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Influence of an “Electroencephalogram-Based” Monitor Choice on the Delay Between the Predicted Propofol Effect-Site Concentration and the Measured Drug Effect

Marko M. Sahinovic, MD, PhD,* Johannes P. van den Berg, MD,* Pieter J. Colin, PhD,* Pedro L. Gambus, MD, PhD,†‡§ Erik W. Jensen, MSc, PhD,|| Mercé Agustí, MD, PhD,† Teresa Ferreiro, CRNA,† and Michel M. R. F. Struys, MD, PhD*¶

BACKGROUND: Clinicians can optimize propofol titration by using 2 sources of pharmacodynamic (PD) information: the predicted effect-site concentration for propofol ($C_{e,prop}$) and the electroencephalographically (EEG) measured drug effect. Relation between these sources should be time independent, that is, perfectly synchronized. In reality, various issues corrupt time independency, leading to asynchrony or, in other words, hysteresis. This asynchrony can lead to conflicting information, making effective drug dosing challenging. In this study, we tried to quantify and minimize the hysteresis between the $C_{e,prop}$ (calculated using the Schnider model for propofol) and EEG measured drug effect, using nonlinear mixed-effects modeling (NONMEM). Further, we measured the influence of EEG-based monitor choice, namely Bispectral index (BIS) versus qCON index (qCON) monitor, on propofol PD hysteresis.

METHODS: We analyzed the PD data from 165 patients undergoing propofol–remifentanyl anesthesia for outpatient surgery. Drugs were administered using target-controlled infusion (TCI) pumps. Pumps were programmed with Schnider model for propofol and Minto model for remifentanyl. We constructed 2 PD models (direct models) relating the Schnider $C_{e,prop}$ to the measured BIS and qCON monitor values. We quantified the models’ misspecification due to hysteresis, on an individual level, using the root mean squared errors (RMSEs). Subsequently, we optimized the PD models’ predictions by adding a lag term to both models (lag-time PD models) and quantified the optimization using the RMSE.

RESULTS: There is a counterclockwise hysteresis between $C_{e,prop}$ and BIS/qCON values. Not accounting for this hysteresis results in a direct PD model with an effect-site concentration which produces 50% of the maximal drug effect (C_{e50}) of 6.24 and 8.62 $\mu\text{g/mL}$ and RMSE (median and interquartile range [IQR]) of 9.38 (7.92–11.23) and 8.41 (7.04–10.2) for BIS and qCON, respectively. Adding a modeled lag factor of 49 seconds to the BIS model and 53 seconds to the qCON model improved both models’ prediction, resulting in similar C_{e50} (3.66 and 3.62 $\mu\text{g/mL}$ for BIS and qCON) and lower RMSE (median [IQR] of 7.87 (6.49–9.90) and 6.56 (5.28–8.57) for BIS and qCON).

CONCLUSIONS: There is a significant “ $C_{e,prop}$ versus EEG measured drug effect” hysteresis. Not accounting for it leads to conflicting PD information and false high C_{e50} for propofol in both monitors. Adding a lag term improved the PD model performance, improved the “pump-monitor” synchrony, and made the estimates of C_{e50} for propofol more realistic and less monitor dependent. (Anesth Analg 2020;131:1184–92)

KEY POINTS

- **Question:** The main question we tried to answer in this study is “What is the influence of the monitor delay on the pharmacodynamic (PD) relationship monitor versus propofol when using C_e targeted target-controlled infusion (TCI) with the Schnider model?”
- **Finding:** The monitor delay causes a PD hysteresis irrespective of which monitor is used.
- **Meaning:** Adding a lag-time of 53 seconds and 49 seconds for qCON index (qCON) and Bispectral index (BIS), respectively, substantially corrects for this hysteresis, improving the PD model performance, increasing the “pump-monitor” synchrony, and making the estimates of effect-site concentration which produces 50% of the maximal drug effect (C_{e50}) for propofol more realistic and less monitor dependent.

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GLOSSARY

3D = 3 dimensional; **ASA** = American Society of Anesthesiologists; **BIS** = Bispectral index; **BSA** = body surface area; **Ce** = effect-site concentration; **Ce₅₀** = effect-site concentration which produces 50% of the maximal drug effect; **Ce_{50,INT}** = effect-site concentration which produces 50% of the maximal drug effect modified by the interaction effect between propofol and remifentanyl; **Ce_{prop}** = effect-site concentration for propofol; **Ce_{Remi}** = effect-site concentration for remifentanyl; **CONSORT** = Consolidated Standards of Reporting Trials; **CUP** = canonical univariate parameter; **CUP_{prop}** = propofol canonical univariate parameter; **EEG** = electroencephalogram; **E_{max}** = maximum achievable drug effect; **FOCE** = first-order conditional estimation; **IIV** = interindividual variability; **IPRED_k** = individually (post hoc) predicted response; **IQR** = interquartile range; **k_{eo}** = effect-compartment equilibrium rate constant; **LBM** = lean body mass; **LM** = laryngeal mask; **M:F** = male:female; **NONMEM** = nonlinear mixed-effects modeling; **OFV** = objective function value; **PD** = pharmacodynamic; **PK** = pharmacokinetics; **PKPD** = pharmacokinetic-pharmacodynamic; **POT_{max}** = maximum influence (potentiation) of remifentanyl on the propofol Ce₅₀; **PSI** = patient state index; **qCON** = qCON index; **RMSE** = root mean squared error; **RUV** = residual unexplained variability; **SD** = standard deviation; **SEF** = spectral edge frequency; **TCI** = target controlled infusion; **TIVA** = total intravenous anesthesia

Pharmacokinetics (PK) describes the time course of the drug plasma concentration. Pharmacodynamics (PDs) describes the time-independent relation between the achieved drug concentration at the drug effect-site (Ce) and the resulting drug effect. The drug needs time to reach the effect-site. This action can be quantified by a first-order process defined as hysteresis and characterized by effect-compartment equilibrium rate constant (k_{eo}). During total intravenous anesthesia (TIVA), drug Ce can be predicted using target-controlled infusion (TCI) technology¹⁻³ or anesthesia drug displays,⁴ while achieved drug effect can be measured by various processed electroencephalographic (EEG) measures.⁵ The concept of Ce takes into account this hysteresis, and as such, the time course of the Ce should match the time course of the drug effect.

Both Ce and EEG information can be displayed to the anesthesiologist, thereby improving clinical decision-making.^{6,7} Both sources of information can only be correlated at a specific moment if all biological and computational time-related issues are taken into account, thereby ideally resulting in perfect time synchronization. In reality, various time-related issues might corrupt the time independency causing additional hysteresis in the dose-response relation.

The clinically applied pharmacokinetic-pharmacodynamic (PKPD) models were developed using different effect measures than those presently used in the operating theater. For propofol, Schnider et al^{8,9} applied the propofol canonical univariate parameter (CUP_{prop}) to measure cerebral drug effect and generate the PD model. CUP_{prop} was developed without any processing delay because analyses were done offline.⁹ Clinically applicable processed EEG monitors require time to calculate an index value and display it on screen. This time delay varies between monitors and is influenced by nonsteady-state conditions as present during clinical anesthesia. Pilge

et al¹⁰ found variable delay times for the Bispectral index (BIS; Medtronic, Dublin, Ireland) during transitions of consciousness. This delay can have an impact on monitor performance.¹¹ Other monitors might have other delay characteristics.

Until today, no information is available on the influence of the monitor delay on the PDs of propofol when using Ce targeted TCI with the Schnider model. As such, we studied the influence of these delays on the propofol PD parameters using 2 clinically available drug effect monitors namely BIS and the qCON index (qCON) monitor (CONOX; Quantum Medical, Barcelona, Spain) during Ce targeted TCI for propofol during clinical anesthesia.

METHODS

Data Collection

Data for this study were collected prospectively from September 2016 until July 2017 during clinical anesthesia for outpatient surgical procedures in the Ambulatory Surgery facility at Hospital CLINIC de Barcelona (Barcelona, Spain). Data collection was part of a larger project to construct a database containing observational PK and PD data on propofol and remifentanyl in clinical practice. We randomly extracted data of 165 patients from this database. The sample size was determined a priori to detect a qCON difference of 12 (assuming a standard deviation of 16) between awake and sedated patients with a power of 99% and a significance level of 0.01. Anonymized data collection was approved by the Ethics Committee of the Hospital CLINIC de Barcelona (Reg no: 2013/8356). All patients gave written informed consent before inclusion. The article was composed to adhere to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. Data from the TCI pumps and EEG monitors were collected in concordance with ICH Guidelines for Good Clinical Practice using dedicated recording software (RUGLOOP II;

Demed, Temse, Belgium). Patients with an American Society of Anesthesiologists (ASA) Physical Status Classification Score of 1–3 were eligible for inclusion. Morbidly obese patients and patients affected by medical conditions or being treated with medications that could affect the EEG tracings were excluded.

General Anesthesia

Patients received propofol and remifentanyl TIVA while undergoing gynecologic and abdominal surgery procedures, for example, hysteroscopy, urinary incontinence repair, open or laparoscopic inguinal or umbilical hernia repair, and laparoscopic cholecystectomy. Both drugs were infused using TCI pumps (Base Primea; Fresenius Vial, Brezins, France). TCI was targeting the C_e using the Schnider PKPD model⁹ for propofol and the Minto PKPD model¹² for remifentanyl. In their original publication, Schnider used the CUP_{Prop} to determine the drug effect of propofol, while Minto used the spectral edge frequency (SEF) to determine the drug effect of remifentanyl.

The general anesthesia approach was that of a routine clinical case. To minimize the influence of the anesthesia care providers on the study outcome, only 2 anesthesiologists were involved in patient care during data collection. Each of them had >10 years of experience in the use of TCI for TIVA.

A typical case started with a remifentanyl infusion of 1.5 ng/mL while the patient was fully monitored. Subsequently, a target C_e for propofol ($C_{e,Prop}$) was chosen by the clinician between 4.5 and 6 µg/mL of propofol. Induction started until loss of response to a verbal command. Next, the target C_e for remifentanyl ($C_{e,Remi}$) was raised to 4 ng/mL when laryngeal mask (LM) was the chosen airway control method or to 6 ng/mL remifentanyl if laryngoscopy and intubation was to be performed. In the latter case, a bolus of 30 mg of rocuronium was administered 2 minutes before attempting laryngoscopy to facilitate endotracheal intubation. Control of the TCI pumps was at the full discretion of the attending anesthesia team. During surgery, target $C_{e,Prop}$ and $C_{e,Remi}$ were tailored to individual patients' needs. At the end of the surgery, TCI C_e targets were set to 0 and patients were left to recover from anesthesia spontaneously, that is, without any external stimulation until opening of the eyes. After that they were prompted to breathe deeply. A complete overview of propofol and remifentanyl C_e targets and BIS and qCON values during the study is given in Supplemental Digital Content, Document, <http://links.lww.com/AA/D13>.

EEG-Based Drug Effect Monitors

The clinical cerebral drug effect of propofol was measured using 2 processed EEG monitors, namely BIS monitor and qCON monitor.

Bispectral Index

BIS is a processed frontal EEG parameter index.¹³ It uses a proprietary algorithm containing fixed, weighted ratio of several EEG-based subparameters (including β -ratio, SynchFastSlow, QUAZI, and burst suppression ratio) obtained by time spectral and bispectral analysis of the raw signal to generate its output.¹⁴ It produces a dimensionless number between a 99 and a 0 representing no drug effect noticeable and a maximal hypnotic drug effect, respectively.

qCON

qCON is also a processed frontal EEG parameter index. qCON development has been previously described in detail by Jensen et al.¹⁵ In short, qCON is calculated by feeding in frequency power ratios of 4 different EEG frequencies bands (4–8, 8–13, 11–22, 33–44 Hz) and the burst suppression ratio into a mathematical model called “Quadratic Equation.” It generates an output on a 0–99 scale where decreasing output numbers indicates increasing hypnotic drug effect. The frequency ratios are calculated and updated every second.

PD Modeling of the Concentration-Effect Relation (Direct PD Model)

Nonlinear mixed-effects modeling (NONMEM) was used to study the relation between predicted propofol and remifentanyl C_e s, and BIS and qCON. All models were fitted to the data using the first-order conditional estimation (FOCE) estimation routine in NONMEM (version 7.3; Icon Development Solutions, Hanover, MD).

Model building was guided by the objective function value (OFV). A decrease in the OFV of 3.84 points was considered significant at the 5% level of significance. Goodness-of-fit of the different candidate models was evaluated graphically in R (R Foundation for Statistical Computing, Vienna, Austria).

A sigmoid maximum achievable drug effect (E_{max}) model, as shown in Equation 1, was used to describe the nonlinear relation between BIS or qCON, and the predicted $C_{e,Prop}$ and $C_{e,Remi}$.

$$PD = PD_0 \times \left(1 - \frac{E_{max} \times C_{e,Prop}^{\gamma}}{C_{e,50,INT}^{\gamma} + C_{e,Prop}^{\gamma}} \right) \quad (1)$$

In this model, the PD end point, BIS or qCON, is related to the $C_{e,Prop}$ according to a nonlinear function with γ defining the steepness of the concentration-effect relation. PD_0 is the baseline BIS or qCON when no drug is present, and E_{max} is the maximum drug effect. The effect-site concentration which produces 50% of the maximal drug effect modified by the interaction effect between propofol and remifentanyl ($C_{e,50,INT}$) is the predicted propofol C_e , which

produces 50% of the maximal drug effect. To account for the interaction between remifentanyl and propofol, a hierarchical interaction model as shown in Equation 2 was used.

$$Ce_{50,INT} = Ce_{50} \times \left(1 - \frac{POT_{max} \times C_{e,Remi}^{\gamma_R}}{Ce_{50,Remi}^{\gamma_R} + C_{e,Remi}^{\gamma_R}} \right) \quad (2)$$

In this interaction model, the predicted C_e producing 50% of maximal drug effect ($Ce_{50,INT}$) is composed of the effect-site concentration which produces 50% of the maximal drug effect (Ce_{50}) when propofol is administered alone (Ce_{50}) and an interaction term that describes the influence of remifentanyl on this Ce_{50} . The predicted Ce_{Remi} decreases the propofol Ce_{50} according to a nonlinear function with γ_R defining the steepness of the curve, the maximum influence (potentiation) of remifentanyl on the propofol Ce_{50} (POT_{max}) being the maximum influence of remifentanyl on the $Ce_{50,Prop}$, and $Ce_{50,Remi}$ being the predicted C_e producing half of this maximum potentiation.

To reduce the number of estimable parameters in the models, we assumed a baseline BIS or qCON (PD_0) value of 100 and a maximum propofol drug effect (E_{max}) of 1.

Interindividual variability (IIV) around the population typical parameters was assumed according to a multivariate lognormal distribution with mean 0 and variances ω^2 . Residual unexplained variability (RUV) was described using additive error models.

Quantification of the Model Fit

To quantify the extent of model misspecification on an individual level, we calculated the root mean squared error (RMSE) for every patient in the dataset according to Equation 3.

$$RMSE_k = \sqrt{\frac{\sum_{i=0}^n (PD_{k,i} - IPRED_{k,i})^2}{n}} \quad (3)$$

In this equation, the RMSE for patient k is calculated from all measured PD variables (n) at times i (qCON or BIS) and the individually (post hoc) predicted response according to the model ($IPRED_{k,i}$).

Developing a PD Model to Accommodate for the Hysteresis (Lag-Time PD Model)

Based on the model described previously, we explored strategies to accommodate hysteresis between the predicted propofol and remifentanyl C_e s and the measured BIS or qCON.

The approach consisted of applying a lag-time to the predicted Ce_{PROP} and Ce_{REMI} from the Schnider and Minto model, respectively. For this, we manually fitted the model to different shifted versions of the original dataset, as used before.¹⁶ The time shift implies that

observed qCON and BIS values were matched with a propofol and remifentanyl C_e observed earlier. In other words, a BIS value that was originally observed at time x with a corresponding propofol C_e of y_x and remifentanyl C_e of z_x is matched in the “new” dataset with C_e of $y_{x-\Delta t}$ and $z_{x-\Delta t}$ that were observed at time $x - \Delta t$, with Δt denoting the lag-time. It is noteworthy to appreciate that across the different shifted datasets, the vector of observed qCON or BIS values was identical, that is, nothing changed to the dependent variable. The OFV was used to construct the discrete 3-dimensional (3D) likelihood surface and derive the (approximate) likelihood profiles for both estimated lag-times.

RESULTS

Patients Characteristics

Records from 165 patients were included in the study. Patient demographic data and drug dosing ranges are shown in Table 1. Nine out of 165 patients were male. Mean (standard deviation [SD]) age was 53.1 (15.4), mean weight was 66.8 kg (12.5 kg), and mean height was 159 cm (0.07 cm).

Available Data

For each patient, a median of 2146 [range: 719–4361] predicted Ce_{PROP} concentrations and 2144 [range: 711–4625] predicted Ce_{REMI} were recorded. Also, a median of 3983 [range: 1162–8413] BIS measurements and a median of 3905 [range: 1302–8428] qCON measurements were available. For an overview of the raw Ce_{PROP} , Ce_{REMI} concentrations and BIS and qCON values collected during the study, see Supplemental Digital Content, Figure 1, <http://links.lww.com/AA/D13>. Data from 6 subjects (3.6%) were excluded from the analysis due to errors in the predicted C_e records or the absence of BIS and/or qCON signal. To reduce the computational burden during model development, we reduced the number of BIS and qCON measurements per subject. For this, a random sample was drawn, thereby only retaining one-tenth of the observations. All data were analyzed using R (R foundation for statistical computing, Vienna, Austria) using the “tidyverse” package.¹⁷

Predicted Ce_{PROP} Using the Schnider Model Versus qCON and BIS

As shown in the left panel of Figure 1, there is a considerable clockwise hysteresis in the predicted Ce_{PROP} versus the BIS and the qCON index. Three patients shown are those with the lowest (top), median (middle), and highest (bottom) RMSE for qCON index. The overall median (interquartile range [IQR]) for RMSE for BIS was 9.38 (7.92; 11.23) and for qCON was 8.41 (7.04; 10.2).

Table 2 shows the PD variable estimates for the direct PD model. Ce_{50} was 6.24 $\mu\text{g/mL}$ (8.4 $\mu\text{g/mL}$) for BIS and 8.62 $\mu\text{g/mL}$ (13.9 $\mu\text{g/mL}$) for qCON. γ was 0.75 for BIS and 0.59 for qCON.

Table 1. Patient/Surgical Procedure Characteristics and Drug Dosing Ranges

	Min	q25	Median	q75	Max	Mean	SD
Age, y	16	39	54	67	82	53.1	15.4
Weight, kg	42	58	65	76	119	66.8	12.5
Height, cm	140	155	159	164	176	159	0.07
LBM, kg	32.4	41.7	44.5	47.7	65.4	44.9	4.95
BSA, kg/m ²	1.29	1.58	1.67	1.80	2.19	1.68	0.15
Ce _{prop} , µg/mL	1	2.50	2.8	3.02	4.5	2.81	0.53
Ce _{remi} , ng/mL	1	2.09	2.6	3.01	4.47	2.66	0.65
Length of session, min	22.4	52.6	68.3	89	147	71.7	25.2

Ce_{prop} and Ce_{remi} denote the median predicted Ce for each session.

Abbreviations: BSA, body surface area; Ce, effect-site concentration; Ce_{prop}, effect-site concentration for propofol; Ce_{remi}, effect-site concentration for remifentanyl; LBM, lean body mass; SD, standard deviation.

Figure 1. Hysteresis plots showing the trajectories for BIS (solid black lines) and qCON (solid grey lines) as a function of the predicted effect-site concentration for propofol (Ce). The left plot shows the raw data, whereas the right plot shows the predicted effect-site concentration offset with a lag-time of 53 s (the optimal lag-time as defined by the lag-time PD model for qCON). Patients shown are those with the lowest (top), median (middle), and highest (bottom) RMSE for qCON. Accounting for hysteresis by introducing a lag-time in the model reduces the RMSE for these patients from 17.3, 8.40, and 4.19 to 11.1, 7.1, and 2.87, respectively. The post hoc predicted qCON in the absence of remifentanyl is shown with a solid red line for illustrative purposes. BIS indicates Bispectral index; Ce, effect-site concentration; PD, pharmacodynamic; qCON, qCON index; RMSE, root mean squared error.

Collapsing the Hysteresis Loop With a Lag-Time PD Model

The OFV is lower for the lag-time PD models compared to the direct PD model, suggesting significant hysteresis between the BIS/qCON and the predicted propofol and remifentanyl Ces according to the Schnider model and Minto model, respectively. Based on the data, we decided to evaluate lag-times between 10 and 70 seconds for propofol and between 0 and 300 seconds for remifentanyl. All possible combinations of propofol and remifentanyl lag-times were explored

(ie, the entire discrete 3D surface was sampled). For qCON, we found a lag-time of 53 seconds and 245 seconds for propofol and remifentanyl. For BIS, the lag-time was 49 seconds for propofol and 97 seconds for remifentanyl.

Table 2 shows the estimated PD parameters for the BIS and the qCON direct PD versus lag-time PD model. Compared to the estimates for the direct PD model, we found that estimated Ce₅₀ is lower (3.66 vs 6.24 µg/mL) and the estimated γ is higher (0.90 vs 0.75) in the lag-time model for BIS. Similarly, compared to

Table 2. Estimated Parameters for the Pharmacodynamic Models for BIS and qCON

Parameter	PD Models for BIS			PD Models for qCON		
	Direct Model		Lag-Time Model	Direct Model		Lag-Time Model
LAG _{Prop} , s	Estimate	IIV	Estimate	Estimate	IIV	Estimate
LAG _{Remi} , s	X	X	49	X	X	53
Ce _{50Prop} , µg/mL	6.24 (8.4) [5.21; 7.27]	72% (17.9) [47; 97]	3.66 (5.2) [3.29; 4.03]	8.62 (13.9) [6.27; 11.0]	96% (28.3) [43; 150]	3.62 (4.8) [3.28; 3.96]
Ce _{50Remi} , µg/mL	0.75 (5.4) [0.67; 0.83]	41% (20.1) [25; 57]	0.90 (4.0) [0.83; 0.97]	0.59 (6.7) [0.51; 0.67]	44% (18.3) [28; 60]	0.93 (4.0) [0.86; 1.00]
Ce ₅₀ , ng/mL	0.67 (9.5) [0.54; 0.79]		1.07 (7.9) [0.90; 1.23]	0.56 (13.7) [0.41; 0.71]		0.89 (15.8) [0.61; 1.16]
γ _{Prop}	3.28 (13.0) [2.44; 4.11]		4.16 (20.4) [2.50; 5.82]	2.83 (18.7) [1.79; 3.87]		2.39 (46.0) [0.23; 4.54]
POT _{max}	0.79 (3.1) [0.74; 0.84]		0.60 (4.3) [0.55; 0.65]	0.85 (3.5) [0.79; 0.91]		0.57 (7.7) [0.48; 0.66]
σ _{additive}	9.90 (4.5) [9.02; 10.7]		8.8 (5.7) [7.81; 9.78]	9.1 (5.0) [8.2; 10]		7.7 (7.2) [6.6; 8.8]
OFV	372,870		356,996	365,879		342,808

Numbers between parentheses indicate relative standard errors (%); 95% confidence intervals are shown in square brackets.

Abbreviations: γ, the Hill coefficient representing the steepness of the concentration–response relationship; σ_{additive}, standard deviation of the residual unexplained variability according to the additive error model; BIS, Bispectral index; Ce₅₀, effect-site concentration which produces 50% of the maximal drug effect; IIV, interindividual variability modeled using a lognormal distribution with variance ω; expressed as percentage according to $\sqrt{e^{-1} \times 100\%}$; LAG, lag-time term added to the model(s); OFV, objective function value; POT_{max}, the maximum influence (potentiation) of remifentanyl on the propofol Ce₅₀; qCON, qCON index.

the estimates for the direct model, we found in the lag-time qCON model that Ce₅₀ was lower (3.62 vs 8.62 µg/mL) and the estimated γ was also higher (0.93 vs 0.59). The estimates for the remifentanyl interaction with propofol (POT_{max}, γ_R, and Ce_{50Remi}) are also significantly influenced by the addition of the lag-time in the model. POT_{max} decreases both for BIS from 0.79 to 0.59 and qCON from 0.85 to 0.56 in the lag-time model.

Likelihood profiles, shown in Supplemental Digital Content, Figure 2, <http://links.lww.com/AA/D13>, demonstrate good precision in the estimates for the lag-time. Confidence bounds derived from these profiles would be within ±1 second of the final estimate (as a 1-second change in the estimate increases the OFV with >3.84 points). Implementing the lag-time PD model decreases Ce versus measured drug effect hysteresis. The right part of Figure 1 shows the reduction in the degree of hysteresis for 3 patients, whereas Supplemental Digital Content, Figures 3–4, <http://links.lww.com/AA/D13>, show a boxplot of paired RMSE estimates for all patients in the dataset for qCON and BIS, respectively. The median decrease in RMSE across patients is 20.3% with an IQR of 7.90% to 31.0% for qCON and 11.9% with an IQR of 4.58% to 19.4% for BIS index.

Figure 2. The predicted BIS and qCON as a function of propofol Ce according to the evaluated PD models. Solid lines represent the direct pharmacodynamic models, while dotted lines represent the lag-time models. To keep the trajectories comparable, lag-time model curves were calculated with Ce remifentanyl set to 0 (ie, no potentiation of propofol effect by remifentanyl). Predicted BIS is shown with black lines, whereas grey lines denote predictions for qCON. BIS indicates Bispectral index; Ce, effect-site concentration; PD, pharmacodynamic; qCON, qCON index.

Figure 3. Simulated propofol Schnider effect-site concentrations (Ce) and corresponding qCON and BIS values during a fictitious course of anesthesia. Three distinct anesthesia stages are marked. These are (1) the induction of anesthesia (pump effect-site target set at 4 µg/mL); (2) the reduction of effect-site target nearing the end of a case (pump effect-site target concentration decreased from 4 to 2 µg/mL); (3) the end of anesthesia (pump effect-site target set at 0 µg/mL). Ce values were calculated using the Schnider pharmacokinetic model and k_{e0} of 0.456 min⁻¹. qCON and BIS values were calculated using the direct and lag-time pharmacodynamic models presented in this article. The remifentanyl drug target Ce was set to 0. Simulations were conducted using PKPD tools for an average individual who participated in our study (54 years old, weight: 65 kg, height: 159 cm). Vertical solid lines and vertical dashed lines mark the moment when a steady state is reached for the Ce and for the direct versus lag-time PD model, respectively. BIS indicates Bispectral index; Ce, effect-site concentration; k_{e0} , effect-compartment equilibrium rate constant; PD, pharmacodynamic; PKPD, pharmacokinetic-pharmacodynamic; qCON, qCON index.

Figure 2 shows the predicted concentration–response curves according to the final lag-time model for the BIS index and the qCON. The predicted dose–response lag-time model curves for both indices have nearly identical trajectories.

Finally, Figure 3 shows a simulated course of propofol Ces (Schnider PK model), qCON, and BIS (lag-time model) values during a typical anesthesia session.

DISCUSSION

This study demonstrates that significant hysteresis exists between the Schnider predicted Ces and

measured qCON and BIS. The implementation of an additional lag-time of 53 and 49 seconds for qCON and BIS substantially corrects for this hysteresis. Once hysteresis is accounted for, propofol PDs for BIS and qCON are nearly identical. This finding has important implications in pharmacological research and daily clinical practice.

When constructing a PD model, it is essential to take the monitor-related delay into account. Not accounting for this delay results in unrealistic and monitor-dependent estimates of PD parameters. A PD model, which does not account for the time delay, produced in our study Ce_{50prop} estimates of 6.24 µg/mL for BIS

and 8.62 $\mu\text{g/mL}$ for qCON. These estimates are very divergent, monitor dependent, and much higher than previously reported.¹⁸ Lag-time PD model on the other hand, a model that incorporates the time delay term in the estimation, produced similar and monitor-independent estimates, which are more in line with previously published values. These are 3.66 and 3.62 $\mu\text{g/mL}$ for BIS and qCON, respectively.

Not accounting for monitor-related delay, limits the monitor's usefulness to detect responsiveness and to optimize drug dose in daily clinical practice. Schneider et al¹⁹ investigated the ability of 2 different EEG-based monitors (BIS and patient state index [PSI]) to distinguish responsive from unresponsive patients during the induction and the end of anesthesia, that is, during nonsteady-state pharmacological conditions. They concluded that despite significant differences in mean values, monitors were unable to reliably differentiate these 2 patient categories, due to high degree of variability. This result can, at least partially, be explained by monitor-related latencies. In this study, we have demonstrated that different monitors cause different latencies and that these latencies are not only monitor but also patient dependent. Pilge et al¹⁰ have further demonstrated that monitor-related latencies are also different during increasing and decreasing drug effect. All these factors combined increase the measured drug effect variability at transitions of responsiveness and decrease their value in drug dose optimization.

Several mechanisms could be responsible for the observed monitor-related latencies. First, currently available monitors need varying amounts of time to calculate and signal changing levels of drug effect. EEG signal needs to be acquired and preprocessed before it is ready for processing by an often proprietary algorithm.^{20,21} All these steps take anywhere from 14 to 155 seconds.^{10,22} Because the index algorithms are not publicly accessible, it remains unclear which part of the process is most responsible for the delay.

Age could also contribute to the monitor-related latency. Due to study design constraints and the method of analysis (ie, the estimation of a single population lag-time), this was not explored in this study. Nevertheless, a possible dependency between patient age and the monitor latency might be an interesting topic for future studies.

Further, it is still unknown how to best define the hypnotic drug effect (the target PD variable). Thus, different monitors and propofol PD models use divergent target PD variables to generate results. This inherently leads to poor EEG monitor/PD model synchrony and thus hysteresis. Schnider et al^{8,9} used a canonical univariate parameter (CUP) for propofol to create a propofol PD model. However, this variable has not

found an application in current generation of monitors. Because every PD variable has a unique temporal characteristic of drug action, a PD model optimized using a particular variable will have less than optimal prediction accuracy for different PD variables. This prediction inaccuracy manifests itself as hysteresis.

This study might be criticized because we did not develop a new kinetic-PD model of propofol for these 2 monitors.²³ However, our primary goal was to devise a clinically applicable method of dealing with hysteresis using commercially available TCI and EEG technology. By devising a method to correct the existing PD model of propofol, we developed a method to improve the monitor/TCI pump synchrony without the need to reprogram or replace the existing TCI pumps. Other methods using multiple serial effect-site compartments might have offered other mathematical solutions for the additional monitor-generated hysteresis. However, these methods are mathematically and computationally elaborate, limiting their applicability in TCI systems and drug advisory displays, and, therefore, were not further explored.

Further limitation of this study is that the male:female (M:F) gender ratio is skewed in our dataset. Even though the mixed-effects approach allows for M:F ratio difference, population estimates for Ce_{50} is conditional on this and should thus be interpreted in the light of this M:F ratio.

In conclusion, there is a significant hysteresis between the Schnider predicted propofol Ce_{50} and the achieved drug effect measured by the qCON and the BIS monitors. This hysteresis is caused by the monitor but is independent of the monitor type used. Adding a lag-time of 53 seconds and 49 seconds for qCON and BIS, respectively, corrects for this hysteresis, improving the PD model performance, increasing the "pump-monitor" synchrony, and making the estimates of Ce_{50} for propofol more realistic and more monitor independent. ■

DISCLOSURES

Name: Marko M. Sahinovic, MD, PhD.

Contribution: This author helped with the data analysis and preparation of the manuscript.

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Name: Johannes P. van den Berg, MD.

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Contribution: This author has contributed to the definition of the qCON and qNOX algorithms and the collection of the data.

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