesthetics. Propofol is mainly metabolized in the liver and is inactivated by hepatic clearance and metabolic enzymes. The main metabolic enzymes involved in propofol breakdown are the oxidation-reduction enzyme, human liver cytochrome P450 2B6 (CYP2B6), and the drug conjugation enzyme, UDP-glucuronosyltransferase1A9 (UGT1A9). Propofol is metabolized by its hydroxylation by CYP2B6 and by its glucuronidation by UGT1A9, resulting in propofol changing into a conjugated compound that has no anesthetic activity and is excreted in urine, as with other metabolites\(^7\).

Genetic polymorphisms in CYP2B6 and UGT1A9 have been reported, along with their allele frequency in the Japanese population\(^8\)\(^–\)\(^10\). Several studies have shown that the allele frequency of the G516T mutation of CYP2B6 was approximately 20%, and the variation among genetic polymorphisms decreased the enzyme activity of CYP2B6\(^8\)\(^–\)\(^12\). In contrast, Saito Y et al. and Girard H et al. have reported that the allele frequency of the I399C>T mutation of UGT1A9 was approximately 64% and that the variant increased the conjugation activity of propofol\(^9\)\(^13\).

Because of enzyme activity changes induced by these mutations, the anesthetic effect of propofol is affected and can result in individual differences in times of emergence from anesthesia. To date, few studies have examined times of emergence in relation to genetic polymorphisms and propofol. Previously we reported differences in waking times from propofol anesthesia and examined genetic polymorphisms of CYP2B6 and UGT1A9 and age, and their relationship with the propofol dose upon waking\(^14\)\(^15\).

In the present study, we investigated the blood propofol pharmacokinetics of patients who were anesthetized by total intravenous anesthesia for respiratory surgery. The aim of our study was to examine the effect of genetic polymorphisms of CYP2B6 and UGT1A9 and sex differences on propofol pharmacokinetics.

### Materials and Methods

#### Ethical considerations

The study was approved by the Ethics Committee of St. Marianna University School of Medicine (No.1529) and registered with the UMIN Clinical Trials Registry (ID 002009). Written informed consent was obtained from each patient before the study.

#### Patients

Patients who were scheduled for respiratory surgery, and treated by total intravenous anesthesia using propofol were enrolled in this study. Exclusion criteria included patients who were scheduled for an intraoperative blood transfusion, and those with significant liver, renal, or respiratory dysfunction, disturbance of consciousness, or dementia.

#### Anesthetic method

Premedication was not administered to all patients. All patients received epidural anesthesia before the induction of anesthesia. An epidural catheter was inserted into vertebral interspaces Th9/10 or Th10/11. General anesthesia was induced with propofol and 0.5 μg/kg/min remifentanil. Tracheal intubation was facilitated with 0.9 mg/kg rocuronium. Anesthesia was maintained by total intravenous anesthesia with propofol, remifentanil, and an oxygen-air mixture. Although local anesthetics and fentanyl were not administered intraoperatively, 0.125% or 0.25% levobupivacaine and fentanyl were administered via epidural catheter for postoperative analgesia after anesthesia. The dose of propofol was determined based on weight (mg/kg/h). An infusion pump (Terufusion TCI pump TE-371, Terumo Co., Tokyo, Japan) without a target-controlled infusion (TCI) system was used with a manually-controlled infusion (MCI) system\(^16\). Before the induction of anesthesia, a bispectral index of EEG (BIS) monitoring (Medtronic, Doblin, Ireland; ver. 2.11) was established, as well as routine monitoring, including automatic non-invasive blood pressure, electrocardiogram and pulse oximeter. An arterial line was placed in either the left or right radial artery for blood sampling after the induction of general anesthesia. Propofol was titrated to BIS values of 40–60. If the BIS value decreased to less than 40, the dose of propofol was decreased. If the BIS value increased to more than 60, the dose of propofol was increased. After surgery, the adminis-
vation of propofol and remifentanil was discontinued and the time taken to wake up (return of conscious‐ness: ROC) was measured. The time from the termi‐nation of propofol infusion until ROC, defined as eyes opening and a handgrip on verbal command, as well as the return of spontaneous respiration, defined as a respiratory rate of 8 breaths/min and lower than 50 mmHg of PETCO₂, were documented. We asked patients to open their eyes every 30s after BIS levels exceeded 70 following the termination of propofol administration, and measured the time with a stop‐watch before meeting the above-mentioned waking criteria.

We collected blood samples at 0, 5, 10, 20, 30 and 60 min after the termination of propofol infusion for the determination of pharmacokinetics and geno‐typing.

DNA analysis

We analyzed genetic polymorphisms of CYP2B6 and UGT1A9 from collected blood samples. Genomic DNA was extracted by the Department of Pharmacogenomics St. Marianna University Graduate School of Medicine, and genetic polymor‐phisms of CYP2B6 and UGT1A9 were analyzed by the Department of Drug Metabolism and Pharmacokinetics, Showa Pharmaceutical University.

Genetic polymorphisms of CYP2B6 were deter‐mined by polymerase chain reaction-restriction frag‐ment length polymorphism (PCR-RFLP) analysis, while genetic polymorphisms of UGT1A9 were de‐termined by the direct sequence method using se‐quencing primers, an ABI BigDye terminator cycle sequencing kit (Applied Biosystems, Foster City, CA, USA), and an ABI PRISM 3730x1 DNA analyzer (Applied Biosystems). Genomic DNA prepared from blood cells of the study participants was analyzed. It has been shown that the CYP2B6*6 allele is a useful biomarker for drug disposition[17], and the intronic single nucleotide polymorphism (SNP) UGT1A9 I399C>T is associated with increased UGT1A9 protein levels and increased glucuronidation activities toward propofol[15][18].

Pharmacokinetic analysis

We also determined blood propofol levels by high performance liquid chromatography (HPLC). Propofol (>99%) was obtained from Sigma-Aldrich (St. Louis, MO, USA) as an analytical standard[19]. Plasma samples (100μL) were treated by adding 400μL of CH₃OH. After vortex mixing, the tubes were centrifuged at 10,000g for 10 min. An aliquot of the supernatant after filter treatment (Millex-LG, 0.20μm, Millipore, Tokyo, Japan) was injected onto an analytical C₁₈ reversed-phase column (150 mm × 4.6 mm, Capcell Pak C₁₈ U120 S5, Shiseido, Tokyo, Japan) maintained at 30°C. The mobile phase was 55% (v/v) acetonitrile at a flow rate of 0.6 mL/min[20]. The elution profiles of propofol were monitored fluoro‐metrically at an excitation wavelength of 270nm and an emission wavelength of 310 nm. Plasma con‐centrations of propofol were kinetically analyzed by Phoenix WinNonlin software version 6 (Pharsight, Mountain View, CA, USA) using a two-compartment analysis[15]. We then calculated the half-life of distribution (t₁/₂α) and elimination (t₁/₂β) and the area under the blood concentration-time curve for 60 min (AUC₀–₆₀). The AUC was calculated using the trape‐zoid method by blood level measurements at each point, from the termination of propofol infusion to 60 min thereafter.

Statistical analysis

Results are presented as the median (interquar‐tile range, IQR). Chi square, Mann-Whitney and Kruskal-Wallis tests were used for statistical analysis (SPSS ver.21; IBM, Tokyo, Japan). Furthermore, stepwise multiple linear regression was used to exam‐ine the factors to pharmacokinetics of propofol. We analyzed age, sex, height, body weight, body mass index (BMI), dose of propofol, CYP2B6, and UGT1A9 as factors to pharmacokinetics of propofol. A P-value less than 0.05 was considered statisti‐cally significant.

Results

Ninety-four patients (51 males, 43 females) who underwent respiratory surgery and total intravenous anesthesia using propofol were enrolled in St. Ma‐rianna University School of Medicine Hospital be‐tween June 2009 and May 2011.

1. Genotyping results

All 94 patients were genotyped for polymor‐phisms in the CYP2B6 and UGT1A9 genes. A wild‐type homozygote (G/G) of CYP2B6 G516T was found in 55 cases (59%), a variant heterozygote (G/T) was found in 35 cases (37%), and a variant homo‐zygote (T/T) was found in 4 cases (4%). The wild‐type homozygote (C/C) of UGT1A9 I399 C>T was present in 14 cases (15%), the variant heterozygote (C/T) was present in 43 cases (46%), and the variant
homozygote (T/T) was present in 37 cases (39%) (Table 1A, 1B). There were no significant differences in the patients’ backgrounds according to the genetic polymorphisms of CYP2B6 and UGT1A9 (Table 1A, 1B).

2. Correlations between genotype and propofol pharmacokinetics

No significant difference was found in changes of blood propofol levels after the termination of propofol infusion, between genetic polymorphisms of CYP2B6 and UGT1A9 (Figure 1A, 1B). No correlation was established between CYP2B6 and UGT1A9 genotypes and pharmacokinetics such as t\textsubscript{1/2α}, t\textsubscript{1/2β}, AUC\textsubscript{0–60}, waking time, and propofol infusion dose (Table 2A, 2B). However, we observed that the C\textsubscript{0} (plasma concentration of propofol just after termination of propofol infusion) significantly increased in homozygotes (T/T) compared with that of heterozygotes (G/T) and homozygotes (G/G) in genetic polymorphisms of CYP2B6 (P=0.025) (Figure 1A, Table 2A).

3. Propofol pharmacokinetics and sex differences

C\textsubscript{0} was significantly higher in female than in male patients (Figure 2, Table 3). Also, the propofol disappearance rate at 10 min after the termination of infusion was 60% (IQR: 54–70) in males and 67% (IQR 62–71) in females. The disappearance rate of propofol was significantly higher in females than in males (P = 0.024) (Figure 2).

There was a significant difference between sex and each of the following factors: age, height, body weight, BMI, and C\textsubscript{0} (Table 3). Stepwise multiple regression analysis revealed that sex (B = 0.32, P = 0.01) was a contributor to C\textsubscript{0} (R = 0.27, P = 0.01).

Discussion

Several reports have shown that genetic polymorphisms of enzymes involved in propofol metabolism affect the length of unconsciousness during propofol anesthesia\textsuperscript{(14,21)}. We hypothesized that genetic polymorphisms of CYP2B6, the main metabolic enzyme for propofol and UGT1A9, as well as sex differences, could affect the pharmacokinetics of propofol.

Table 1A. Patient Demographics for CYP2B6

<table>
<thead>
<tr>
<th>CYP2B6</th>
<th>Wild type</th>
<th>Heterozygote</th>
<th>Homozygote</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G</td>
<td>55 (59%)</td>
<td>35 (37%)</td>
<td>4 (4%)</td>
<td>—</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66 (62 - 72)</td>
<td>66 (59 - 71)</td>
<td>63 (53 - 67)</td>
<td>0.155</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160</td>
<td>163</td>
<td>159</td>
<td>0.370</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58 (48 - 63)</td>
<td>60 (52 - 66)</td>
<td>63 (57 - 70)</td>
<td>0.128</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>22 (20 - 24)</td>
<td>22 (20 - 24)</td>
<td>24 (21 - 28)</td>
<td>0.123</td>
</tr>
<tr>
<td>Sex (Male / Female)</td>
<td>27 / 28</td>
<td>23 / 12</td>
<td>1 / 3</td>
<td>0.154</td>
</tr>
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</table>

Table 1B. Patient Demographics for UGT1A9

<table>
<thead>
<tr>
<th>UGT1A9</th>
<th>Wild type</th>
<th>Heterozygote</th>
<th>Homozygote</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/C</td>
<td>14 (15%)</td>
<td>43 (46%)</td>
<td>37 (39%)</td>
<td>—</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68 (66 - 74)</td>
<td>66 (59 - 70)</td>
<td>65 (61 - 70)</td>
<td>0.456</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161</td>
<td>160</td>
<td>162</td>
<td>0.583</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>52 (47 - 60)</td>
<td>60 (50 - 66)</td>
<td>59 (52 - 65)</td>
<td>0.107</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>21 (19 - 22)</td>
<td>23 (20 - 24)</td>
<td>22 (20 - 25)</td>
<td>0.206</td>
</tr>
<tr>
<td>Sex (Male / Female)</td>
<td>7 / 7</td>
<td>24 / 19</td>
<td>20 / 17</td>
<td>0.960</td>
</tr>
</tbody>
</table>

BMI : body mass index
Data are median (IQR) or number
The allele frequencies of CYP2B6 G516T and UGT1A9 I399C>T mutations identified in our study were 23% and 62%, respectively. These frequencies are similar to past reports of approximately 20% and 64% of the allele frequencies of Japanese past reports.
Table 2A. Pharmacokinetic Analysis of Polymorphisms of CYP2B6

<table>
<thead>
<tr>
<th></th>
<th>CYP2B6</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G/G</td>
<td>G/T</td>
<td>T/T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2\alpha}$ (min)</td>
<td>2.3 (1.4 - 5.5)</td>
<td>2.8 (1.8 - 6.6)</td>
<td>1.5 (1.0 - 2.8)</td>
<td>0.621</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2\beta}$ (min)</td>
<td>47 (42 - 87)</td>
<td>54 (44 - 88)</td>
<td>54 (46 - 64)</td>
<td>0.376</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-40}$ (min : $\mu$g/mL)</td>
<td>26 (22 - 35)</td>
<td>25 (18 - 33)</td>
<td>23 (21 - 26)</td>
<td>0.411</td>
<td></td>
</tr>
<tr>
<td>ROC (min)</td>
<td>15 (12 - 17)</td>
<td>13 (10 - 16)</td>
<td>11 (8 - 14)</td>
<td>0.078</td>
<td></td>
</tr>
<tr>
<td>Dose (mg/kg/h)</td>
<td>0.08</td>
<td>0.08</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_0$ ($\mu$g/mL)</td>
<td>1.5 (1.2 - 1.9)</td>
<td>1.1 (0.8 - 1.7)</td>
<td>1.9 (1.6 - 2.2)*</td>
<td>0.025</td>
<td></td>
</tr>
</tbody>
</table>

$^*$T/T vs. G/G and G/T

Table 2B. Pharmacokinetic Analysis of Polymorphisms of UGT1A9

<table>
<thead>
<tr>
<th></th>
<th>UGT1A9</th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C/C</td>
<td>C/T</td>
<td>T/T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2\alpha}$ (min)</td>
<td>3.1 (1.3 - 5.7)</td>
<td>2.8 (1.4 - 5.7)</td>
<td>2.5 (1.8 - 5.8)</td>
<td>0.871</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2\beta}$ (min)</td>
<td>66 (49 - 120)</td>
<td>48 (42 - 82)</td>
<td>47 (43 - 86)</td>
<td>0.089</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-60}$ (min : $\mu$g/mL)</td>
<td>25 (22 - 32)</td>
<td>26 (21 - 33)</td>
<td>25 (19 - 35)</td>
<td>0.880</td>
<td></td>
</tr>
<tr>
<td>ROC (min)</td>
<td>14 (12 - 17)</td>
<td>12 (11 - 16)</td>
<td>14 (10 - 17)</td>
<td>0.750</td>
<td></td>
</tr>
<tr>
<td>Dose (mg/kg/h)</td>
<td>0.08</td>
<td>0.08</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_0$ ($\mu$g/mL)</td>
<td>1.5 (1.2 - 1.9)</td>
<td>1.5 (0.9 - 1.8)</td>
<td>1.4 (1.0 - 1.8)</td>
<td>0.751</td>
<td></td>
</tr>
</tbody>
</table>

$t_{1/2\alpha}$ : half-life of distribution
$t_{1/2\beta}$ : half-life of elimination
AUC$_{0-60}$ : area under the blood concentration-time curve for 60 min
ROC : duration of return of consciousness
Dose : propofol infusion dose
$C_0$ : plasma concentrations of propofol just after termination of infusion

Data are median (IQR)

in CYP2B6 G516T$^{10}$ and UGT1A9 I399C>T mutations$^9$, respectively. In our study, no significant differences were found between genetic polymorphisms and waking times after propofol anesthesia.

Approximately 70% of propofol is metabolized via glucuronic acid conjugation by UGT1A9, while the remaining 30% is metabolized by CYP2B6, CYP2C9, sulphotransferase (SULT) 1A, and NAD (P) quinone oxidoreductase (NQO1). UGT1A9 plays a large role in propofol metabolism, thereby suggesting that any polymorphisms in this gene have a major impact on the metabolism of propofol. Several studies have demonstrated that genetic polymorphisms affect propofol’s induction dose of unconsciousness, in addition to affecting its blood levels and clearance after the termination of propofol infusion$^{15,22,23}$. In our study, the CYP2B6 G516T mutation exhibited a significant difference between G/T, G/G, and T/T mutations for $C_0$. However, this mutation did not show significant differences in changes of other blood propofol concentrations. On the other hand, the UGT1A9 I399C>T mutation did not show any significant difference in changes of blood propofol levels after the termination of propofol infusion. We also did not find any significant difference between genetic polymorphisms for $t_{1/2\alpha}$, $t_{1/2\beta}$, and AUC$_{0-60}$. These results suggest that, while genetic polymorphisms of CYP2B6 influenced the pharmacokinetics of propofol, the effects of UGT1A9 polymorphisms on the pharmacokinetics of propofol were few. Our data thus demonstrate that genetic polymorphisms of CYP2B6 may influence propofol pharmacokinetics.

Whereas, the glucuronic acid conjugation of propofol increased with UGT1A9 I399C>T muta-
Polymorphism and Sex Differences

Fig. 2. Change in blood propofol levels over time for each sex after the termination of propofol infusion.

Table 3. Patient Demographics and Pharmacokinetics between Sexes

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51</td>
<td>43</td>
<td>—</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67 (64 - 74)</td>
<td>63 (58 - 68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 (161 - 169)</td>
<td>157 (153 - 162)</td>
<td>0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63 (58 - 67)</td>
<td>52 (47 - 59)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 (21 - 24)</td>
<td>20 (20 - 24)</td>
<td>0.044</td>
</tr>
<tr>
<td>t₁/₂α (min)</td>
<td>2.5 (1.8 - 6.2)</td>
<td>2.5 (1.3 - 5.3)</td>
<td>0.311</td>
</tr>
<tr>
<td>t₁/₂β (min)</td>
<td>56 (44 - 99)</td>
<td>48 (42 - 62)</td>
<td>0.171</td>
</tr>
<tr>
<td>AUC₀–₆₀ (min · µg/mL)</td>
<td>23 (18 - 34)</td>
<td>26 (22 - 34)</td>
<td>0.230</td>
</tr>
<tr>
<td>ROC (min)</td>
<td>14 (11 - 17)</td>
<td>13 (11 - 17)</td>
<td>0.735</td>
</tr>
<tr>
<td>Dose (mg/kg/h)</td>
<td>0.08 (0.06 - 0.09)</td>
<td>0.08 (0.07 - 0.09)</td>
<td>0.417</td>
</tr>
<tr>
<td>C₀ (µg/mL)</td>
<td>1.4 (0.9 - 1.8)</td>
<td>1.7 (1.2 - 2.1)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

BMI: body mass index

t₁/₂α: half-life of distribution

t₁/₂β: half-life of elimination

AUC₀–₆₀: area under the blood concentration-time curve for 60 min

ROC: return of consciousness

Dose: propofol infusion dose

C₀: plasma concentrations of propofol just after termination of infusion

Data are median (IQR) or number

So, we had expected the AUC₀–₆₀ to be reduced with the mutation rather than in the absence of the mutation in the gene because of the fast rate of metabolism of propofol. However, we did not find significant differences between UGT genetic polymorphisms, further demonstrating that genetic polymorphisms in UGT1A9 had little effect on propofol pharmacokinetics.
We used a manually, not target-controlled, propofol infusion system. The TCI system infused target level adjustment was by constant infusion and set a dose of propofol (μg/mL) as effect site concentration based on age and body weight. In our study, we set a propofol infusion dose (mg/kg/h) based on body weight, with the goal of a 40–60 BIS level. Therefore, we expected that, if a metabolic pathway became inhibited due to the CYP2B6 G516T mutation, the blood level of propofol would then increase and the level of BIS would decrease, requiring anesthesiologists to decrease the dose of propofol per hour. On the other hand, we also expected that, if a metabolic pathway due to the UGT1A9 mutation became upregulated, then the blood level of propofol would decrease and the level of BIS would increase, requiring anesthesiologists to increase the dose of propofol per hour. In our study, there was no significant difference between genetic polymorphisms for a dose per weight per time. This suggests that there was little effect of injection method on metabolic pathways influenced by CYP and UGT genetic polymorphisms.

Similarly, Choong E et al. reported that there were no significant impacts of CYP2B6 and UGT1A9 polymorphisms on propofol biotransformation after intravenous infusion using the TCI system. Our results showed that there was no significant difference in pharmacokinetics between genetic polymorphisms, consistent with the findings of Choong E et al. Thus, our data highlight the lack of effect of two genetic polymorphisms in CYP2B6 and UGT1A9 on the rate of metabolism.

In our study, no significant differences were noted for \( t_{1/2α} \) and \( t_{1/2β} \) between genetic polymorphisms. The α phase is a distribution phase. Propofol, a highly lipid soluble drug, distributes to organs and disappears rapidly from the blood after the termination of infusion. Changes in cardiac output affect α phase. In contrast, our study was carried out during anesthesia, and patients with cardiac dysfunction were excluded, so that the cardiac output of patients was kept constant. Furthermore, metabolic enzymes do not influence α phase, so there was little effect on \( t_{1/2α} \) between genetic polymorphisms. The β phase is an elimination phase. After propofol redistributes to the whole body, propofol slowly disappears from the blood and is eliminated from the body.

The main metabolic organ of propofol is the liver, and its hepatic clearance is dependent on hepatic blood flow. Furthermore, the hepatic clearance of propofol is high and is dependent on blood flow changes but not on a decrease in metabolic activity. Total body clearance is more dependent on hepatic blood flow than metabolism. Both hepatic and renal blood flows were kept constant in our study. For \( t_{1/2β} \) to be affected more by hepatic clearance than by metabolic activity, this would mean polymorphisms do not affect \( t_{1/2β} \).

In our study, the median value of serum total protein was 7.1 g/dL (IQR 6.7–7.4), and the median value of serum albumin was 4.3 g/dL (IQR 4.1–4.4). The serum protein-binding rate of propofol is reported as 97–98%. During hypoproteinemia, the protein binding rate of propofol decreases, leading to an increase in blood levels of unbound propofol which, in turn, may affect the pharmacokinetics and depth of anesthesia. Several studies have demonstrated sex differences for propofol, with the average time of emergence after anesthesia shorter in females than in males, suggesting that males have a higher susceptibility to propofol than females. Several studies have also demonstrated significantly higher levels of the propofol metabolites propofol glucuronide (PG), 4-hydroxypropofol (OHP), 4-hydroxypropofol-1-O-β-D-glucuronide (Q1G), and 4-hydroxypropofol-4-O-β-D-glucuronide (Q4G) in females than in males, suggesting that propofol metabolism is faster in females compared with males. In females, elimination and metabolic clearance are promoted by a hormone balance involving estrogen and the menstrual cycle. The results of our study suggest that the need to control perioperative blood propofol levels to maintain a similar depth of anesthesia is higher in females than in males. Moreover, our study showed a significant difference between males and females in \( C_p \). No significant difference was found for \( t_{1/2α} \) and the median time of emergence from anesthesia between the sexes.

Because males have more muscle and females have more fat, this would be expected to affect the distribution and times of emergence of a lipid soluble drug such as propofol, with shorter times of emergence in females. In our study, there were significant differences in BMI between males and females. Although the age of patients for both sexes was high, the volume of fat and muscle were similar for both groups. These characteristics may lead to the lack of significant differences in the distribution of propofol.
and times of emergence between the sexes. Hoymork et al. found the time of emergence was shorter in females than in males, although there were no significant differences in propofol doses, duration of infusion, and BIS levels just after the termination of propofol and at the return of consciousness between males and females\(^30\). Although they infused propofol with TCI system, our study differed in that we infused propofol with MCI system. Additionally, they reported a blood propofol level at waking that was higher in males than in females; the time of emergence for males was also slower than for females\(^30\). Furthermore, a significant dissociation was found in the predictive effect site level and the measurement of blood levels of propofol of males in their study\(^30\). It was suggested that prediction effect site and blood levels do not correlate in males. Therefore, we speculate that only blood levels are not involved at waking time.

We found a significant difference between males and females in blood levels of propofol just after the termination of infusion (\(C_0\)) and in the rate of decline of blood propofol levels for 10 min after the termination of propofol infusion.

The most important finding in our results was that sex was independently associated with \(C_0\) in multiple regression analysis. Hence, our pharmacokinetics results agree with the theory that the metabolism of propofol is faster in females and that susceptibility to propofol is higher in males.

**Limitations**

Several studies have found that genetic polymorphism of CYP2B6 is prevalent, and it is hard to think only one genetic polymorphism to influence metabolism of propofol. Therefore, we need to examine the effects of other SNPs aside from the SNP which we examined in our present study on the metabolism of propofol. Additionally, because we did not analyze propofol metabolites, we did not determine their relationship with sex differences and genetic polymorphisms; this also requires further study.

**Conclusion**

We suggest that the differences between females and males in the \(C_0\) and rate of decline of the propofol blood concentration may cause individual differences in sensitivity and recovery of consciousness from propofol anesthesia. We conclude that CYP2B6, but not UGT1A9, polymorphisms and sex differences affect propofol pharmacokinetics.

Further study is required to elucidate individual differences in the susceptibility to and pharmacokinetics of propofol.

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