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Predictive ability of propofol effect–site concentrations during fast and slow infusion rates

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Background: The performance of propofol effect–site pharmacokinetic models during target-controlled infusion (TCI) might be affected by propofol administration rate. This study compares the predictive ability of three effect–site pharmacokinetic models during fast and slow infusion rates, utilizing the cerebral state index (CSI) as a monitor of consciousness.
Methods: Sixteen healthy volunteers, 21–45 years of age, were randomly assigned to receive either a bolus dose of propofol 1.8 mg/kg at a rate of 1200 ml/h or an infusion of 12 mg/kg/h until 3–5 min after loss of consciousness (LOC). After spontaneous recovery of the CSI, the bolus was administered to patients who had first received the infusion and vice versa. The study was completed after spontaneous recovery of CSI following the second dose scheme. LOC was assessed and recorded when it occurred. Adequacies of model predictions during both administration schemes were assessed by comparing the effect–site concentrations estimated at the time of LOC during the bolus dose and during the infusion scheme.
Results: LOC occurred 0.97 ± 0.29 min after the bolus dose and 6.77 ± 3.82 min after beginning the infusion scheme ($P < 0.05$). The Ce estimated with Schnider (ke0 = 0.45/min), Marsh (ke0 = 1.21/min) and Marsh (ke0 = 0.26/min) at LOC were 4.40 ± 1.45, 3.55 ± 0.64 and 1.28 ± 0.44 μg/ml during the bolus dose and 2.81 ± 0.61, 2.50 ± 0.39 and 1.72 ± 0.41 μg/ml, during the infusion scheme ($P < 0.05$). The CSI values observed at LOC were 70 ± 4 during the bolus dose and 71 ± 2 during the infusion scheme (NS).
Conclusion: Speed of infusion, within the ranges allowed by TCI pumps, significantly affects the accuracy of Ce predictions. The CSI monitor was shown to be a useful tool to predict LOC in both rapid and slow infusion schemes.

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Propofol administration using effect–site target-controlled infusion (TCI) has been shown to more accurately predict the desired time course of drug effect than plasma TCI.[1] The performance of effect–site TCI systems, however, might be affected by the administration rate of propofol.[2]

Ideally, in situations in which propofol effect–site concentrations (Ce) are changing, these changes should accurately characterize the observed effect. Discrepancies might occur, however, between the time profile of propofol effect and the predicted Ce changes after rapid bolus doses.[2–4] These discrepancies arise because in situations in which the plasmatic concentrations of the drug are rapidly changing, compartmental pharmacokinetic models, used in TCI systems, often fail to provide accurate predictions.[2] The reasons for these failures are multiple and have been extensively documented.[2,5–10] However, in our opinion, the literature has not clearly shown the magnitude of potential errors than can be observed during effect–site TCI. The poor understanding of these errors might potentially lead to erroneous clinical decisions.

From a clinical perspective, possible discrepancies between the time profile of the propofol effect and the Ce changes predicted by TCI devices are only relevant to characterize at infusion rates within the range allowed by TCI infusion pumps, which are much slower than rapid manual bolus doses.

The hypothesis of the study is that propofol's speed of infusion, within the range allowed by TCI infusion pumps, affects the predictive ability of TCI effect–site models. We therefore performed this study to compare the effect–site concentrations estimated at the time loss of consciousness (LOC) during the bolus dose and during the infusion scheme.

Methods

After Institutional Ethics Committee approval (Clínica Alemana, Santiago, Chile), written informed

consent was obtained from 16 healthy volunteers, aged 20–50 years. Exclusion criteria included a body mass index >30%, any known cerebrovascular disease, long- or short-term (within the previous 48 h) intake of any drug acting on the central nervous system and any known adverse effect to the study drug.

After arrival to the laboratory room, standard monitoring (heart rate, non-invasive arterial pressure and arterial oxygen saturation) was initiated and a peripheral intravenous line was installed. At this time, the sensors of the cerebral state monitor (CSM v2, Danmeter A/S, Odense, Denmark), used to measure propofol hypnotic effect,[11] were attached according to the manufacturer's recommendations. The CSM updates the CSI each 1 s and has a fixed smoothing time of around 10 s.[12] The data of the CSM were automatically recorded at intervals of 1 s using the Danmeter A/S CSM capture V2.02 onto a computer hard disk.

All patients were breathing spontaneously through a facemask delivering 100% oxygen at 10 l/min throughout the study period. Before propofol administration [Fresenius Vial Infusion Systems, Brézins, France connected to the Anestfusor™ TCI program (School of Medicine Universidad de Chile)*], a baseline period of 2 min was recorded. During this period, patients were kept undisturbed with the room in silence. Then, for the first step of the study, subjects were randomly assigned to receive either a fixed bolus dose of propofol 1.8 mg/kg at a rate of 1200 ml/h or an infusion of 12 mg/kg/h. The infusion scheme was stopped 3–5 min after LOC, defined as loss of response to verbal command. After spontaneous recovery of the CSI to basal values, the second step of the study was started. This step was similar to the first one but now the bolus dose of propofol was administered to subjects who had previously received the infusion dose, and the infusion scheme was administered to patients who had received the bolus dose. The study was completed after spontaneous recovery of CSI to baseline values following this second dose scheme. During both dose schemes, LOC was assessed every 10 s from the start of propofol administration using response to verbal command criteria and recorded when it occurred.

Three sets of pharmacokinetic parameters were used to predict the effect–site concentrations of propofol during the study period. (1) Schnider model[13] with an effect–site equilibration rate constant (ke0) of 0.456/min,[4] (2) Marsh model[14] with a ke0 of 1.21/min[1] and (3) Marsh model with a ke0 of 0.26/min.[14] The adequacy of model predictions during both administration schemes was assessed by comparing the effect–site concentrations estimated at the time of LOC during the bolus dose and during the infusion scheme.

*http://www.smb.cl/en/anestfusor_serie2_proen.html (accessed 20 March 2009).

Table 1

Demographic data.

	($n = 16$)
Age (years)	28 ± 6.2 (21–44)
Female/male ratio (n)	10/6
Weight (kg)	59 ± 15 (51–107)
Height (cm)	168 ± 10 (150–190)

Values are mean ± SD (range).

Normality of data was tested using the Kolmogorov–Smirnov test. Comparisons between both administration schemes were performed with paired Student's t-test or the Wilcoxon signed rank test. A P-value <0.05 was considered statistically significant. Assuming a subject variability of 50% for the propofol concentrations required to produce LOC, a sample size of 16 patients was estimated necessary to detect a 50% difference in the Ce values during both administration schemes (power 0.8, α 0.05). Statistical analysis was performed using R (language and environment for statistical computing, freely available from†). Data are mean ± SD (range).

Results

All subjects ($n = 16$) were included in the analysis. Demographic data are shown in Table 1. Propofol administration schemes are summarized in Table 2. The observed time course of CSI is shown in Fig. 1.

Basal CSI values recorded for 2 min before the bolus and the infusion schemes were 91.7 ± 5 and 90.8 ± 6, respectively (NS). Similarly, no differences were found between basal CSI values during the first (92.7 ± 5) and the second steps (89.9 ± 5) of the study (NS). Minimum CSI values reached after the bolus and infusion schemes were 46 ± 8 and 55 ± 7, respectively ($P<0.05$). LOC occurred 0.97 ± 0.29 min after beginning the bolus dose and 6.77 ± 3.82 min after beginning the infusion scheme ($P<0.05$). Time to LOC after the bolus was not affected by the randomization order Step 1 (0.97 ± 0.3 min) and Step 2 (0.97 ± 0.2 min) (NS). Similarly, no differences

†http://www.r-project.org/

Table 2

Propofol administration scheme and general data.

	Bolus	Infusion
Propofol dose (mg)	119 ± 32 (81–192)	129 ± 40 (90–264)
Administration time (s or min)	36 ± 9 (24–56) s	10.7 ± 4.1 (4.7–20.2) min
Administration rate (ml/h)	1200	79 ± 22 (41–128)

Values are mean ± SD (range).

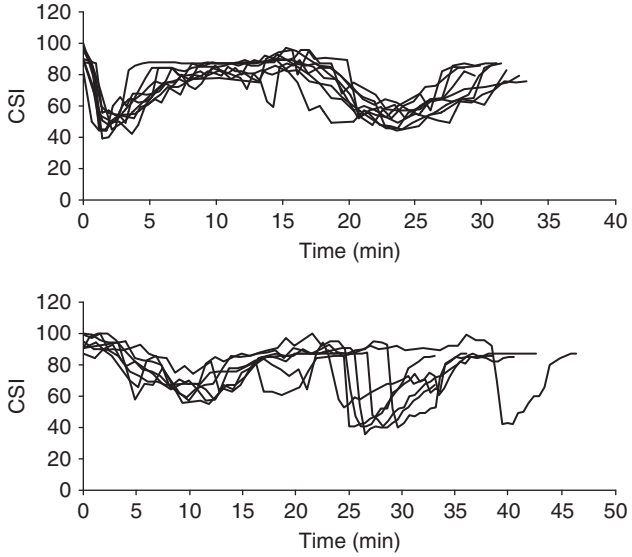

Fig. 1. Time course of the measured cerebral state index (CSI) values during both administration schemes. Patients receiving the bolus dose first (upper panel), and patients receiving the slow infusion first (bottom panel).

were found in the time to LOC after the infusion scheme in Step 1 (6.34 ± 4.4) and in Step 2 (7.44 ± 1.8) (NS). The Ce values estimated at LOC are shown in Table 3. The CSI values observed at LOC were 70 ± 4 during the bolus dose and 71 ± 2 during the infusion scheme (NS).

Discussion

The most important finding of our study is the considerable difference between predicted propofol Ce at the time of LOC following fast and slow infusion schemes. This result is interesting considering that the maximum infusion rate used in our study was only 1200 ml/h (the maximum infusion rate allowed by the TCI infusion pump). Our results indicate that, independent of the TCI model used, the value of Ce predicted at the time of LOC after a bolus dose should not be used as a reference value to titrate hypnosis during anaesthesia maintenance.

In our study, we used three commercially available effect–site pharmacokinetic models to estimate propofol Ce during fast (1200 ml/h) and slow (79 ± 22 ml/h) infusion rates given by a TCI infusion pump. Each model used has its own effect–site equilibration rate, which did not vary according to the infusion rate used. With this design, we mimic the way TCI is commonly used in routine clinical practice,[15] and are able to quantify the real magnitude of discrepancies observed between model predictions during fast and slow infusion rates. The considerable difference encountered in Ce predictions at the time of LOC after both infusion schemes, with all tested models, is clinically relevant and might lead to erroneous clinical decisions if not considered.

Current propofol models available in TCI devices poorly predict propofol arterial concentration early after a bolus dose, when the maximal effect is observed. Struys et al.[2] showed that arterial propofol concentrations, measured over 5 min after a bolus dose of 2.5 mg/kg given over 10 s, were poorly predicted by both Marsh and the Schnider pharmacokinetic models. Recently, Glen and Servin[16] compared the performance of different propofol models during stepwise infusion of propofol 21 mg/kg/h for 5 min, 12 mg/kg/h for 10 min and 6 mg/kg/h for the rest of the procedure. The authors found that, although the overall performance of all models was good, errors were higher during the rapid infusion scheme. Similarly, Kazama et al.[17] showed that Schnider[4] and Schuttler[18] pharmacokinetic models could not predict an accurate induction dose at a high rate.

To adequately predict the hypnotic effect of propofol during bolus doses or rapid infusion schemes, early distribution of the drug should be adequately characterized (front-end kinetics).[10] Early drug concentrations produced by rapid intravenous administration depend on the initial volume in which the dose is distributed and its further dilution by distribution from that vo-

Table 3

Propofol predicted effect-site concentrations at LOC.

Model	Ce-Bolus (μg/ml)	Ce-Infusion (μg/ml)
Schnider (ke0 of 0.45 min), TTPE of 1.7 min	4.40 ± 1.45	2.81 ± 0.61*
Marsh (ke0 of 1.21 min), TTPE of 1.7 min	3.55 ± 0.64	2.50 ± 0.39*
Marsh (ke0 of 0.26 min), TTPE of 4.5 min	1.28 ± 0.44	1.72 ± 0.41*

Values are mean ± SD (range).
*$P < 0.05$.
TTPE, predicted time to peak effect after a rapid manual bolus dose; LOC, loss of consciousness.

lume.[10,19] Physiologically based models that consider factors such as vascular mixing with cardiac output and lung kinetics have been derived for this purpose.[8,20] These models can also account for changes in cerebral kinetics due to changes in cerebral blood flow.[20]

After a bolus dose, mixing is not instantaneous in the central compartment. Normally, there is a lag between the time of drug administration and its appearance at the arterial sampling site. In addition, extraction of propofol by the lung at the first pass results in delayed emergence of arterial concentration peaks shortly after an intravenous injection.[10,19] Traditional compartment models, however, assume instantaneous mixing of drug immediately after the bolus dose is given. This assumption produces an overestimation of the central volume. Because, bolus doses depend on the size of the central volume, overestimation of this volume might result in large bolus doses that will exceed the target concentration every time the target is increased.[10,19]

The models used in our study have very different estimates of central volume. The Schnider model[13] derived from arterial samples has a fixed V_c of 4.27 l while a much larger central volume of 0.228 l/kg (16 l in a patient of 70 kg) is present in the Marsh model.[14] In spite of these differences, when Marsh and Schnider models were used with ke0s predicting the same time to peak effect of 1.7 min, both models showed a similar error pattern, with a higher Ce estimated at LOC during the bolus dose than during slow infusion (Table 3). From a clinical point of view overestimation of the Ce during TCI will not lead to an overdose but an underdose. On the contrary, when the ke0 of Marsh model predicted a longer time to peak effect of 4.5 min (low plasma effect–site equilibration rate), the model underestimated the Ce values at LOC during the bolus dose (Table 3). This is a good example of the relevant influence that the ke0 has in model Ce predictions and in the bolus dose given, independent of the pharmacokinetic model used.

In our study, higher Ce were estimated at the time of LOC after the bolus dose when the ke0 used predicted a time to peak effect of 1.7 min. This might suggest the need for a lower ke0 during the bolus dose and a higher ke0 during the slow infusion scheme, which is in apparent contradiction with the Struys et al. study.[2] In that study, the authors showed that the apparent plasma effect–site equilibration, calculated with the predicted propofol plasma concentrations of the Schnider pharmacokinetic model,[13] was higher for bolus injections than for infusions. Although, it is still unclear which ke0 values should be used for predicting effect–site concentration during TCI,[2,17] the apparent contradiction between Struys and our results is only apparent, because our results only suggest that the TTPE of 1.7 min is too rapid for the TCI scenario but do not support the need for different ke0s at the infusion rates used. This is in agreement with the Struys study,[2] showing similar ke0s if a bolus dose of 2.5 mg/kg was given over a 1-, a 2- or a 3-min infusion (very similar to the TCI scenario), but a higher ke0 if the dose was given in 10 s. In addition, a lower ke0 for the TCI scenario is consistent with the Kazama et al. study,[17] showing that the predicted propofol effect–site concentrations of Schnider model at LOC using a TTPE of 1.7 min were overestimated at high (150 mg/kg/h) and slow (40 mg/kg/h) infusion rates.

In the clinical scenario, the greater amount of endogenous catecholamines at induction might also differentially affect bolus or infusion schemes. An increased blood flow to inert tissues might increase dose requirements especially during bolus doses because a smaller fraction of the dose would be delivered to the brain.[19] In summary, the early hypnotic effect of propofol during bolus doses or rapid infusion given by TCI is difficult to predict by traditional models.

The effect of propofol can be continuously measured by electroencephalographic (EEG) monitors. These monitors can be used during TCI to guide

propofol administration. The cerebral state index (CSI), calculated by the CSM, is a relatively new index to measure the hypnotic effect of anaesthetics. The CSI algorithm was derived using adult EEG data and it is scaled from 100 (fully awake) to 0 (isoelectric EEG). This index is derived from four sub-parameters of the EEG estimated from the time domain analysis (burst-ratio) and from the frequency domain analysis (α-ratio, β-ratio, β-ratio–α-ratio). These sub-parameters are then used as inputs of a fuzzy logic interference system that calculates the CSI.[11]

The response measured by EEG monitors might vary based on their own algorithms and time delays.[21,22] The values of the CSI were almost identical when falling asleep after the two different administration schemes. This is an interesting result, which indicates a very low delay in the CSI signal compared with the clinical endpoint. This result supports the potential utility of this monitor during effect–site TCI, especially in situations where rapid changes in propofol concentration, and consequently, inaccuracies in Ce predictions, are expected. In addition, this result further indicates that speed of infusion does not affect the pharmacodynamics of propofol.[3,17]

The lack of real plasma measurements is a problem in this study, because the ke0 concept is based on the difference between plasma and effect. Still, there will be a discussion on what plasma levels are relevant during a rapid induction: mixed arterial? central venous? brain venous? We have based our results on pharmacokinetic models currently available in TCI devices. Because the aim of the present study was to compare the predictive ability of these models based on the CSI and LOC responses, we considered that measuring propofol plasma concentrations was not necessary.

Another possible limitation of this study is that the volunteers received the second propofol injection directly after the first. It is possible that, even by randomizing the volunteers, this could lead to a bias. To assess this potential limitation, we have explored the effect of randomization order in the times to LOC and in the Ce predicted at LOC within both administration schemes. Our results do not suggest a bias from this factor.

Conclusion

Speed of infusion, within the ranges allowed by TCI pumps, significantly affect the accuracy of Ce predictions. The value of Ce predicted at the moment of LOC after a TCI induction dose should not be used as a reference value to titrate hypnosis during anaesthesia maintenance. The CSI monitor was shown to be a useful tool to predict LOC in both rapid and slow infusion schemes.

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