

# Clinical Evaluation of Two Ke0 in the same Pharmacokinetic Propofol Model: Study on Loss and Recovery of Consciousness

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**Summary:** Simoni RF, Esteves LO, Miziara LEPE, Cangiani LM, Alves GGO, Romano ALP, Hansen PU, Vianna PTG – Clinical Evaluation of Two Ke0 in the same Pharmacokinetic Propofol Model: Study on Loss and Recovery of Consciousness.

**Background and objective:** The constant equilibrium between the plasma and effect site (ke0) is used by pharmacokinetic models to calculate a drug concentration in its site of action (Ce). It would be interesting if Ce of propofol was similar at loss and recovery of consciousness. The objective of this study was to evaluate the clinical performance of two different ke0 (fast = 1.21 min<sup>-1</sup>, and slow = 0.26 min<sup>-1</sup>) in relation to Ce during loss and recovery of consciousness using Marsh pharmacokinetic model.

**Methods:** Twenty healthy adult male volunteers participated in this study. In all volunteers propofol was administered as target-controlled infusion, Marsh pharmacokinetic model for fast ke0 and, at a different time, the same pharmacokinetic model with slow ke0 was used. Initially, propofol was infused with a serum target-controlled infusion of 3.0 µg.mL<sup>-1</sup>. Loss of consciousness and recovery of consciousness were based on response to verbal stimulus. Ce was recorded at the moment of loss and recovery of consciousness.

**Results:** On loss and recovery of consciousness, the Ce for fast ke0 was different (3.64 ± 0.78 and 1.47 ± 0.29 µg.mL<sup>-1</sup>, respectively, p < 0.0001), while with slow ke0 the Ce was similar (2.20 ± 0.70 and 2.14 ± 0.43 µg.mL<sup>-1</sup>, respectively, p = 0.5425).

**Conclusions:** Clinically, the slow ke0 (0.26 min<sup>-1</sup>) incorporated in the Marsh pharmacokinetic model showed better performance than the fast ke0 (1.21 min<sup>-1</sup>), since the calculated concentration of propofol at the effect site on loss and recovery of consciousness was similar.

**Keywords:** Pharmacokinetics; Propofol, administration and dosage; Intraoperative Awareness; Drug Delivery Systems.

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## INTRODUCTION

The target-controlled system for propofol was developed by Kenny et al. <sup>1</sup>, but its commercial use started only in 1997 <sup>2</sup>. This system uses Marsh pharmacokinetic model, published on the same decade <sup>3</sup>.

The first generation of these systems only showed on its screen the target-dose and estimated plasma concentration

(Cp). A delay in the relationship between Cp and clinical effect became evident. Several authors measured different plasma concentrations of propofol at the moment of loss and recovery of consciousness, with a wide variation between minimal and maximal values (0.8 to 5.4 µg.mL<sup>-1</sup>) <sup>4-11</sup>. This is basically caused by a delay in the balance between Cp and concentration of drug at its site of action located inside the central nervous system known as effect site <sup>6</sup>.

The equilibrium rate between plasma and effect site depends on several factors such as cardiac output, cerebral blood flow, and pharmacologic properties that determine the transference rate through the blood brain barrier (liposolubility and degree of ionization). The time of equilibrium between plasma concentration and effect site can be mathematically described as a first order constant, known as ke0.

In fact, the expression ke0 should be used to describe the rate of drug elimination from its effect site, but it has been estimated that the volume of effect site is insignificant, and, therefore, there is no need to separate the constant that enters and exits the site of action. Ke0 can be defined as the proportional variation of the concentration gradient between plasma and effect site in relation to the unit of time. In theory, the higher the value of Ke0, the higher the rate of entry of a drug at the site of action; therefore, the time taken for this to

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occur will be less. Thus, drugs with short  $T_{1/2,ke0}$  have elevated  $ke0$  and fast onset of action.

The value of  $ke0$  is integrated in the target-controlled infusion allowing the insertion on the screen of the target-controlled infusion the estimated concentration of propofol in its effect site ( $C_e$ ).

It has been recommended that the pharmacokinetic model with its pharmacodynamic equivalent that contains the values of  $ke0$  should be validated in studies with continuous infusion and in patient populations in which the models are being tested<sup>12</sup>. All values of  $ke0$  proposed are correct for the method used; however, they have little validation in clinical studies.

Currently, four target-controlled systems are commercialized in Brazil. The values of  $ke0$  for propofol incorporated in these systems (Marsh model) can be  $0.26 \text{ min}^{-1}$  (slow  $ke0$ ) or  $1.21 \text{ min}^{-1}$  (fast  $ke0$ ).

An interesting way to assess these  $ke0$  values proposed for propofol would be to observe the  $C_e$  at the moment of loss and recovery of consciousness. Although there is evidence that the concentration of propofol in its site of action (central nervous system – GABA receptor) is similar at the time of loss and recovery of consciousness, clinically this would allow an interesting individualized titration of the target dose of propofol reducing the possibility of intraoperative awakening episodes.

Recently, a study demonstrating a direct relationship between  $C_e$  on loss and recovery of consciousness with  $ke0$  of  $0.26 \text{ min}^{-1}$  (slow  $ke0$ ;  $T_{1/2,ke0} = 2.60 \text{ min}$ ) was published<sup>13</sup>. However, there is little information in literature on the clinical performance of  $1.21 \text{ min}^{-1}$   $ke0$  (fast  $ke0$ ;  $T_{1/2,ke0} = 0.57 \text{ min}$ ).

The objective of the present study was to evaluate the clinical performance of two different  $ke0$  (slow and fast) regarding the  $C_e$  of propofol during loss and recovery of consciousness using Marsh pharmacokinetic model<sup>3</sup>. The hypothesis tested was that the calculated  $C_e$  of propofol is similar for slow  $ke0$  on loss and recovery of consciousness, which differ from that of fast  $ke0$ .

## METHODS

After approval by the Research Ethics Committee and signing of informed consent, 20 healthy adult male volunteers participated in this study. The sample size was based on a previous pilot study. Considering that the difference in proportionality between the calculated concentration of propofol at the site of action ( $C_e$ ) with slow and fast  $ke0$  ( $0.26 \text{ min}^{-1}$  and  $1.21 \text{ min}^{-1}$ , respectively) was 40% and the strength of analysis with an alpha error of 5% and beta error of 20%, it was demonstrated that 20 volunteers per group would be necessary.

Selected volunteers presented at a predetermined location after a 6-hour fasting period. All volunteers were monitored with electrocardiogram for heart rate (HR) (DII and V1 derivations), peripheral oxygen saturation ( $SpO_2$ ), non-invasive mean arterial pressure (MAP), and bispectral index (BIS). Oxygen under nasal catheter,  $2.0 \text{ L}\cdot\text{min}^{-1}$ , was administered; the left antecubital vein was punctured and connected to a ve-

nous catheter with propofol (Propovan® – Cristália Produtos Químicos e Farmacêuticos Ltda.). Saline infusion to replace the fasting period or insensible losses was not used.

Propofol was administered as target-controlled infusion using Marsh pharmacokinetic model, slow  $ke0$ , and, at a latter opportunity, using the same pharmacokinetic model with a fast  $ke0$ . An infusion pump (Anesthesia Pilot II® – Fresenius-Kabi) coupled to the infusion management (ANESTFUSOR® – University of Chile, Santiago) was used (Figure 1). The administration sequence of propofol was randomized and computer generated.

Initially, propofol was infused as a target-plasma concentration of  $3 \mu\text{g}\cdot\text{mL}^{-1}$ , based on a previous study<sup>13</sup>. The loss of consciousness (LOC) was defined as loss of response to verbal stimulus (calling the volunteer by his name using a normal tone of voice). This verbal stimulus was repeated three times at 30-second interval by another investigator who was unaware of the calculated concentration at the site of action ( $C_e$ ).

If loss of consciousness did not occur after the equilibrium of  $C_e$  and  $C_p$  at  $3.0 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $C_p$  was increased by  $0.5 \mu\text{g}\cdot\text{mL}^{-1}$ , and so forth, until the volunteer could not respond to the verbal stimulus. After loss of consciousness, target-controlled infusion was maintained for 15 minutes. After this period,  $C_p$  was decreased to zero until recovery of consciousness (ROC) was observed, defined as response to a verbal stimulus (calling the volunteer by his name using a normal tone). This stimulus was repeated three times at 30-second intervals by another investigator who was unaware of the calculated  $C_e$ . This methodology was similar to that of a prior study<sup>13</sup>.

The calculated concentration at the site of action and BIS were recorded whenever the volunteer lost and recovered his consciousness. The maximum and minimum BIS during infusion and the dose of propofol were also recorded.

Paired Student *t* test was used in the statistical analysis of parametric parameters and results were expressed as mean and standard deviation. Non-parametric parameters were analyzed by Wilcoxon test for paired samples and the results



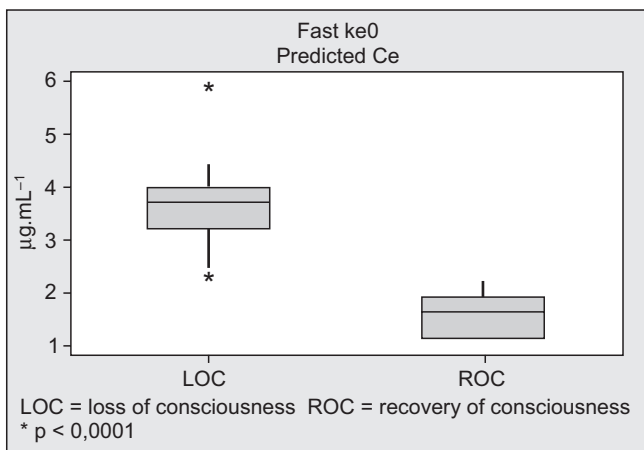
**Figure 1** – Target-Controlled Infusion of Propofol. Infusion pump, RS232 adapter and Anestfusor.

expressed as median. A p lower than 0.05 was considered statistically significant.

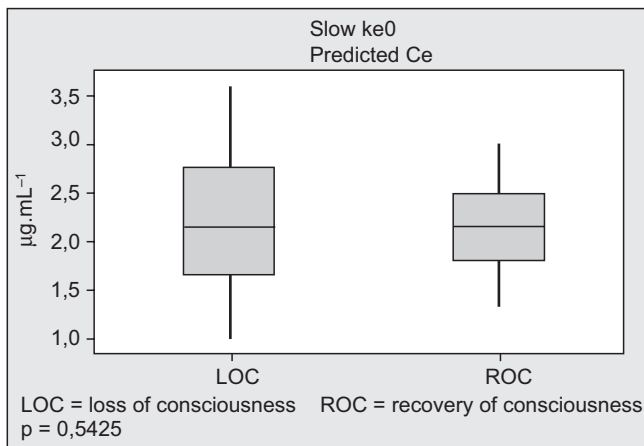
## RESULTS

The age, weight, height, and mean body mass index of volunteers are presented in Table I. The mean Ce calculated for the fast ke0 on loss and recovery of consciousness was different ( $3.64 \pm 0.78$  and  $1.47 \pm 0.29 \mu\text{g}\cdot\text{mL}^{-1}$ ,  $p < 0.0001$ ), while with slow ke0 the calculated mean Ce was similar ( $2.20 \pm 0.70$  and  $2.13 \pm 0.43 \mu\text{g}\cdot\text{mL}^{-1}$ , respectively,  $p = 0.5425$ ) (Figures 2 and 3).

A correlation between the calculated concentration of propofol in its site of action on loss and recovery of consciousness with slow and fast ke0 ( $p = 0.0249$  and  $p = 0.0023$ , respectively) was observed (Figures 4 and 5).



**Figure 2** – Ce on Loss and Return of Consciousness with Fast ke0. Ce: calculated propofol concentration at the site of action.

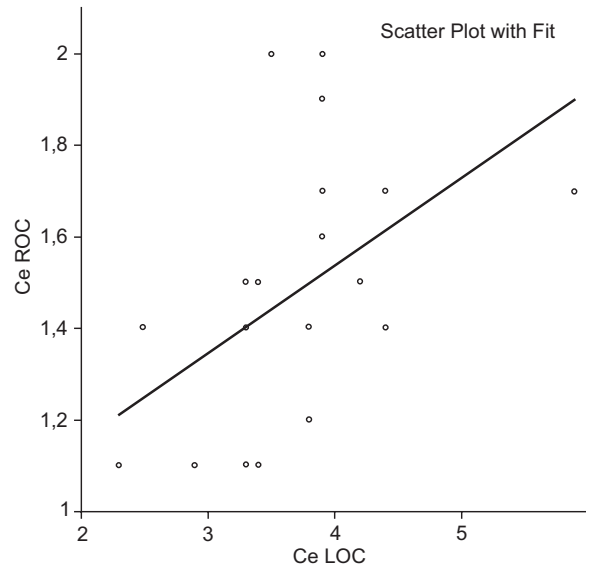


**Figure 3** – Ce at Loss and Return of Consciousness with Slow ke0. Ce: predicted concentration of propofol at the site of action.

**Table I** – Demographic Data and Body Mass Index

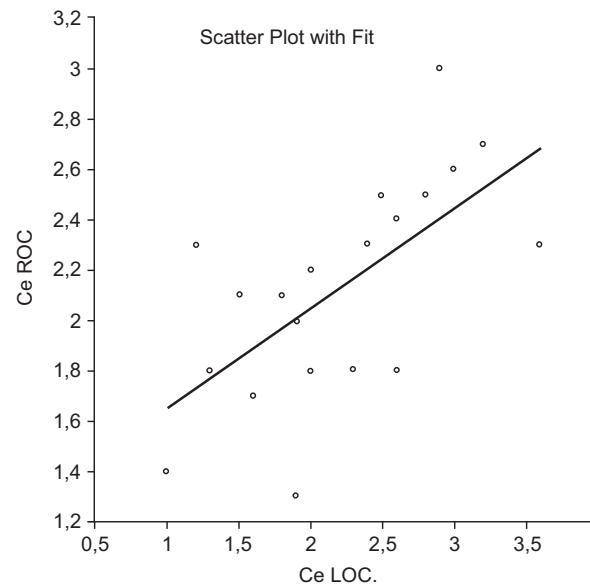
Age (years)	30 (25-41)
Weight (kg)	82 (74-97)
Height (cm)	177 (170-184)
BMI ( $\text{kg}\cdot\text{m}^{-2}$ )	26 (23-31)

Results expressed as mean (minimum and maximum).



**Figure 4** – Linear Regression between the Ce of Propofol at LOC and ROC with Fast ke0.

Ce: calculated concentration at the site of action; LOC: loss of consciousness; ROC: recovery of consciousness. Statistically significant correlation ( $R^2 = 0.25$ ,  $p = 0.0249$ ) and positive inclination ( $p = 0.0249$ ).



**Figure 5** – Linear Regression between Ce of Propofol at LOC and ROC with Slow ke0.

Ce: calculated concentration at the site of action; LOC: loss of consciousness; ROC: recovery of consciousness. Statistically significant correlation ( $R^2 = 0.41$ ,  $p = 0.0023$ ) and positive inclination ( $p = 0.0023$ ).

**Table II** – Initial Hemodynamic Data and after Loss of Consciousness

	Fast ke0	Slow ke0
Mean arterial pressure		
Initial	92.9 ± 8.5	92.2 ± 9.5
5 min after LOC	77.0 ± 6.6	75.3 ± 4.9
10 min after LOC	75.0 ± 6.6	74.4 ± 5.8
15 min after LOC	73.4 ± 6.3	72.4 ± 5.6
Heart rate		
Initial	76.3 ± 11.9	76.4 ± 14.6
5 min after LOC	73.8 ± 8.2	72.1 ± 10.9
10 min after LOC	75.4 ± 8.9	72.5 ± 12.1
15 min after LOC *	75.9 ± 10.3	72.2 ± 10.1
SpO <sub>2</sub>		
Initial	98.5 ± 0.9	98.2 ± 0.7
5 min after LOC	97.8 ± 1.2	97.4 ± 1.1
10 min after LOC	97.8 ± 1.2	97.2 ± 1.1
15 min after LOC	97.2 ± 1.4	97.2 ± 1.7

Results are expressed as mean and standard deviation; LOC: loss of consciousness; SpO<sub>2</sub>: peripheral oxygen saturation; \* p = 0,0084.

**Table III** –Bispectral Index

	Fast ke0	Slow ke0
BIS		
Initial	97 (97-98)	98 (97-98)
LOC	54 (42-70) **	58 (46-72) +
Minimum*	31 (19-44)	36 (24-46)
Maximum+	58 (43-63)	61 (47-65)
ROC	65 (59-79)	66 (54-75)

Results are expressed as median (minimum and maximum); LOC: loss of consciousness; ROC: recovery of consciousness; \*p = 0.0062; +p = 0.0263; \*\*p = 0.0002 vs. ROC; +p < 0.0001 vs. ROC.

**Table IV** – Time of Loss and Recovery of Consciousness, Propofol Dose, Total Infusion Time, and Concentration of Propofol Achieved

	Fast ke0	Slow ke0
Time LOC (min)	5.15 ± 1.73	7.40 ± 5.22*
Time ROC (min)	8.35 ± 2.62	5.60 ± 1.76**
Propofol		
Dose (µg.kg <sup>-1</sup> .min <sup>-1</sup> )	233.85 ± 33.97	187.82 ± 6.17 **
Total infusion time (min)	20.15 ± 1.73	22.40 ± 5.22 *
Cp achieved (µg.mL <sup>-1</sup> )	3.8 ± 0.7	3.1 ± 0.2 **

Results are expressed as mean and standard deviation; Cp: plasma concentration; LOC: loss of consciousness; ROC: recovery of consciousness; \*p = 0.0607; \*\*p < 0.0001.

The variation in MAP, HR, and SpO<sub>2</sub> at the initial period and at 5, 10, and 15 minutes after loss of consciousness, and the initial BIS on loss and recovery of consciousness with the minimum and maximum values during infusion, can be seen in Tables II and III.

Time until loss and recovery of consciousness, dose of propofol used, time of propofol infusion, and mean target-plasma dose achieved with fast and slow ke0 are in Table IV.

Significant respiratory depression (SP < 92%) or any other adverse event was not observed during the study. The use of Guedel airway or any other instrument to maintain patent airways was not necessary.

## DISCUSSION

The objective of the preset study was to evaluate the performance of two equilibrium constants (ke0 = 1.21 min<sup>-1</sup> and ke0 = 0.26 min<sup>-1</sup>) incorporated in the Marsh pharmacokinetic model in relation to the Ce of propofol on loss and recovery of consciousness, assessed by the response to a predefined auditory stimulus.

The first study to determine the ke0 was published by Sheiner et al.<sup>14</sup> in 1979 using a neuromuscular blocker (d-tubocurarine) where it is possible to objectively evaluate its effects. However, to date there is no direct method to estimate the concentration of intravenous anesthetics at the site of action. But the value of ke0 can be estimated by indirect methods, non-parametrically (based on blood samples), or parametrically (based on plasma concentration calculated by a pharmacokinetic model).

There is no consensus in literature on the ideal method to obtain the value of ke0 for propofol. Thus, as a consequence of the current methodology<sup>15-20</sup>, there is a large variability among proposed values (between 0.20 and 1.21 min<sup>-1</sup>). This difference has a partial relationship with the infusion rate of propofol used. By using electroencephalogram, it has been demonstrated that the equilibrium of propofol in its site of action is faster after a bolus injection than with a continuous infusion<sup>21</sup>. However, with rates up to 60 mg.min<sup>-1</sup> a difference in the value of ke0 was not observed<sup>22</sup>.

The use of a single infusion pump attached to the infusion management program (ANESTFUSOR), in which the ke0 in the same Marsh model varies, eliminated the bias of using two infusion systems with different accuracies.

When the Ce of propofol was correlated with the degree of sedation (OAAS) using BIS values, a better performance was observed with the original Marsh model (ke0 = 0.26 min<sup>-1</sup>) when compared to the Schnider model (ke0 = 0.45 min<sup>-1</sup>)<sup>23</sup>, since while the concentration of propofol on its site of action calculated by the Marsh model increased, the degree of sedation also increased and BIS decreased proportionally. The inverse relationship was also observed.

The results of the present study indicate that by the method used the slow ke0 (0.26 min<sup>-1</sup>) had a better performance, since the Ce of propofol at loss and recovery of consciousness was similar (2.20 and 2.13 µg.mL<sup>-1</sup>, respectively). This result was similar to that of other authors who used the same method<sup>13</sup>, although there is no evidence that this is actually occurring within the central nervous system.

Despite the great difference observed between the Ce at loss and recovery of consciousness (3.64 and 1.47 µg.mL<sup>-1</sup>, respectively) with the fast ke0 there was a positive correlation. This correlation was also observed in another study that evaluated the loss and recovery of consciousness according

to the same criteria<sup>24</sup>. Other authors have alerted about the non-linearity found between the Ce of propofol by fast ke0 and anesthesia induction, highlighting a greater reliability of slow ke0 as a titration guide<sup>25</sup>.

Slow ke0 (0.26 min<sup>-1</sup>) was first used on first generation IAC systems to estimate the effective concentration, which was always associated with the Marsh model. This value was extracted by using auditory evoked potentials (AEPex), but the details of this method are unknown, since this study was published only as a summary<sup>15</sup>. This value of ke0 is very similar to the 0.20 min<sup>-1</sup> proposed by other authors<sup>16,20</sup>.

The fast ke0 (1.21 min<sup>-1</sup>) was suggested later by Struys et al.<sup>19</sup>, using the time to peak effect (TTPE) and BIS. After a bolus dose, the maximum clinical effect will occur when concentration on the site of action reaches its maximal level. Time to peak effect is defined as the time interval between the end of the bolus injection and peak clinical effect. This time is not dependent on the size of bolus. Using a fast ke0 with the Marsh model, the TTPE was approximately 1.6 minutes, which is similar to the result reported by another study<sup>17</sup>. Obtaining a result outside the equilibrium phase of propofol represents a disadvantage of this method<sup>26</sup>, making it difficult to observe a single maximal effect in a real clinical situation due to several factors such as signal interference (BIS),.

The amount of propofol used was significantly greater with the fast ke0 than with slow ke0. This was translated into lower BIS values during infusion and consequently longer awakening time with fast ke0. This can be explained by the fact that when the ke0 of 1.21 min<sup>-1</sup> was used, many volunteers did not lose consciousness after the fast initial equilibrium of Ce and Cp at 3.0 µg.mL, which required a gradual increase in Cp until loss of consciousness. Therefore, with fast ke0, mean Cp during the assay was greater than the Cp of volunteers with slow ke0 (3.8 and 3.1 µg.mL<sup>-1</sup>, respectively).

Despite the greater amount of propofol used with fast ke0, significant hemodynamic repercussions were not observed, as the mean reduction in MAP was no more than 20%, while the HR remained stable during the study. Similar values were obtained with slow ke0. In only one moment (15 minutes after loss of consciousness) the HR was significantly different between groups.

Gender is an important variable in the pharmacokinetic of propofol<sup>27</sup>. A study has demonstrated that female patients recover faster after anesthesia with propofol, alfentanil, and nitrous oxide<sup>28</sup>. The calculated plasma concentration in females tends to be overestimated<sup>29</sup>. Recently, it has been demonstrated that there is the need to correct the depuration and volume of the central compartment of propofol according to gender and age to improve the previsibility of the Marsh model<sup>30</sup>. To decrease bias, this study was conducted with the same gender (males) and within the same age range (young adults).

The better performance with slow ke0 might be partly explained by the method used in the present study of evaluating loss and recovery of consciousness. Most likely, the proposed auditory stimulus had better correlation with the evoked auditory potential (AEPex) than with BIS. Note that the AEPex was the tool used to extract the value of ke0 in the original Marsh model<sup>15</sup>.

It has been demonstrated in literature that the auditory evoked potential index (AEP index), BIS, and entropy have a positive correlation with the Ce of propofol<sup>31-34</sup>. They are all able to assess the degree of sedation and separate the state of being awake from being anesthetized. However, studies have demonstrated that the AEP index and entropy are more accurate in distinguishing the transition from the individual condition of unconsciousness to the state of consciousness<sup>31,34,35</sup>.

In the present study BIS values were statistically different at loss and recovery of consciousness in both ke0 investigated. This difference could be explained by a delay in processing the BIS signal, and the value seen on the screen refers to a previous moment. This delay can vary from 5 to 60 seconds according to the context and its changing tendencies<sup>36</sup>. However, intergroup results were similar (Table III).

Limiting factors of this study include the type of model used and the lack of measurements of the plasma concentration of propofol. The model with volunteers did not resemble a real surgical situation as the volunteers only received an auditory stimulus. It is known that the Ce of propofol necessary for loss of consciousness is greater in the presence of pain or surgical stimulation<sup>32,37</sup>. Thus, this model simulates only procedures with little nociceptive stimulus or in case of painful stimulus is blocked by regional anesthesia. The lack of measurement of plasma propofol concentration did not allow a more detailed interpretation of the results.

Recently, the task force of the American Society of Anesthesiologists included total intravenous anesthesia as a risk factor for intraoperative awakening<sup>38</sup>. Note that in the United States the target-controlled infusion was not approved by the FDA for clinical use. As demonstrated in another study<sup>13</sup>, conducting total intravenous anesthesia with propofol based in populational means (Cp50 or Ce50) can predispose the patient to intraoperative awakening and to retain memory of the procedure, since there is a wide pharmacodynamic variability. Even with slow ke0, which showed similar Ce of propofol at loss and recovery of consciousness, the variation of Ce at loss of consciousness was from 1.0 to 3.6 µg.mL<sup>-1</sup>, while with the fast ke0, this variation ranged from 2.3 to 5.9 µg.mL<sup>-1</sup>. Note that the present study was undertaken with a very homogeneous group of volunteers.

In agreement with other authors<sup>33</sup>, we suggest that to reduce the incidence of intraoperative awakening slow ke0 associated with the Marsh model and titration of the maintenance target dose based on the calculated dose-effect for loss of consciousness should be used. Most likely, this target dose will need small adjustments to correct the inherent mathematical error of the pharmacokinetic model, and in situations in which the nociceptive stimulus is not completely blocked.

Corroborating the initial hypothesis, we conclude that the slow ke0 (0.26 min<sup>-1</sup>) incorporated in the Marsh pharmacodynamic model showed better clinical performance than the fast ke0 (1.21 min<sup>-1</sup>), as the calculated effect concentration at loss and recovery of consciousness was similar, although there is no evidence that this actually occurs in the central nervous system.

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**Resumen:** Simoni RF, Esteves LO, Miziara LEFG, Cangiani LM, Alves GGO, Romano ALP, Hansen PU, Vianna PTG – Evaluación Clínica de Dos ke0 en el Mismo Modelo Farmacocinético de Propofol: Estudio de la Pérdida y de la Recuperación de la Conciencia.

**Justificativa y objetivos:** La constante de equilibrio entre el plasma y el sitio efector (ke0), se usa por los modelos farmacocinéticos para prever la concentración del fármaco en su región de acción (Ce). Sería interesante que el Ce de propofol fuese similar en la pérdida y en la recuperación de la conciencia. El objetivo de este estudio, fue evaluar el desempeño clínico de dos diferentes ke0 (rápida = 1,21 min<sup>-1</sup> y lenta = 0,26 min<sup>-1</sup>), con relación a la Ce durante la pérdida y la recuperación de la conciencia, usando el modelo farmacocinético de Marsh.

**Método:** Participaron en este estudio, 20 voluntarios adultos sanos del sexo masculino. A todos los voluntarios se les administró propofol en régimen de infusión objeto controlada, modelo farmacocinético de Marsh ke0 rápida y en otro momento, se usó el mismo modelo farmacocinético con a ke0 lenta. Inicialmente, el propofol se infundió en concentración-objeto plasmática de 3,0 µg.mL<sup>-1</sup>. La pérdida de la conciencia y la recuperación de la conciencia estuvieron basadas en la respuesta al estímulo verbal. La Ce fue anotada en el momento de la pérdida y de la recuperación de la conciencia.

**Resultados:** En la pérdida y en la recuperación de la conciencia, la Ce por la ke0 rápida, fue diferente (3,64 ± 0,78 y 1,47 ± 0,29 µg.mL<sup>-1</sup>, respectivamente, p < 0,0001), mientras que con la ke0 lenta la Ce fue parecida (2,20 ± 0,70 y 2,13 ± 0,43 µg.mL<sup>-1</sup>, respectivamente, p = 0,5425).

**Conclusiones:** Desde el punto de vista clínico, la ke0 lenta (0,26 min<sup>-1</sup>) incorporada al modelo farmacocinético de Marsh, presentó un mejor desempeño que la ke0 rápida (1,21 min<sup>-1</sup>), pues la concentración de propofol prevista en su región de acción en la pérdida y en la recuperación de la conciencia fue similar.

**Descriptor:** ANESTÉSICO, Venoso: propofol; COMPLICACIONES: despertar intraoperatorio.