SCIENTIFIC ARTICLE

Comparative study between fast and slow induction of propofol given by target-controlled infusion: expected propofol concentration at the effect site. Randomized controlled trial☆

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Abstract

Background and objective: Studies have shown that the rate of propofol infusion may influence the predicted propofol concentration at the effect site (Es). The aim of this study was to evaluate the Es predicted by the Marsh pharmacokinetic model (ke0 $0.26\,min^{-1}$) in loss of consciousness during fast or slow induction.

Method: The study included 28 patients randomly divided into two equal groups. In slow induction group (S), target-controlled infusion (TCI) of propofol with plasma, Marsh pharmacokinetic model (ke0 $0.26\,min^{-1}$) with target concentration (Tc) at $2.0\text{-}\mu g\,mL^{-1}$ were administered. When the predicted propofol concentration at the effect site (Es) reached half of Es value, Es was increased to previous Es + $1\,\mu g\,mL^{-1}$, successively, until loss of consciousness. In rapid induction group (R), patients were induced with TCI of propofol with plasma ($6.0\,\mu g\,mL^{-1}$) at effect site, and waited until loss of consciousness.

☆ Study developed at CET/SBA of Instituto Penido Burnier e Centro Médico de Campinas.
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Results: In rapid induction group, Tc for loss of consciousness was significantly lower compared to slow induction group (1.67 ± 0.76 and $2.50 \pm 0.56 \,\mu g\,mL^{-1}$, respectively, $p = 0.004$).
Conclusion: The predicted propofol concentration at the effect site for loss of consciousness is different for rapid induction and slow induction, even with the same pharmacokinetic model of propofol and the same balance constant between plasma and effect site.

Estudo comparativo entre indução rápida e lenta de propofol em infusão alvo-controlada: concentração de propofol prevista no local de ação. Ensaio clínico aleatório

Resumo
Justificativa e objetivo: Estudos mostraram que a taxa de infusão de propofol pode influenciar na concentração prevista de propofol no local de ação (Ce). O objetivo deste estudo foi avaliar a Ce prevista pelo modelo farmacocinético de Marsh ($ke0\ 0{,}26\,min^{-1}$) na perda da consciência durante indução rápida ou lenta.
Método: Participaram deste estudo 28 pacientes, divididos aleatoriamente em dois grupos iguais. No grupo indução lenta (L), foram induzidos com propofol em infusão alvo-controlada (IAC) plasmática, modelo farmacocinético de Marsh ($ke0\ 0{,}26\,min^{-1}$), com concentração alvo (Ca) em $2{,}0\,\mu g.ml^{-1}$. Quando a concentração de propofol prevista no local de ação (Ce) atingia metade do valor da Ca, aumentava-se a Ca para Ca anterior + $1\,\mu g.ml^{-1}$. Assim sucessivamente até o momento da perda da consciência do paciente. No grupo indução rápida (R), os pacientes foram induzidos com propofol em IAC plasmática com Ca em $6{,}0\,\mu g.ml^{-1}$ e aguardava-se a perda da consciência do paciente.
Resultados: No grupo indução rápida, a Ce na perda da consciência foi significativamente mais baixa em relação ao grupo de indução lenta ($1{,}67 \pm 0{,}76$ e $2{,}50 \pm 0{,}56\,\mu g.ml^{-1}$, respectivamente, p = 0,004).
Conclusão: A concentração prevista de propofol no local de ação durante a perda da consciência é diferente numa indução rápida e numa indução lenta, até com o mesmo modelo farmacocinético de propofol e a mesma constante de equilíbrio entre o plasma e o local de ação.

Introduction

Recently several studies have shown a good correlation between the predicted propofol concentration at the effect site (Es) by Marsh pharmacokinetic model ($ke0$ $0.26\,min^{-1}$) and sedation degree, bispectral index (BIS) values, entropy, evoked potential index, and loss and recovery of consciousness.[1–5]

Because of this good correlation with pharmacodynamics, some authors suggested that the target concentration of propofol should be titrated during maintenance of anesthesia based on Es reached in loss of consciousness.[3,4,6]

However, other studies show that the rate of infusion of propofol may influence the balance between the plasma concentration and the concentration at the effect site; that is, in the first-order mathematical constant called Ke0.[7,8]

The main objective of this study was to evaluate the Es predicted by the Marsh pharmacokinetic model ($ke0$ $0.26\,min^{-1}$) on loss of consciousness during rapid or slow induction of patients undergoing laparoscopic cholecystectomy under total intravenous anesthesia with propofol and remifentanil. Es was also evaluated during anesthesia maintenance and recovery.

The hypothesis to be tested is that, even using the same pharmacokinetic model and the same equilibrium constant between plasma and effect site, the effect site in rapid induction is different from that in slow induction during loss of consciousnesses.

Method

After approval by the Research Ethics Committee and receiving the written informed consent, 28 patients, aged between 18 and 65 years, of both sexes, ASA physical status 1 and 2, and undergoing laparoscopic cholecystectomy under total intravenous anesthesia with propofol and remifentanil, were enrolled in this randomized clinical trial.

The sample size was based on a previous pilot study. Taking into account that the difference of proportionality

Table 1 Age, weight, height and sex of patients per group.

Group	Age (years)	Weight (kg)	Height (cm)	Sex (m/f)
S	43.1 ± 11.8	70.7 ± 16.9	167.1 ± 9.3	5/9
R	46.8 ± 12.0	76.5 ± 8.64	166.2 ± 8.8	6/8

S, slow induction group; R, rapid induction group; $p > 0.05$.

Table 2 Induction, duration of surgery, awakening times, and propofol and remifentanil consumption.

	L	R
Induction time (min)	4.54 ± 0.67	1.46 ± 1.02[a]
Duration of surgery (min)	47.6 ± 13.2	50.6 ± 13.1
Awakening time (min)	7.21 ± 3.81	7.07 ± 5.18
Propofol ($mg\,kg^{-1}\,h^{-1}$)	8.27 ± 2.15	8.40 ± 1.68
Remifentanil ($\mu g\,kg^{-1}\,min^{-1}$)	0.16 ± 0.02	0.13 ± 0.03

[a] $p < 0.001$.

between the propofol concentrations provided on the effect site during loss of consciousness with rapid and slow infusion was 67%, the power analysis with alpha of 1% and beta of 5% showed that 11 patients would be required per group. Three more patients per group were added to compensate for possible losses during the clinical trial.

No patient received premedication and all were monitored with electrocardiogram (DII and V1), pulse oximetry, non-invasive mean arterial blood pressure (MAP), bispectral index (BIS), and end-tidal CO_2 after tracheal intubation.

Patients were randomly allocated into two equal groups through a defined sequence by computer. The slow induction group (Group S) received propofol by plasma target-controlled infusion (TCI), Marsh pharmacokinetic model (ke0 $0.26\,min^{-1}$), with target concentration (Tc) of $2.0\,\mu g\,mL^{-1}$. When the predicted propofol concentration at the effect site (Es) reached half the value of Tc, Tc was increased to previous Tc + $1\,\mu g\,mL^{-1}$, and so on until the patient's loss of consciousness (loss of verbal response and eye-blink reflex). The rapid induction group (Group R) received plasma propofol via TCI with $6\,\mu g\,mL^{-1}$ Tc and waited until patient's loss of consciousness.

In both groups, after loss of consciousness, TCI remifentanil was initiated to an effect site of $5\,g\,mL^{-1}$ (Minto's pharmacokinetic model), rocuronium $0.6\,mg\,kg^{-1}$ was administered, and after two minutes tracheal intubation was performed.

During the intraoperative period, Tc of propofol was adjusted to maintain BIS between 35 and 50, while Tc of remifentanil was adjusted to maintain MAP between $\pm 20\%$ of the initial MAP.

After surgery, both infusions were turned off.

Es of propofol was recorded at the time of loss and recovery of consciousness (BIS = 70) and every minute of the intraoperative period.

All patients received dipyrone $30\,mg\,kg^{-1}$ and ketoprofen $1.5\,mg\,kg^{-1}$ for postoperative analgesia and methadone $0.1\,mg\,kg^{-1}$ as rescue analgesic in the Post-Anesthesia Care Unit.

For infusion management and data collection, the Anestfusor® software, coupled to two Pilot 2 syringe pumps (Fresenius-Kabi) and BIS, was used.

For statistical analysis of parametric data, Student's t-test was used and the difference was considered significant when p values were <0.05.

Results

There was no significant difference between demographic variables of the two groups ($p > 0.05$) (Table 1).

Induction time in Group S was higher compared to Group R, 4.54 and 1.46 min, respectively ($p < 0.001$). There was no

significant difference in surgery and awakening times and consumption of propofol and remifentanil between the two groups ($p > 0.05$) (Table 2).

The predicted propofol effect-site concentration (Es) in loss of consciousness was higher in Group S compared to Group R, 2.50 and $1.67\,\mu g\,mL^{-1}$ respectively ($p = 0.004$). Es was significantly different at loss and recovery of consciousness in Group S, 2.5 and $1.60\,\mu g\,mL^{-1}$, respectively ($p < 0.001$). In Group R, Es was lower at loss of consciousness compared to intraoperative Es, 1.67 and $2.52\,\mu g\,mL^{-1}$, respectively ($p = 0.002$). There was no significant difference between groups regarding Es values' intraoperative and at recovery of consciousness ($p > 0.05$). There was also no significant difference in Es during loss and recovery of consciousness in Group R ($p > 0.05$) (Fig. 1).

Discussion

The main difference found in this study was the Es predicted by the Marsh pharmacokinetic model (ke0 $0.26\,min^{-1}$) during loss of consciousness between rapid and slow induction.

Although the same pharmacokinetic model and the same equilibrium constant plasma/effect-site (Ke0) have been used, Es at loss of consciousness was significantly lower in Group R compared to Group S, 1.67 and $2.50\,\mu g\,mL^{-1}$, respectively. This difference was also found by other authors.[8]

Studies have shown that the pharmacokinetic models of propofol used in target-controlled infusion systems are poorly accurate for early prediction of propofol actual blood concentration after bolus or rapid infusion, when maximum
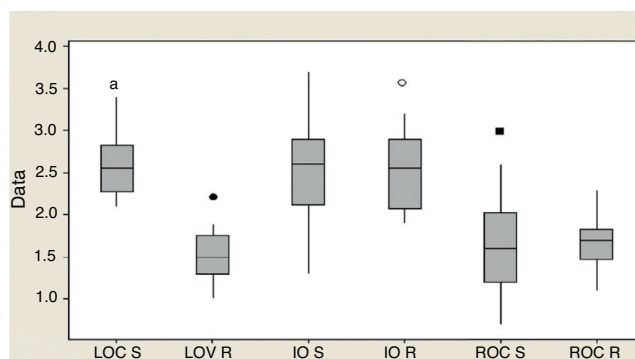

Figure 1 Effect-site concentration of propofol ($mcg\,mL^{-1}$). S, slow induction group; R, rapid induction group; LOC, loss of consciousness; IO, intraoperatively; ROC, recovery of consciousness; [a] vs ● $p = 0.004$; [a] vs ■ $p < 0.001$; ● vs ○ $p = 0.002$.

effect is observed.[7,9–11] These conventional nipple multi-compartmental pharmacokinetic models assume that drug mixing in central compartment occurs immediately and the mixture immediately appears in the arterial circulation. In fact, there is a delay between the drug administration and its appearance in arterial blood. This has been reported in several studies.[7,12,13]

Among other factors, this delay depends on the pulmonary extraction of propofol during the first pass.[14,15] In Marsh pharmacokinetic model, this initial error is evident during the first five minutes, which makes the model not so precise for these first minutes.[7]

By assuming an instantaneous mixture after a bolus injection, the traditional pharmacokinetic models overestimate the central volume. Because the bolus dose depends on the size of the central compartment, its overestimation may result in a large bolus, which may exceed the target concentration whenever the target is increased.[14,15]

Because of this poor predictability of pharmacokinetic model in the first minutes after a bolus injection, some authors have shown that the rate of propofol infusion can influence the equilibrium constant between plasma and effect site.[7] Apparently, the plasma/effect-site equilibrium constant is faster for bolus administration than for slower infusions. This may answer why different ke0 are found in the literature, even when using the same pharmacokinetic model.[7]

Maybe there are physiological reasons for these different values of ke0 obtained through bolus and slower infusions. One study showed that propofol reduces cerebral blood flow in a dose-dependent manner.[16] So, when using a bolus injection to extract ke0, the achieved high concentrations of propofol may reduce cerebral blood flow. On the other hand, when slower infusions are used, this propofol effect on cerebral blood flow should be reduced.

With the use of a conventional continuous infusion scheme, the values for propofol $t\frac{1}{2}$ ke0 in literature vary between 2.3 and 3.5 min.[17–19] The Marsh pharmacokinetic model, which is present in the first target-controlled infusion system commercially available (Diprifusor), was based on data from a slow infusion and is associated with a $t\frac{1}{2}$ ke0 of 2.65 min.[17]

As an option to reduce this initial error of the propofol pharmacokinetic models, some authors have proposed to incorporate into the Schnider model different ke0 values for different infusion rates.[7] If the maximum infusion rate remains between 300 and 900 mL h^{-1}, $t\frac{1}{2}$ ke0 should be about 2.2 min (ke0 = 0.32 min^{-1}). However, if the infusion is similar to a bolus injection, a shorter $t\frac{1}{2}$ ke0 of 1.2 min should be used.

For other pharmacokinetic models of propofol as the Marsh, for example, if the pump is capable of delivering a bolus induction in a minute or less, the time must be implemented to maximum effect of 1.5 min.[7] With these options, this model predicted effect concentration is more accurate over time.

Some authors have assessed more appropriate pharmacokinetic models for this initial kinetic phase and the correlation with possible covariates such as age, weight, and infusion rate.[20] In these more sophisticated models, it was demonstrated that the use of a single ke0 value is appropriate and can be applied to the target controlled

infusion systems, which use syringe pumps with infusion rate between 10 and 160 mg kg^{-1} h^{-1}. Therefore, for these studies, pharmacodynamics is not influenced by the rate of propofol infusion.[20,21]

The mean values of Es in rapid and slow induction groups were similar during the intraoperative and recovery of consciousness times, 2.52 ± 0.43 and 2.52 ± 0.76 µg mL^{-1}, respectively, and 1.63 ± 0.42 and 1.60 ± 0.58 µg mL^{-1}, respectively.

As shown in some studies, Es of propofol for loss and recovery of consciousness are similar when using the Marsh pharmacokinetic model (ke0 0.26 min^{-1}).[3,4] Therefore, some authors suggested that the target concentration of propofol should be titrated during maintenance of anesthesia based on Es during loss of consciousness.[3,4,6] The main objective would be to reduce the possibility of patient awakening during surgery. It is worth noting that this is only valid when analgesia is complete throughout the procedure.

To date, the literature on the subject does not allow saying that the actual propofol concentration at the effect site is similar at loss and recovery of consciousness or that it is really different.

Recently, a study showed that regardless of the pharmacokinetic model of propofol used (Schnider: ke0 0.45 min^{-1} and time to peak effect 1.7 min; Marsh: ke0 1.21 min^{-1} and time to peak effect 1.7 min; or Marsh: ke0 0.26 min^{-1} and time to peak effect of 4.5 min), the predicted value of propofol at the effect site during loss of consciousness after a bolus injection should not be used as reference value for titration of hypnosis during maintenance of anesthesia, as the effect concentration of propofol predicted by these models during loss of consciousness is very different (4.40, 3.55 and 1.28 µg mL^{-1}, respectively).[8]

In this study, the rapid and slow induction groups showed similar Es at recovery of consciousness. However, Es at loss and recovery of consciousness was similar only in the rapid induction group (Fig. 1).

Based on the presented results, we can conclude that in cases of rapid induction with Marsh model (ke0 0.26 min^{-1}), Es at loss and recovery of consciousness is similar (1.63 and 1.60 µg mL^{-1}, respectively). However, Es during the intraoperative period should be about 50% higher.

In cases of slow induction, the target maintenance dose may be similar to the Es during loss of consciousness. This result was expected, as the ke0 used in this study was derived from slow infusion data.[17] Consequently, the predicted effect-site concentration of propofol over time is more precise.

Although the goal was to evaluate the predicted effect-site concentration of propofol, the main limitation of this study was not measuring the plasma concentration of propofol at different times.

Another aspect to be considered is that the use of patients of both sexes may have increased the study bias, as sex is an important variable in propofol pharmacokinetics.[22] However, there was no significant difference between groups in the number of patients of both genders.

Conclusion

The predicted effect-site concentration of propofol at loss of consciousness is different in a rapid induction and in a slow

induction, even with the same pharmacokinetic model of propofol and the same equilibrium constant between plasma and effect site. Recognizing this difference is crucial to perform a total intravenous anesthesia with target-controlled infusion of propofol safely for the patient.

Conflicts of interest

The authors declare no conflicts of interest.

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