A comparison between bispectral index analysis and auditory-evoked potentials for monitoring the time to peak effect to calculate the plasma effect site equilibration rate constant of propofol

M.-Z. Zhang, Q. Yu, Y.-L. Huang, S.-J. Wang, X.-R. Wang

Shanghai Jiao Tong University School of Medicine, Renji Hospital, Department of Anaesthesiology, Shanghai, China

Summary
Background and objectives: To the best of our knowledge, the value of the plasma effect site equilibration rate constant ($k_{eo}$) of propofol has not been reported in Chinese patients. The aim of this prospective, randomized study was to examine the characteristics of the time to peak effect ($T_{PEAK}$) of propofol, a pharmacokinetic-independent descriptor of blood–brain equilibration, and $k_{eo}$ derived from $T_{PEAK}$ with A-line auditory-evoked potential monitor and Aspect A-2000 bispectral index monitor in Chinese patients. Methods: Two-hundred ASA I patients received a submaximal bolus dose of propofol (1.5 mg kg$^{-1}$). $T_{PEAK}$ was randomly measured by means of the A-line auditory-evoked potential monitor (Group AAI, $n = 100$) or the Aspect A-2000 bispectral index monitor (Group BIS, $n = 100$). Using $T_{PEAK}$ and four previously validated pharmacokinetic parameter sets of propofol, the $k_{eo}$ was estimated according to a method proposed recently. Results: The mean $T_{PEAK}$ was $145 \pm 35$ s (50–224 s) and $74\pm24$ s (38–143 s) in Groups AAI and BIS, respectively ($P < 0.01$ between groups). There were no correlations between the patient’s age and $T_{PEAK}$ ($r = 0.147$ and 0.031 for Groups AAI and BIS). The median $k_{eo}$ in Group AAI was 0.64 min$^{-1}$ with the model of Marsh, 0.17 min$^{-1}$ with the Schnider model, 0.78 min$^{-1}$ with the Tackley model and 0.93 min$^{-1}$ with the Shafer model. The median $k_{eo}$ in Group BIS was 1.87 min$^{-1}$ with the model of Marsh, 0.83 min$^{-1}$ with the Schnider model, 2.14 min$^{-1}$ with the Tackley model and 2.48 min$^{-1}$ with the Shafer model ($P < 0.01$ between groups and models). Conclusions: The $T_{PEAK}$ of propofol measured by the A-line auditory-evoked potential monitor is different from that measured by the Aspect A-2000 bispectral index monitor. The $T_{PEAK}$ of propofol from auditory-evoked potential index and bispectral index, and the values of $k_{eo}$ calculated based on $T_{PEAK}$ are different from previous reports and appear to be not affected by age. Further studies need to be taken to validate clinically the $k_{eo}$ values of propofol.

Keywords: ANAESTHETICS, intravenous; PROPOFOL; MONITORING PHYSIOLOGIC, bispectral index, auditory evoked potentials; PHARMACOLOGY; PHARMACOKINETICS .

Introduction
The target-controlled infusion (TCI) device for propofol allows achieving rapidly and maintaining a predetermined plasma concentration. It is well-known that the effect site concentration, not the plasma concentration, best correlates with drug effect [1]. Therefore, the effect site seems to be a more logical target. When the effect site is targeted, the dose-calculating scheme requires the plasma effect site equilibration rate constant ($k_{eo}$) [2]. Because of a lack of the $k_{eo}$ value of propofol, targeting the effect site concentration is seldom
used in our population. Recently, Minto and colleagues [3] proposed an approach for linking pharmacokinetics to pharmacodynamic model, based on the time of peak effect, TPEAK, which can be used to calculate the \( k_{e0} \). We do not know whether the TPEAK and the \( k_{e0} \) derived from the TPEAK of propofol have particular characteristics with different effect measurements in a Chinese population. The first goal of this study was to examine the characteristics of the time to peak effect (TPEAK) of propofol and \( k_{e0} \) derived from TPEAK with the A-line auditory-evoked potential (AEP) monitor and Aspect A-2000 bispectral index (BIS) monitor in Chinese patients. A derived and equally important goal was to calculate the \( k_{e0} \) of propofol with four pharmacokinetic models using the TPEAK method, and to investigate the effect of age on TPEAK and \( k_{e0} \)’s.

Methods

After obtaining Renji Hospital Ethics Committee approval and patient’s written informed consent, 200 ASA I patients scheduled to undergo elective surgery during general anaesthesia were recruited. The patients with known or suspected cardiac, liver, renal, or metabolic disease, significant obesity (>120% of ideal weight), long- or short-term (within the previous 48 h) intake of any sedative and analgesic drug, auditory dysfunction or any known adverse effect to the study drug were excluded. No premedication was given before the experiments. After overnight fasting, the patients were brought to a quiet operating room where a cannula was inserted into an antecubital vein for the injection of propofol and for fluid replacement (Ringer’s lactate solution of 300–500 mL pre-experiment). Routine monitoring included noninvasive blood pressure (BP), electrocardiogram, end-tidal carbon dioxide and pulse oximetry throughout the study. On the day of surgery, the patients were allocated randomly to receive either the A-line AEP monitor (Group AAI, \( n = 100 \)) or the Aspect A-2000 BIS monitor (Group BIS, \( n = 100 \)).

Three electrodes (A-line electrodes; Medicotest A/S, Oelstykke, Denmark) were positioned at the mid forehead (+), the left forehead (reference) and the left mastoid (—). Impedance was maintained at \(<5 \text{k}\Omega\). A bilateral click stimulus of 70 db and 2 ms duration was applied by means of headphones and the midlatency AEPs elicited were processed continuously using the A-line AEP monitor, Version 1.61 (Danmeter A/S, OdenseM, Denmark). The index was obtained as ‘normal auditory-evoked potential (AAI)’, which displays the on-line measured index at a rate of 1 Hz.

The EEG was obtained from four Zipprep electrodes placed on both sides of the outer malar bone (Art1 and Art2) with Fpz as the reference and Fp1 as the ground. The EEG bispectrum was monitored using a commercially available EEG monitor (A-2000, BIS 3.0 algorithm, rev. 0.40 software; Aspect Medical Systems, Newton, MA, USA). The bispectral smoothing rate was set to 15 s. Data from the A-2000 monitor were recorded on a laptop computer.

When there were no warnings of poor-quality signal on the screen of the monitors, a bolus dose of propofol producing a submaximal effect (the minimum AAI or BIS value was \( \geq 0 \)) was injected (1.5 mg kg\(^{-1}\)) manually as fast as possible (always in \(<5 \text{s}\)) and followed by a flush of saline. Besides the confirmation of the presence or absence of the eyelash reflex, no other stimulation was applied. When a minimum AAI or BIS value was obtained and partial recovery from propofol was evident, as suggested by increasing AAI or BIS values, the study was ended and anaesthesia continued according to the attending anaesthesiologist.

The AAI values and BIS values recorded by the monitors were imported into an Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet for off-line determination of the time of peak effect (TPEAK, time from the beginning of injection of propofol until the minimum AAI or BIS value). Because the monitor initially needs a period of time to process the AEPs, BIS and give the first values, the subsequent values are shown with a time delay of approximately 6 and 7 s for AAI and BIS, respectively [4,5]; for subsequent analysis, we subtracted 6 and 7 s from the TPEAK-determined off-line.

Because at TPEAK the maximum effect site concentration (\( C_{e0} \)) of propofol occurs and equals that of plasma (\( C_{p0} \)), after a bolus, we can calculate these concentrations (\( \mu \text{g mL}^{-1} \)) with the dose (mg) and the Unit Disposition Function of the effect site at TPEAK (\( C_{e}(T_{\text{PEAK}}) \)) with Eq. (1). Then using \( C_{e}(T_{\text{PEAK}}) \) the value of \( k_{e0} \) was calculated with Eq. (2):
Table 1. The pharmacokinetic models used in this study.

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<tbody>
<tr>
<td>$V_1$ (L kg$^{-1}$)</td>
<td>0.2280</td>
<td>0.320</td>
<td>0.350</td>
</tr>
<tr>
<td>$K_{10}$ (min$^{-1}$)</td>
<td>0.1190</td>
<td>0.0827</td>
<td>0.086</td>
</tr>
<tr>
<td>$K_{12}$ (min$^{-1}$)</td>
<td>0.1120</td>
<td>0.1050</td>
<td>0.060</td>
</tr>
<tr>
<td>$K_{31}$ (min$^{-1}$)</td>
<td>0.0550</td>
<td>0.0640</td>
<td>0.015</td>
</tr>
<tr>
<td>$K_{31}$ (min$^{-1}$)</td>
<td>0.0490</td>
<td>0.0220</td>
<td></td>
</tr>
<tr>
<td>$K_{31}$ (min$^{-1}$)</td>
<td>0.0035</td>
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Table 2. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group AAI (n = 79)</th>
<th>Group BIS (n = 78)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>51±18</td>
<td>49±16</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165±7</td>
<td>166±28</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60±10</td>
<td>62±10</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>42/37</td>
<td>38/40</td>
</tr>
<tr>
<td>Baseline (AAI or BIS) value</td>
<td>74±17</td>
<td>96±23</td>
</tr>
<tr>
<td>Minimum (AAI or BIS) value</td>
<td>17±4</td>
<td>36±12</td>
</tr>
</tbody>
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Data are expressed as numbers or mean ± SD, $P > 0.05$ between groups.
AAI: auditory-evoked potential index; BIS: bispectral index.

and colleagues [6], Schnider and colleagues [7], Tackley and colleagues [8] and Shafer and colleagues [9]. The parameters of Schnider's model [7] are $V_1$ (L) = 4.27, $V_2$ (L) = 18.9-0.391×(age−53), $V_3$ (L) = 238, $Cl_1$ (L min$^{-1}$) = 1.89+(weight−77)×0.0456+(LBM−59)×(−0.0681)+(height−177)×0.0624, $Cl_3$ (L min$^{-1}$) = 1.29−0.024×(age−53), $Cl_3$ = 0.836. LBM (lean body mass) = 1.1×weight−128×(weight/height)$^2$ for male, LBM = 1.07×weight−148×(weight/height)$^2$ for female. The details of the other three models are shown in Table 1.

Statistical analysis

Mean and SD or median and interquartile ranges (25%, 75%) were calculated for all variables according to the distribution with the Kolmogorov-Smirnov test for normality. Paired and unpaired t-tests and U-tests for variables were performed when appropriate. Correlation analysis between $T_{\text{PEAK}}$ and age was with Pearson analysis. $P < 0.05$ was considered significant.

Results

Since AAI or BIS values cannot reach the evident minimum recording with some disturbance, 43 patients, without losing the eyelash reflex, with respiratory depression needing jaw support to maintain normal ventilation or with cough were excluded from statistic analysis. One hundred and fifty-seven patients were included in the final analysis: 79 patients in Group AAI and 78 patients in Group BIS.

Patient characteristics for the two groups and AAI/BIS values are shown in Table 2. There was no significant difference between groups regarding age, height, weight or gender.

The mean $T_{\text{PEAK}}$ of 145 ± 35 s (50–224 s) in Group AAI was longer than the mean $T_{\text{PEAK}}$ of 74 ± 24 s (38–143 s) in Group BIS ($P < 0.01$). $T_{\text{PEAK}}$ of AAI ($r^2 = 0.022$, $P = 0.195$) and BIS ($r^2 = 0.001$, $P = 0.785$) showed no correlation with age as displayed in Figure 1.

Figure 2 shows the full time course of measured AAI, BIS and fitted propofol concentrations for two representative patients. The $k_{40}$s determined with Eq. (2) matched the measured $T_{\text{PEAK}}$ in Groups AAI and BIS are shown in Table 3. The $k_{40}$ did not have normal distribution in Group AAI (the Kolmogorov-Smirnov test, $P < 0.05$ with all four pharmacokinetic models). The calculated median $k_{40}$ had significant difference between different models in Groups AAI and BIS ($P < 0.001$). The median $k_{40}$ also had significant difference between groups when calculated with the same pharmacokinetic model ($P < 0.001$).

Discussion

The main findings of this study include that the peak effect time ($T_{\text{PEAK}}$) of propofol measured by the A-line AEP monitor after a bolus propofol dose is longer than that measured by the BIS monitor; $T_{\text{PEAK}}$ is not affected by age. Furthermore, no matter which effect measurement was used, the detected $T_{\text{PEAK}}$ and $k_{40}$ based on $T_{\text{PEAK}}$ are distinguished from previous reports [4,10,11]. Of course, to compare the $T_{\text{PEAK}}$ measured by BIS and AEP it is best to use both simultaneously in the same patient.
Some studies [12,13] have tested the accuracy of TCI devices for propofol, which incorporate an internal model, i.e. models of Marsh and colleagues [6] and Tackley and colleagues [8] in Chinese patients. An accurate determination of a given drug's $k_{\text{e0}}$ is useful for targeting the effect site instead of the plasma concentration, for designing and interpreting clinical pharmacologic research. The concentration of drug in the effect site cannot be measured. But we can characterize the time course of drug with electroencephalographic-derived indices, such as the BIS and AEP. Knowing the time course of drug effect, we can characterize the rate of drug flow into and out of the effect site [14]. Minto and colleagues [3] proposed an approach for calculating $k_{\text{e0}}$ with pharmacokinetic parameters based on the $T_{\text{PEAK}}$ after the administration of a bolus dose that produces a submaximal effect. Recently, Muñoz and colleagues [4] reported the $k_{\text{e0}}$ values of propofol for children and adults with $T_{\text{PEAK}}$ using A-line AEP monitor successfully.

Although Schnider and colleagues [10] found $T_{\text{PEAK}}$ increased with age, our findings did not support this view no matter which effect measurement was used. The mean $T_{\text{PEAK}}$ of 145 s found with AAI in the present study is far longer than the $T_{\text{PEAK}}$ of 80 s observed by Muñoz and colleagues [4], whereas the mean $T_{\text{PEAK}}$ of 74 s found with BIS is shorter than the $T_{\text{PEAK}}$ of 96 s observed by Schnider and colleagues [10] and 108 s observed by Flashon and colleagues [11]. Another finding of the present study is that the $T_{\text{PEAK}}$ determined by AAI and BIS is absolutely different. This is unlike the difference between Muñoz and colleagues' [4] finding for AAI and Schnider and colleagues' [10] for BIS. How should we explain these differences?
First, we believe that when BIS was used to detect the $T_{\text{PEAK}}$, the difference (and that in $k_{\text{EO}}$) might come partly from the injection time. We injected propofol in less than 5 s, whereas in the study of Schnider and colleagues [10], the injection lasted 18 s (13–24 s), and that might have lead to different $T_{\text{PEAK}}$. The effect of the injection time on the $T_{\text{PEAK}}$ can be interpreted as follows. Ludbrook and colleagues [15] who demonstrated that propofol decreases local cerebral blood flow in humans in a concentration-dependent manner. This might partly explain why the $T_{\text{PEAK}}$ and $k_{\text{EO}}$ of propofol is different between our study (injection time <5 s), which might acutely decrease cerebral blood flow, and Schnider and colleagues’ [10] (injection time 13–24 s), where the changes in cerebral blood flow would be attenuated by the lower peak arterial concentration. Moreover, PKPD tools for excel (An Excel 5.0 program written by Charles Minto and Thomas Schnider) were used to predict the $T_{\text{PEAK}}$ site concentration with pharmacokinetic parameters from Marsh and colleagues [6] and $k_{\text{EO}}$ 1.87 min⁻¹ (present study from BIS). The $T_{\text{PEAK}}$ occur at 75, 81 and 86 s with injection time 5, 13 and 24 s, respectively. Peak plasma concentration decreased with the increase in injection time. However, when AAI was used to detect the $T_{\text{PEAK}}$, our study method was the same as Munoz and colleagues [4], but the result is widely different from them. Thus, it is unlikely that the difference is only related to injection time.

Second, we suppose that the reason might be related to anthropometric differences in the populations under study, and that might have led to different pharmacodynamics (e.g. $T_{\text{PEAK}}$) and/or pharmacokinetics. Differences in sensitivity to anaesthetics have already been described among races. For instance, West Africans show reduced metabolic activation of paracetamol [16] and increased sensitivity to alcohol, possibly because of polymorphism of alcohol dehydrogenase [17]. African blacks show slower recovery from general anaesthesia with propofol compared with Caucasian patients [18]. The different sensitivity toward drugs may be caused by genetic factors, life habits, etc. On the one hand, Chinese people have particular life and feeding habits, which may lead to differences in body composition and which may play a role in the distribution and elimination of administered drugs. On the other hand, from the genetic point of view, differences in tissue gene constellation of polymorphism of plasma proteins, fat distribution, skeletal muscle fibre type proportions and serum plasma lipoproteins [18] may play some role. However, compared to pharmacodynamics, pharmacokinetic difference between different races might play a much more important role. It is possible that differences between different races may alter drug absorption, distribution, metabolism, elimination or excretion. Early distribution kinetics determined the rate and extent of drug distribution to the brain and other tissues [19]. The $T_{\text{PEAK}}$ of a drug after a bolus depends on two simultaneously occurring processes: one is the decreasing plasma concentration, and the other is the increasing effect site concentration. The faster the decrease of plasma concentration, the sooner the occurrence of $T_{\text{PEAK}}$ [4]. Unfortunately, we cannot carry out a further control study synchronously. It is clear that most of the genetic, environmental, or other unknown variables, and their effect, require to be studied for accounting for these pharmacodynamic or pharmacokinetic differences.

Third, the AAI derived from the processing of midlatency AEPs is very different from the electroencephalographic-derived measures. AAI reflects the earliest cortical response to stimulus, can be used as a reliable indicator of loss of consciousness during anaesthesia with propofol [20,21]. BIS has been reported to correlate well with the propofol concentration in plasma [22–24]. Studies comparing AAI and BIS have also already shown that AAI is a better discriminator between the awake and anaesthetized states in patients for whom anaesthesia is induced with propofol [21,25]. Since BIS is optimized to correlate with increasing sedation but AAI does better at indicating the transition between consciousness and unconsciousness, it is not surprising that AAI does not have the same $T_{\text{PEAK}}$ as BIS at correlating with changes in the propofol concentrations. In other words, the strengths of the AAI are seen in indicating the transition to unconsciousness whereas BIS does better at tracking the entire gradual progression of the sedative state. Moreover, in view of the difference of EEG signal’s origin and statistics between AAI and BIS, it maybe reasonable to look upon the effect of propofol on AAI and BIS as coming from different effect sites, accordingly both may have different $T_{\text{PEAK}}$ and $k_{\text{EO}}$. This hypothesis is similar to the Kazama and his colleagues’ study [5], which suggested that the effect of propofol on BIS is more rapid than its effect on systolic BP.

Because the calculation of $k_{\text{EO}}$ is based on $T_{\text{PEAK}}$, preceding explanation is also suitable for the result of $k_{\text{EO}}$ s. Our results also confirmed the findings published by Munoz and colleagues [4] and Wakeling and colleagues [26]. When the $T_{\text{PEAK}}$ found was used to calculate the $k_{\text{EO}}$, the results were significantly different depending on the pharmacokinetic model used. For example, using the pharmacokinetic model of propofol of Schnider and colleagues [7] and Marsh and colleagues [6] with
the $T_{\text{PEAK}}$ from AAI, we found a median value for the $k_{\alpha}$ of 0.17 and 0.64 min$^{-1}$, respectively. It is necessary for these $k_{\alpha}$ values to be validated before being used in clinic.

In conclusion, we have measured the $T_{\text{PEAK}}$ of propofol with the A-line AEP monitor and the Aspect A-2000 bispectral index monitor. Both give different times to peak effect, which were not affected by age in Chinese patients. The finally calculated $k_{\alpha}$ is particular to the model used to derive this parameter. The $k_{\alpha}$'s derived from $T_{\text{PEAK}}$ monitored with the A-line AEP monitor must be further validated to determine whether it can be used with the corresponding models to target effect site concentration.

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References

