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Relationship between Bispectral Index, electroencephalographic state entropy and effect-site EC_{50} for propofol at different clinical endpoints

M. Iannuzzi[2]*, E. Iannuzzi[1], F. Rossi[2], L. Berrino[2] and M. Chiefari[1]

[1]*Department of Anaesthesiological, Surgical and Emergency Sciences, Second Service of Anaesthesia and* [2]*Department of Experimental Medicine, Second University of Naples, Naples, Italy*

**Corresponding author. E-mail: micheleiannuzzi@libero.it*

Background. State entropy (SE) is a newly available monitor for depth of anaesthesia. We investigated whether the relationship between predicted effect-site propofol concentration and Bispectral Index (BIS) and SE values is useful for predicting loss of verbal contact and loss of consciousness during steady-state conditions.

Methods. Twenty unpremedicated patients undergoing elective major abdominal surgery were recruited. A target-controlled infusion of propofol was administered using Schneider's pharmacokinetic model. The propofol infusion was set at an initial site effect concentration of 1.0 $\mu g\ ml^{-1}$ and increased by 1.0 $\mu g\ ml^{-1}$ steps every 4 min up to 6.0 $\mu g\ ml^{-1}$. A 4-min interval was chosen to ensure that steady-state effect-site concentrations were obtained. Propofol site effect concentrations and BIS and SE values were recorded at loss of verbal contact (LVC) and loss of consciousness (LOC). Population values for predicted effect-site concentrations at the clinical endpoints were estimated and correlated with BIS and SE values.

Results. For LVC, the effect-site concentration for 90% of patients was 1.1 (1.1–3.2) $\mu g\ ml^{-1}$ and for LOC it was 2.8 (2.8–5.65) $\mu g\ ml^{-1}$. LVC occurred in 90% of patients at a BIS value of 70.2 (70.2–90.2) and an SE value of 60.3 (60.3–75.5), and LOC occurred at a BIS value of 38.2 (38.2–70.4) and an SE value of 42.2 (42.2–60.4).

Conclusions. LVC and LOC occurred within a defined range of predicted effect-site concentrations. SE had a smaller range than BIS and greater correlation with effect-site concentration and may be more useful than BIS in predicting both LVC and LOC.

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The concept of minimum alveolar concentration (MAC) for volatile anaesthetics is well known and widely used to clinically ensure that patients receive sufficient anaesthesia to prevent awareness.[1] A similar concept exists for i.v. anaesthetics agents and is referred to as the effective concentration 50 or EC_{50}.[2] It is defined as the concentration of an i.v. anaesthetic at which 50% of patients will not respond to skin incision. This is a clinically useful concept as it is now possible to predict concentrations of propofol in the blood and at the site effect using different pharmacokinetic models.[3 4]

The aim of this study was to determine which value of predicted effect-site propofol concentration, Bispectral Index (BIS) or electroencephalographic state entropy (SE) best predicted loss of verbal contact (LVC) and loss of consciousness (LOC) during steady-state conditions. SE is an alternative approach for assessing depth of anaesthesia which quantifies the degree of spatial and temporal integration of cerebral neuronal activity using entropy principles.[5] A computer-controlled infusion pump which delivers propofol using different pharmacokinetic models and displays the predicted and effect site propofol concentrations is now commercially available (Base Primea; Fresenius-Vial, Brezins, France). We predicted effect-site concentrations of propofol at LVC and LOC and recorded BIS and SE at the same time.

Methods

Twenty patients undergoing elective major abdominal surgery were recruited. The study was approved by the

university ethics committee and all patients gave written informed consent. Exclusion criteria were age <18 or >65 yr, recent administration of sedative or opioid drugs, and impairment of renal, hepatic, cardiac or respiratory function. No sedative or opioid drugs were administered before induction of anaesthesia. All patients had a 16 G and 18 G venous cannula inserted for fluid infusion and anaesthetic drugs administration respectively. Standard monitoring was established. Monitoring for BIS (Xp Version; Aspect Medical Systems, Newton, MA, USA) and EEG SE (Entropy Module; Datex Ohmeda, Helsinki, Finland) was established before drug administration. Sensors were positioned according to the manufacturer instructions.

Target-controlled infusion of propofol was administered using the Base Primea Infusion System, which uses Schneider's pharmacokinetic model.[6] This system displays predicted effect-site concentration (an estimate of the drug concentration at its site of action). The target effect-site concentration of propofol was computed to yield a time to peak effect of 1.6 min,[7] which has been confirmed clinically.[8] The propofol infusion was started to provide an effect-site concentration of 1.0 $\mu g\,ml^{-1}$ and increased stepwise by 1.0 $\mu g\,ml^{-1}$ every 4 min up to 6.0 $\mu g\,ml^{-1}$. A 4-min interval was chosen to assure that steady-state effect-site concentrations were obtained.[9] At each step, an observer assessed the level of sedation using an alertness/sedation scale.[10 11]

BIS, SE and predicted effect-site concentrations and predicted blood concentrations of propofol were recorded at LVC and LOC.

A quantal response model (probit analysis) was used to calculate EC_{05}, EC_{50} and EC_{95} at each endpoint, based on predicted effect-site concentration and the probability of LVC and LOC was calculated using logistic regression. The curves were fitted using the likelihood ratio goodness-of-fit test.

The standard logistic model for propofol concentrations using BIS and SE is:

$$P=C+(1-C)(1/1+e^{-(\beta^0+\beta^1 x1)}),$$

where P is the probability of unconsciousness for predicted effect-site concentration or the probability of consciousness for BIS and SE. C is the initial estimate of the natural response rate, β^0 is the intercept and β^1 is the estimate of the coefficients of the independent variable $x1$ (propofol concentration, BIS or SE).[12]

The ability of BIS and SE to describe LVC and LOC was evaluated using the prediction probability (P_K). P_K represents a measure of performance by which an indicator can predict correctly the rank order of an arbitrary pair of distinct observed anaesthetic depths. An ideal anaesthetic depth indicator is described by a monotonically decreasing or increasing function. The prediction probability P_K has a value of 1 when the indicator predicts the observed anaesthetic depth perfectly and the correlation is positive. P_K has a value of 0 when the indicator predicts the observed anaesthetic depth perfectly and the correlation is negative. P_K has a value of 0.5 when the indicator predicts no better than chance.

Data were computed by the Pk MACRO datasheet for Microsoft Excel. Analysis was performed with SPSS Software Version 10.1 for Windows XP and GraphPad Prism Software Version 6.0 for Windows XP (GraphPad Software Inc., San Diego, CA, USA).

Results

Twenty patients (10 male), with mean age 39.8 (range 19–65) years, height 166.5 (8.3) cm and weight 71.6 (14.2) kg, were studied.

Induction of anaesthesia was smooth in all cases, although six patients (30%) reported pain during injection of propofol. Haemodynamic variables remained stable and no significant hypotension occurred. Heart rate, mean arterial blood pressure and Sa_{O_2} were recorded at baseline, LVC and LOC (Table 1).

At baseline, before any drug administration, BIS and SE values (mean (SD) (range)) were respectively 96.15 (1.9) (91–98) and 90.95 (0.8) (88–93). At the time of LVC, the effect-site EC_{05}, BIS and SE were 1.1 $\mu g\,ml^{-1}$ (1.04–1.15), 90.2 (85.7–94.7) and 75.5 (72.5–78.5) respectively; the effect-site EC_{50}, BIS and SE were 2.2 $\mu g\,ml^{-1}$ (2.09–2.31), 81.4 (77.3–85.4) and 71.7 (68.1–75.2) respectively; and the effect-site EC_{95}, BIS and SE were 3.2 $\mu g\,ml^{-1}$ (3.04–3.36), 70.2 (66.6–73.7) and 60.3 (58.3–63.3) respectively.

At the time of LOC, the effect-site EC_{05}, BIS and SE were respectively 2.8 $\mu g\,ml^{-1}$ (2.66–2.94), 70.4 (66.8–73.9), 60.4 (57.3–63.4); the effect-site, BIS and SE were respectively 4.14 $\mu g\,ml^{-1}$ (3.94–4.34), 59.7 (56.7–65.6), 50.3 (47.7–52.8); the effect-site EC_{95}, BIS and SE were 5.65 $\mu g\,ml^{-1}$ (5.37–5.93), 38.2 (36.2–40.1) and 42.2 (40.1–43.3).

No gender differences were observed at any endpoint, either for BIS or SE ($\chi^2 \geqslant 0.05$).

The ability of the indicators to predict LVC and LOC are presented as P_K values. The P_K values of BIS for LVC and LOC were 0.90 (0.02) and 0.82 (0.13) respectively and those of SE for LVC and LOC were 0.95 (0.04) and 0.94 (0.03). P_K values did not differ significantly (Fig. 1). Good correlations between BIS and the predicted effect-site concentration of propofol (r^2=0.771) and between SE and the predicted effect-site concentration of propofol (r^2=0.844) were noted.

Table 1 Cardiovascular and respiratory data. Mean (SD). *P<0.001 (Student's t-test)

	Baseline	Loss of verbal contact	Loss of consciousness
Heart rate (beats min^{-1})	82.1 (14.1)	80.2 (10.4)	75.4 (11.2)
Mean arterial pressure (mm Hg)	90.5 (12.2)	82.2 (8.2)	72.3 (8.5)*
Sa_{O_2} (%)	98.1 (1.1)	97.8 (1.0)	98.1 (0.8)

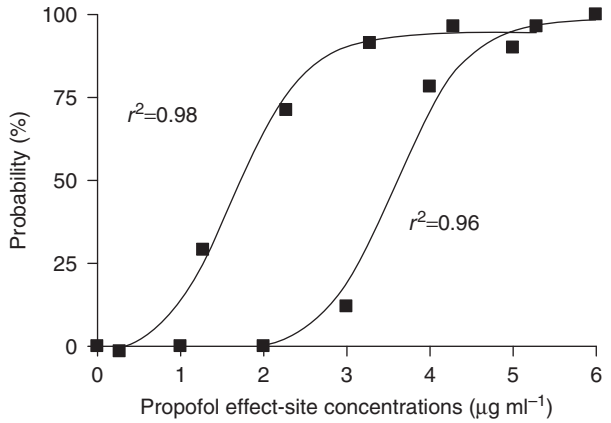

Fig 1 Predicted effect-site concentrations of propofol (μg ml^{-1}) *vs* probability of loss of verbal contact (left) and probability of loss of consciousness (right).

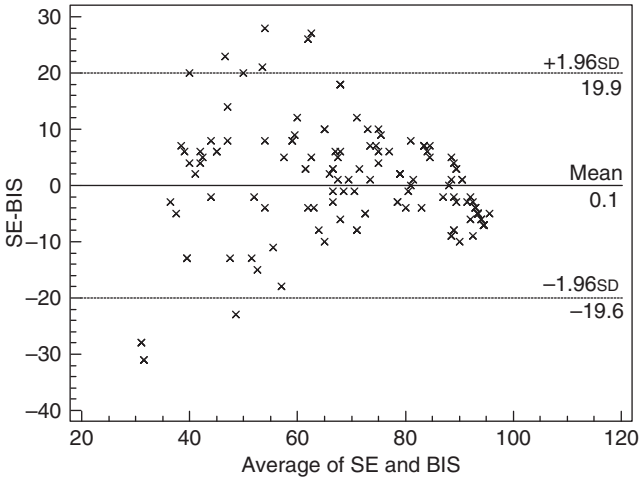

Fig 2 Bland and Altman analysis of the relationship between SE and BIS scores.

A Bland–Altman plot was used to compare the two measurement systems. SE and BIS showed good comparability (mean difference 0.1). The upper and lower limits of agreement were 19.9 and 19.6. BIS and SE differed by more than 20% only in six cases over 140 measurements (4.3%) (Fig. 2).

Discussion

We wished to investigate whether predicted effect-site propofol concentrations and values of SE and BIS are useful for predicting LVC and LOC.[13] Awareness is a danger when neuromuscular blocking agents are used because the most important sign of awareness, patient movement, is abolished. Anaesthetists have used the concept of MAC to ensure they are delivering sufficient volatile anaesthetic to the patient to ensure unconsciousness. The EC_{50} is a concept analogous to MAC and can be an estimate of how much i.v. drug needs to be administered to obtain an effect in 50% of the population.[14] Unfortunately, unlike volatile agents, drug concentrations cannot be measured in real time but a prediction can be made using pharmacokinetic models. Equilibration of the effect-site with blood concentration takes four to five times the k_{eo} half-life [$T_{1/2}(k_{eo})$], where $T_{1/2}$ (k_{eo})=0.693/k_{eo}. We used Schneider's pharmacokinetic model, which uses a k_{eo} of 0.45 min^{-1}, resulting in a time to peak effect of 1.6 min and an effect-site steady-state concentration in approximately 4 min.[9] A pharmacokinetic model widely used in target-controlled infusion anaesthesia uses a k_{eo} of 0.2 min^{-1} and would take around 15 min for blood and effect-site concentrations to equilibrate.[15] We believe that the ability to clearly display the effect-site concentration should be an integral part of any target-controlled infusion system and that during induction and recovery the predicted effect-site concentration is a more useful clinical correlate than predicted blood concentration.[16] For LOC the effect-site concentration that included 90% of patients was 3.2 μg ml^{-1} and for loss of consciousness it was 5.65 μg ml^{-1}. Although the range of predicted blood concentrations is useful in the assessment of whether a patient will be unconscious, neither the MAC nor the predicted concentration range guarantees lack of awareness.

Two previous studies[12,17] have evaluated the relationship of predicted effect-site propofol concentrations to clinical endpoints. They tested Caucasian and Chinese populations and found similar results. The EC_{50} for effect-site propofol concentration at LOC was 2.8 and 2.7 μg ml^{-1} in the Caucasian in Chinese populations respectively and the EC_{95} was 4.1 and 3.8 μg ml^{-1}. These two studies found large differences in the predicted blood concentrations because of the different rates at which propofol was given in the two studies. However, the predicted effect-site values were similar in the two studies. We believe that this reinforces the value of the effect-site rather than the blood concentration in determining the pharmacodynamic effects of propofol in the individual patient. In our study, we tried to achieve a steady-state concentration of propofol at the effect site, to better determine the pharmacodynamic effects in the individual. We also believe that in our study the higher EC_{90} values for loss of consciousness were due to the achievement of steady-state conditions and the pharmacokinetic model we used.

For a cerebral monitor to be reliable in assessing the depth of anaesthesia, it should display a strong correlation between the observed variable (e.g. BIS, SE) and the patient's state of consciousness, independent of the anaesthetic drugs and with minimal interpatient variability. In a recent editorial, Kalkman and Drummond[18] suggested that these conditions have not yet been achieved with any of the available cerebral monitoring devices.

In this study, LVC occurred in 90% of patients at a BIS value of 70.2 (70.2–90.2) and an SE value of 60.3 (60.3–75.5) and LOC at a BIS value of 38.2 (38.2–70.4) and an SE value of 42.2 (42.2–60.4). The range for SE is

smaller than that of BIS, and SE showed a better correlation with propofol predicted–site concentrations (r^2=0.84).

In this small study using a specific anaesthetic technique and pharmacokinetic model, SE appeared to be more useful than BIS in predicting both LVC and LOC. However, further studies using the SE monitor in larger surgical populations are needed to determine its future role in clinical practice.

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