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Precision and Bias of Target-Controlled Prolonged Propofol Infusion for General Anesthesia and Sedation in Neurosurgical Patients

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Abstract

The aim of this study was to determine the relationship, precision, and bias of a propofol target-controlled infusion (TCI) system during prolonged infusion in neurosurgical patients. We retrospectively included patients undergoing general anesthesia for elective neurosurgical removal of brain tumors and postoperative sedation in the intensive care unit over a period of 3 months. TCI of propofol (Diprifusor – Marsh model) and remifentanil were used for general anesthesia and sedation. We compared propofol blood concentration (C_{meas}) measured by liquid chromatography–mass spectroscopy with predicted concentrations (C_{pred}) by the TCI system at 40 minutes (T0), 2 hours (T1), and 4 hours (T2) and every 8 hours after starting the drug infusion and at the time of emergence from sedation. Ninety-four paired determinations of C_{meas} and C_{pred} from 15 adult ASA I patients (8 men and 7 women 54.9 ± 13 years old; BMI, 24 ± 3.2 kg/m^2) were analyzed. Mean duration of drug administration was 31 ± 6 hours. The coefficient of determination (R^2) of the linear regression model for the relationship of C_{meas} and C_{pred} was 0.43. At the time of emergence, C_{meas} was 0.5 ± 0.18 μg/mL. The bias of the TCI system (median performance error) was -34.7%, and the precision (median absolute performance error) was 36%. Wobble and divergence were 0.3% and 12.3%, respectively. This study found bias of the system out of the range of tolerability and showed a high tendency toward overestimation. These findings may lead to undersedation when propofol TCI is used for prolonged infusion.

Keywords

anesthetic techniques, computer-assisted continuous infusion, pharmacokinetics, propofol infusion, propofol TCI, TCI anesthesia, target controlled infusion

The pharmacokinetics of propofol have been comprehensively studied in the past.[1–5] Propofol has a suitable pharmacokinetic profile for use by infusion or target-controlled infusion (TCI).[6–12] TCIs have been used in research and clinical practice for more than 2 decades.[13–15] A widely used pharmacokinetic model of propofol TCI was developed by Marsh and colleagues,[16] and it was found to have good delivery performance. It was chosen for the commercially available Diprifusor[16,17] system. Recently, TCI has also been applied in the intensive care unit (ICU).[18–20] However, when applied in clinical care, TCI systems may not be as accurate as previously suggested,[11–13] leading various investigators to refine the infusion model.[21–28] We hypothesized that when propofol TCI with the pharmacokinetic model reported by Marsh is used for prolonged time, it can lose precision and accuracy.[16] The aim of this retrospective study was to determine the relationship, precision, and bias of the Diprifusor in combination with remifentanil patients undergoing neurosurgery under general anesthesia and in need of postoperative ICU sedation.

Methods

We obtained the approval from the Ethics Committee for this study. We retrospectively revised the clinical charts of neurosurgical patients (preoperative Glasgow Coma Scale of 15) scheduled for elective removal of brain tumors under general anesthesia and postsurgical ICU sedation over a period of 3 months at the Orthopedic and Trauma Center of Turin, Italy.

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Patients were included if: (1) TCI mode (propofol and remifentanil) was used for surgery and ICU sedation, and (2) propofol blood concentration (C_{meas}) was assessed using liquid chromatography–mass spectroscopy per our internal protocol at the time of propofol TCI use.[29] Exclusion criteria were: patients younger than 18 years, ASA greater than 1, hypertriglyceridemia, alcohol or drug abuse, significant hepatic or renal impairment; propofol administration by bolus injection or an alternative agent before surgery or other sedatives other than propofol during the study period; intraoperative or postoperative hemodynamic instability, as defined by median arterial pressure less then 60 mm hg with the need for vasoactive agents; severe arrhythmia or myocardial infarction; intraoperative fluid replacement greater than 6 and 2 mL/kg/h in the postsurgical period; need for blood, plasma or albumin transfusion; severe metabolic or respiratory acidosis, defined as a pH less then 7.35 or a body mass index (BMI) > 30 kg/m^2. Any adverse events that occurred during sedation or recovery were recorded, as were all deaths during sedation.

Patient Monitoring

During general anesthesia, patients were monitored by a 12-lead spontaneous cortical electrical activity (EEG) and Bispectral Index (Medtronic, Minneapolis, Minnesota).[30] The level of sedation was monitored using the Richmond Agitation Sedation Scale (RASS).[30] In the postoperative period, pain was measured by the Behavioral Pain Scale (BPS).[31] Noninvasive blood pressure, invasive blood pressure, heart rate, peripheral oxygen saturation, electrocardiogram, and end-tidal CO_2, ($EtCO_2$; GE Datex Ohmeda S5 Compact $EtCO_2$ Anesthesia Gas Patient Monitor, Madison, Wisconsis, United States) were recorded. Body temperature was also recorded through an esophageal probe and kept at 35.5°C to 36.5°C.

Times of Assessment

Samples were collected and data were registered at the following times for all patients using TCI for both anesthesia and ICU sedation per our internal protocol: 40 minutes (T0), 2 hours (T1), 4 hours (T2), 8 hours (T3), and 16 hours (T4) after infusion start; every 8 hours (T5, T6, T7, etc.); and at the time of recovery from deep sedation, as defined as patients reaching RASS -2 after discontinuation of the infusions.

At these times, blood samples were collected and concentrations were measured using liquid chromatography–mass spectroscopy.[29] Quality control samples (known samples for determining the accuracy of the method) were 94%–98% accurate. The precision of the assay (%CV) varied between 2% and 4%.[29] At the same points, clinical variables, BIS value, and RASS score were measured.

End Points, Definitions, and Data Analysis

The primary objective of the study was to retrospectively compare predicted (C_{pred}) and measured (C_{meas}) blood propofol concentrations. Measured values of blood propofol concentrations were compared with those calculated by the TCI system to evaluate its predictive performance (ie, bias, inaccuracy, and divergence) as described by Varvel et al.[27] For this purpose, performance error (PE) was calculated as previously described by Varvel.[27]

$$PE_{ij}\,(\%) = \left[\left(Cmeas_{ij} - Cpred_{ij}\right)/Cpread_{ij}\right] \cdot X100$$

where $Cpred_{ij}$ is the predicted blood propofol concentration in sample j from patient i and $Cmeas_{ij}$ is the measured blood concentration of propofol in that sample.

Bias (median performance error, MDPE) indicates whether measured concentrations are systematically above or below targeted values. MDPE was worked out as follows:

$$MDPE_i\,(\%) = median\{PE_{ij},\, j = 1, \ldots .N_i\}$$

Inaccuracy (median absolute performance error, MDAPE) provides information on the typical size of the difference between measured and targeted concentrations (imprecision). MDAPE was computed as follows:

$$MDAPE_i\,(\%) = median\left\{IPEI_{ij},\, j = 1, \ldots, N_i\right\}$$

for both formulas, N_i is the number of blood samples for individual i.

Divergence describes any time there are related changes in measured concentrations away from or toward the targeted concentration.[32] Wobble describes the intraindividual variability in error. Data were also analyzed using regression analysis.[32] C_{meas} was used as the response variable (Y) and C_{pred} as the explanatory variable (X). We compared continuous variables normally distributed with the Student t test and described them by mean and standard deviation. In case of not normal distribution, we used the Mann-Whitney U test and expressed the results as median and interquartile range. Statistical analysis was performed using MedCalc for Windows, version 17.9, (MedCalc Software, Mariakerke, Belgium) and Microsoft Excel (version 2013).

Intraoperative Period

According to the anesthetic protocol for neurosurgical patients, all patients had 2 intravenous lines for propofol and remifenanil infusion in one arm and a sampling arterial line inserted in the other arm. Intraoperative fluid replacement was provided with a 0.9% NaCl

solution. An indwelling arterial catheter was inserted in the radial artery to measure invasive pressure and to collect any blood samples. All patients received total intravenous anesthesia administered by TCI (Diprifusor, Macclesfield, UK); propofol 1% (Diprivan, AstraZeneca in 50-mL prefilled syringes) using the Marsh pharmacokinetic model.[16] Analgesia was provided with remifentanil (Ultiva 100 μg/mL; Glaxo SmithKline Inc., Brentford, UK) continuous infusion (Fresenius, Brezins, France) using the pharmacokinetic model by Minto.[33] At the induction of anesthesia, TCI was set at predicted propofol plasma concentration (C_{pred}) of 4 μg/mL with a remifentanil effect-site concentration (C_{pred}) between 3 and 6 ng/mL. A value of RASS -5 was chosen as an indicator of patient loss of consciousness at the induction of anesthesia. All patients were intubated after reaching a BIS value lower or equal to 40. Rocuronium (0.8 mg/kg) was used as a neuromuscular blocking agent. Mechanical ventilation was set to maintain an $EtCO_2$ equal to 30 to 35 mm Hg and an oxygen saturation (SpO_2) greater or equal to 97%. Premedication was never used in any patient. In all patients, the following targets were used for maintenance of anesthesia: C_{pred} of propofol set between 3 and 5 μg/mL, C_{pred} of remifentanil set between 5 and 6 ng/mL and then reduced to 3 ng/mL or lower after durectomy. TCI was targeted to a BIS value between 35 and 50. Remifentanil target concentrations were also adjusted according to heart rate and arterial blood pressure. A change of more than 30% from baseline values, if not related to blood loss, indicated an adjustment of the target concentration in the same direction. When clinically needed, anesthesia was deepened to reach EEG burst suppression.

Postoperative Period

In the postsurgical period, the same propofol and remifentanil TCI infusion system was used in all patients without interruption. The protocol for postoperative sedation included propofol and remifentanil targeted to reach a RASS of -4 or -3, a BIS value between 40 and 60, and a BPS[31] not greater than 3. Propofol TCI were initially adjusted to C_{pred} between 2 and 3 μg/mL. Infusions were also adjusted according to heart rate and arterial blood pressure values. As during the intraoperative period, a change of more than 30% from baseline values if not related to blood loss indicated an adjustment of the target concentration in the same direction. In addition, propofol and remifentanil C_{pred} were increased if RASS, BIS, or BPS targets were not reached. One hour before stopping remifentanil, acetaminophen 15 mL/kg was given in all patients.

Table 1. Patient Characteristics

Sequential Number	Age	Sex	Weight (kg)	Height (cm)	BMI
1	54	F	60	154	25
2	64	F	65	155	27
3	70	M	84	175	27
4	24	M	83	183	25
5	67	F	54	163	20
6	35	M	55	168	19
7	47	M	75	172	25
8	52	M	79	164	29
9	62	M	70	167	25
10	47	F	54	163	20
11	74	F	72	156	29
12	56	M	74	176	24
13	44	F	58	158	23
14	57	M	70	170	24
15	71	F	53	160	20

M, male; F, female; BMI, body mass index.
Weight is reported in kilograms; height is reported in centimeters. BMI, body mass index, was calculated as weight (kilograms)/height (meters)^2.

Marsh Propofol Pharmacokinetic TCI Model

The Marsh model is 1 of the 2 generally employed and commercially available models for propofol TCI.[13,34] In this model, compartmental volumes are proportional to weight with constant rates for slow and fast redistribution. It was adopted from the Gepts 3-compartmental model, which was derived from a cohort of 3 groups of 6 patients who received a constant infusion rate of propofol at 3, 6, and 9 mg/kg per hour.[3] The Marsh model is similar to the Gepts model except for the central compartment volume, which was increased to 0.228 L/kg. The characteristics of this model were published in 1991 along with the results of a study evaluating its performance and with an adaptive model in children.[16] A full description of the model is outside the aim of this study and is available elsewhere.[13,15,35]

Results

Fifteen adult neurosurgical ASA I patients (8 men and 7 women 54.9 $\pm$ 13 years old with a BMI of 24 $\pm$ 3.2 kg/m^2) were included for a total of 94 paired determinations of C_{mean} and C_{pred}. Table 1 shows the demographic characteristics of all included patients.

Mean time of propofol and remifentanil administration was 31 $\pm$ 6 hours. Mean time of surgery was 4 $\pm$ 0.5 hours. During surgery, mean remifentanil C_{pred} was 4.1 $\pm$ 0.8 ng/mL. Remifentanil C_{pred} was never modified in the postoperative period, 2.4 $\pm$ 0.4 ng/mL. In the postoperative period propofol C_{pred} was increased to maintain the sedation target in 5 patients: patient 2 between the 8th and the 16th hours, patients 6 and 9 between the 8th and the 16th hours, patient 7 between the 16th and the 36th hours, and patient 12

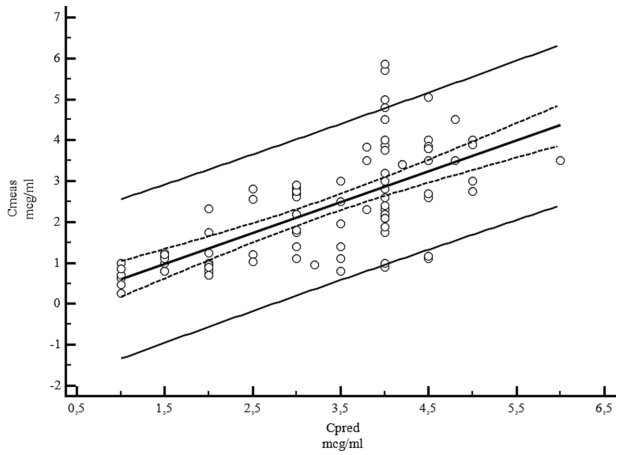

Figure 1. Scatterplot and fit line show the relationship between predicted propofol concentration (C_{pred}) and measured blood concentration (C_{meas}). Each circle represents a set of C_{pred}/C_{meas} (in micrograms per milliliter) for 1 patient at 1 time. The thick solid line is the regression line. There are also 2 sets of lines, one showing the 95% confidence interval (dashed) and the other the 95% prediction interval (solid).

between the 8th and the 16th hours and between the 24th and the 36th hours.

Regarding the linear regression model, regression coefficients were an intercept of -0.13 (standard error, 0.29) and a slope of 0.75 (standard error, 0.08). The coefficient of determination (R^2) was 0.46. Figure 1 graphically shows the relationship between propofol C_{pred} (X variable) and C_{meas} (Y variable) in a scatterplot with a fit line. Figure 2 shows the trend of C_{meas}/C_{pred} over time for each patient. The trend shows a ratio that tends to decrease from T1 to T6 (means 0.85 and 0.73, respectively). For all patients the bias of the TCI system (MDPE) was -34.7% and the precision (MDAPE) 36%. The divergence was 0.3. The median wobble was 12.3%.

Discussion

Our study demonstrated that the precision of the propofol TCI Diprifusor system (MADPE) was low but still in the range of normality.[33,34] However, the bias (MDPE) was out of the range of acceptance.[33,34] Our data also showed that: (1) there was a high tendency of the system to overpredict the set C_{pred} values, and (2) the divergence between C_{pred} and C_{meas} increased over time.

Propofol and remifentanil are widely used for both anesthesia and postoperative ICU sedation in neurosurgery for brain tumors. These kind of surgical procedures are relatively long, and a variable postoperative sedation time is often required to optimize patients' hemodynamics, cerebral perfusion pressure, and intracranial pressure.[36] These conditions are favorable to study the relationship between propofol TCI C_{pred} and C_{meas} in prolonged infusion. Prolonged infusion may lead to oversedation, which has several detrimental effects, such as hemodynamic and respiratory impairment, prolonged mechanical ventilation, increased risk of delirium, and late neurological examination after surgery.[37] Nevertheless, in our study we found the system to overpredict the set C_{pred} value without no apparent clinical sign of drug accumulation.[1–3,5] Barr et al[11] found that plasma propofol concentrations corresponding to Ramsay sedation scores of 2, 3, 4, and 5 were 0.25, 0.6, 1.0, and 2.0 μg/mL. When comparing Ramsay 5 to RASS -5, our C_{mean} values were not significantly different from Barr's data. Frolich et al[10] found little systematic bias but poor precision using a lower mean propofol TCI predicted dose than ours. McMurray et al[12] found that the measurement of blood propofol concentrations showed a tendency of Diprifusor TCI to underpredict measured values (measured values higher than indicated, positive bias) in postcardiac surgery patients. Moreover, they demonstrated the tendency of the system to overpredict (negative bias) in general ICU patients. Although their population was different from ours, McMurray's data[12] are in accord with our results that found TCI to overpredict actual C_{meas} values in the ICU. In their study, analgesia was provided with a morphine infusion (1–2 mg/h) or with an equianalgesic dose of alfentanil or fentanyl. However, Wietasch et al[38] found that when remifentanil was combined with propofol, the TCI system (Marsh model) had poor performance and precision (MDAPE, 60.7%) with systematic underestimation of propofol plasma concentrations (MDPE, 58.6%). This was also found by McMurray et al[12] in postcardiac surgery patients. Nevertheless, remifenanil doses were higher than the one we used in the postoperative period (C_{pred} of remifentanil between 2 and 3 ng/mL). Barr et al studied the association between fentanyl and propofol in 30 medical and surgical ICU patients. They found that when fentanyl was given together with propofol, there were no differences in the observed relationship between depth of sedation and plasma propofol concentrations compared with subjects who received propofol alone.[11] This suggests that the effect of fentanyl on sedation was minimal. In addition, as mentioned above, remifenanil dosage in our study was lower than in Wietasch's study. In addition, all patients in our study were classified as ASA I, with normal BMI without hepatic or renal failure or high Apache II scores. These different results can be partly attributed to altered distribution/redistribution and/or drug elimination.[39]

A positive bias (overestimation of the pump) could lead to an increase in propofol C_{pred} with the potential risk of hemodynamic impairment or propofol infusion syndrome[40] if propofol infusion lasts more than 48 hours at an infusion rate of more than 5 mg/kg

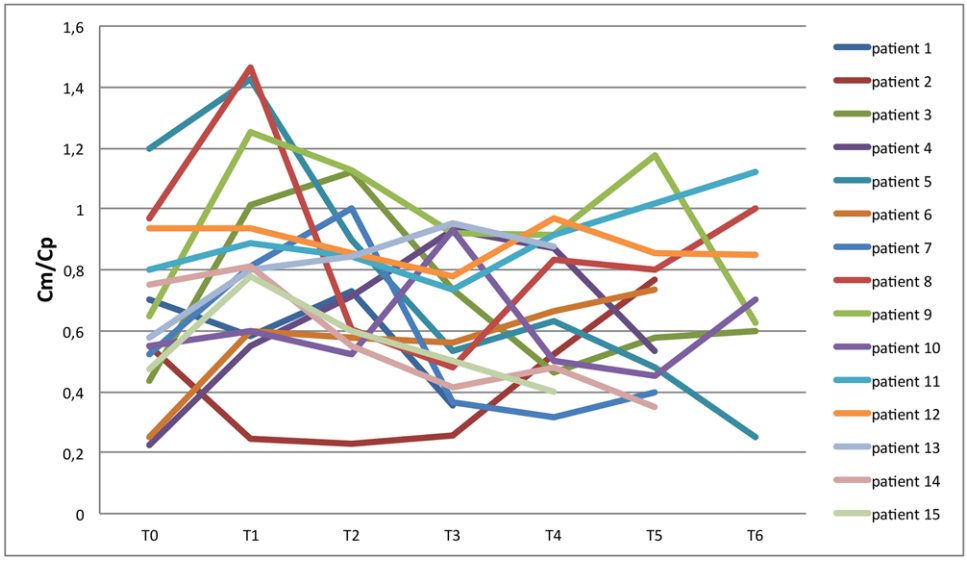

Figure 2. Trend of C_{meas}/C_{pred} over time. In the *x* axis are the times of assessment (from T0 to T6); in the *y* axis is the ratio between propofol C_{meas} and C_{pred} (C_m/C_p). Each line represents 1 patient.

per hour. Five of the 15 patients needed an increase in propofol C_{pred} to reach the target RASS and BIS scores,[41,42] although sedation in our patients lasted less than 48 hours. An increased propofol clearance may be explained with a higher cardiac output and a more rapid blood flow to the organs.[43,44] Although we did not measure cardiac output, no vasoactive drug was infused in any included patient. Another possible mechanism could be the increased distribution of the drug in adipose tissue.[12,42] However, patients included in our analysis had a normal body weight (BMI, 24 ± 3.2 kg/m^2). Of note, fat fills slowly and probably clears nearly all the propofol that flows through it. If the blood flow to the fat increases over the time of sedation, it would also increase the distributional clearance of propofol to the fat until steady state is reached after days of continuous infusion.[4,42]

With increasing peripheral tissue saturation, the rate at which plasma propofol concentrations decrease after discontinuation of the infusion becomes less dependent on redistribution and more dependent on metabolic clearance. Time to reach RASS -2 was fast in all our patients, suggesting that propofol did not accumulate extensively in fat, probably because of the short duration of sedation and because our patients had a normal BMI. McMurray et al found that patients undergoing sedation (mean time, 17 hours) without TCI after coronary revascularization were extubated after a mean time of 7.6 minutes.[45]

Last but not least, it has recently been found that patients with brain tumors showed 40% higher propofol clearance than control patients.[35] Among the tested models, the authors also evaluated the possibility that antiepileptic drugs (AEDs) increased clearance in the tumor group because of the induction of cytochrome P450 activity. Older-generation AEDs such as carbamazepine, phenytoin, phenobarbital, and primidone are known enzyme inducers.[46] Interestingly, all patients in our study received at least 1 AED.

Our study has several limitations. First, the study was retrospective, and the number of patients enrolled was small. However, serial measurements of propofol concentration were included per patient. In addition, other studies dealing with the pharmacokinetics of long-term propofol infusions used for sedation in ICU patients enrolled a limited number of patients.[4,5,16,39] Second, remifentanil was used in association with propofol.[47] As mentioned above, the use of remifentanil may potentially interfere with propofol blood concentration.[38,39,48,49] Third, we did not measure cardiac output in our patients as well as propofol clearance[5] and urinary metabolites. These measurements would have permitted defining the role of the mentioned potential mechanisms of altered propofol pharmacokinetics (increased systemic propofol clearance and increased propofol distribution into fat).[42,50] Fourth, RASS scale was used, together with BIS, for sedation monitoring. Although the end point of our study was not targeted to find the range of target blood propofol concentration required to sedate adult intensive care patients using Diprifusor TCI, BIS can be prone to artifacts[51] and has not been recommended as the primary method to monitor depth of sedation. However, the use of objective measures of brain function (eg, BIS) may be used as an adjunct to subjective sedation assessments in adult ICU patients who are

receiving neuromuscular blocking agents or in very deeply sedated patients.[52]

Fifth, our study was carried out in neurosurgical patients without any comorbidities potentially affecting propofol clearance.[53] The algorithms guiding TCI pumps are based on pharmacological data obtained from healthy volunteers, which are then extrapolated, on the basis of sophisticated pharmacokinetic and pharmacodynamic modeling, to predict plasma concentrations of the drug and its effect on general population. It may be argued that these models may be less accurate when applied in the ICU when patients have considerable blood loss, hypothermia, or temporary changes in plasma composition (eg, hypoalbuminemia).[53]

Conclusions

The main finding of our study was that the bias of the propofol TCI system (Marsh model) was out of the range of tolerability, showing a high tendency toward overestimation. However, if anesthesia and sedation are carefully monitored, Propofol TCI seems to be a safe option in the ASA I neurosurgical population. This altered pharmacokinetic behavior should be taken into consideration to allow a more individualized dosing of propofol TCI and remifentanil when given in prolonged infusion in this patient population. Future pharmacokinetic propofol models should take into account real patients' data to optimize precision and bias.

References

1. Shafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *Anesthesiology.* 1988;69(3):348–356.
2. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet.* 1989;17(5):308–326.
3. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg.* 1987;66(12):1256–1263.
4. Albanese J, Martin C, Lacarelle B, Saux P, Durand A, Gouin F. Pharmacokinetics of long-term propofol infusion used for sedation in ICU patients. *Anesthesiology.* 1990;73(2):214–217.
5. Bailie GR, Cockshott ID, Douglas EJ, Bowles BJ. Pharmacokinetics of propofol during and after long-term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth.* 1992;68(5):486–491.
6. Gepts E. Pharmacokinetic concepts for TCI anaesthesia. *Anaesthesia.* 1998;53(suppl 1):4–12.
7. Servin FS. TCI compared with manually controlled infusion of propofol: a multicentre study. *Anaesthesia*. 1998;53(suppl 1):82–86.
8. Barvais L, Rausin I, Glen JB, et al. Administration of propofol by target-controlled infusion in patients undergoing coronary artery surgery. *J Cardiothorac Vasc Anesth.* 1996;10(7):877–883.
9. Hoymork SC, Raeder J, Grimsmo B, Steen PA. Bispectral index, serum drug concentrations and emergence associated with individually adjusted target-controlled infusions of remifentanil and propofol for laparoscopic surgery. *Br J Anaesth*. 2003;91(6):773–780.
10. Frolich MA, Dennis DM, Shuster JA, Melker RJ. Precision and bias of target controlled propofol infusion for sedation. *Br J Anaesth.* 2005;94(4):434–437.
11. Barr J, Egan TD, Sandoval NF, et al. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic-pharmacodynamic model. *Anesthesiology*. 2001;95(2):324–333.
12. McMurray TJ, Johnston JR, Milligan KR, et al. Propofol sedation using Diprifusor target-controlled infusion in adult intensive care unit patients. *Anaesthesia.* 2004;59(7):636–641.
13. Absalom AR, Mani V, De Smet T, Struys MMRF. Pharmacokinetic models for propofol–defining and illuminating the devil in the detail. *Br J Anaesth*. 2009;103(1):26–37.
14. Absalom AR, Glen JIB, Zwart GJC, Schnider TW, Struys MMRF. Target-controlled infusion: a mature technology. *Anesth Analg.* 2016;122(1):70–78.
15. Struys MMRF, De Smet T, Glen JIB, Vereecke HEM, Absalom AR, Schnider TW. The history of target-controlled infusion. *Anesth Analg.* 2016;122(1):56–69.
16. Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth*. 1991;67(1):41–48.
17. Glen JB. The development of "Diprifusor": a TCI system for propofol. *Anaesthesia.* 1998;53(suppl 1):13–21.
18. Clouzeau B, Bui H-N, Vargas F, et al. Target-controlled infusion of propofol for sedation in patients with non-invasive ventilation failure due to low tolerance: a preliminary study. *Intensive Care Med.* 2010;36(10):1675–1680.
19. Clouzeau B, Bui H-N, Guilhon E, et al. Fiberoptic bronchoscopy under noninvasive ventilation and propofol target-controlled infusion in hypoxemic patients. *Intensive Care Med.* 2011;37(12):1969–1975.
20. Smuszkiewicz P, Wiczling P, Przybylowski K, et al. The pharmacokinetics of propofol in ICU patients undergoing long-term sedation. *Biopharm Drug Dispos.* 2016;37(8):456–466.
21. Struys MM, De Smet T, Depoorter B, et al. Comparison of plasma compartment versus two methods for effect compartment–controlled target-controlled infusion for propofol. *Anesthesiology.* 2000;92(2):399–406.
22. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology.* 1998;88(5):1170–1182.
23. Vuyk J, Oostwouder CJ, Vletter AA, Burm AG, Bovill JG. Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion. *Br J Anaesth.* 2001;86(2):183–188.
24. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology*. 1999;90(6):1502–1516.
25. Levitt DG, Schnider TW. Human physiologically based pharmacokinetic model for propofol. *BMC Anesthesiol.* 2005;5(1):4.
26. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL. Response surface model for anesthetic drug interactions. *Anesthesiology.* 2000;92(6):1603–1616.
27. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *J Pharmacokinet Biopharm.* 1992;20(1):63–94.
28. White M, Kenny GN, Schraag S. Use of target controlled infusion to derive age and gender covariates for propofol clearance. *Clin Pharmacokinet*. 2008;47(2):119–127.
29. Pavan I, Buglione E, Massiccio M, Gregoretti C, Burbi L, Berardino M. Monitoring propofol serum levels by rapid and sensitive reversed-phase high-performance liquid chromatography

during prolonged sedation in ICU patients. *J Chromatogr Sci.* 1992;30(5):164–166.
30. Deogaonkar A, Gupta R, DeGeorgia M, et al. Bispectral Index monitoring correlates with sedation scales in brain-injured patients. *Crit Care Med.* 2004;32(12):2403–2406.
31. Young J, Siffleet J, Nikoletti S, Shaw T. Use of a Behavioural Pain Scale to assess pain in ventilated, unconscious and/or sedated patients. *Intensive Crit Care Nurs.* 2006;22(1):32–39.
32. Mertens MJ, Engbers FHM, Burm AGL, Vuyk J. Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. *Br J Anaesth.* 2003;90(2):132–141.
33. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology.* 1997;86(1):10–23.
34. Viterbo JF, Lourenco AP, Leite-Moreira AF, Pinho P, Barros F. Prospective randomised comparison of Marsh and Schnider pharmacokinetic models for propofol during induction of anaesthesia in elective cardiac surgery. *Eur J Anaesthesiol.* 2012;29(10):477–483.
35. Sahinovic MM, Eleveld DJ, Miyabe-Nishiwaki T, Struys MMRF, Absalom AR. Pharmacokinetics and pharmacodynamics of propofol: changes in patients with frontal brain tumours. *Br J Anaesth.* 2017;118(6):901–909.
36. Dinsmore J. Anaesthesia for elective neurosurgery. *Br J Anaesth.* 2007;99(1):68–74.
37. Hughes CG, McGrane S, Pandharipande PP. Sedation in the intensive care setting. *Clin Pharmacol.* 2012;4:53–63.
38. Wietasch JKG, Scholz M, Zinserling J, et al. The performance of a target-controlled infusion of propofol in combination with remifentanil: a clinical investigation with two propofol formulations. *Anesth Analg.* 2006;102(2):430–437.
39. Frenkel C, Schuttler J, Ihmsen H, Heye H, Rommelsheim K. Pharmacokinetics and pharmacodynamics of propofol/alfentanil infusions for sedation in ICU patients. *Intensive Care Med.* 1995;21(12):981–988.
40. Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and pathophysiology. *Minerva Anestesiol.* 2009;75(5):339–344.
41. Buckley PM. Propofol in patients needing long-term sedation in intensive care: an assessment of the development of tolerance. A pilot study. *Intensive Care Med.* 1997;23(9):969–974.
42. Ypsilantis P, Mikroulis D, Politou M, et al. Tolerance to propofol's sedative effect in mechanically ventilated rabbits. *Anesth Analg.* 2006;103(2):359–365.
43. Myburgh JA, Upton RN, Grant C, Martinez A. Epinephrine, norepinephrine and dopamine infusions decrease propofol concentrations during continuous propofol infusion in an ovine model. *Intensive Care Med.* 2001;27(1):276–282.
44. Kurita T, Morita K, Kazama T, Sato S. Influence of cardiac output on plasma propofol concentrations during constant infusion in swine. *Anesthesiology.* 2002;96(6):1498–1503.
45. McMurray TJ, Collier PS, Carson IW, Lyons SM, Elliott P. Propofol sedation after open heart surgery. A clinical and pharmacokinetic study. *Anaesthesia.* 1990;45(4):322–326.
46. Johannessen SI, Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuropharmacol.* 2010;8(3):254–267.
47. Bouillon TW, Bruhn J, Radulescu L, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology.* 2004;100(6):1353–1372.
48. Pavlin DJ, Coda B, Shen DD, et al. Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. *Anesthesiology.* 1996;84(1):23–37.
49. Absalom A, Amutike D, Lal A, White M, Kenny GNC. Accuracy of the "Paedfusor" in children undergoing cardiac surgery or catheterization. *Br J Anaesth.* 2003;91(4):507–513.
50. Ypsilantis P, Politou M, Mikroulis D, et al. Organ toxicity and mortality in propofol-sedated rabbits under prolonged mechanical ventilation. *Anesth Analg.* 2007;105(1):155–166.
51. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. *Anesthesiology.* 2003;99(1):9–17.
52. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):263–306.
53. Bienert A, Wiczling P, Grzeskowiak E, Cywinski JBJ, Kusza K. Potential pitfalls of propofol target controlled infusion delivery related to its pharmacokinetics and pharmacodynamics. *Pharmacol Rep.* 2012;64(4):782–795.