ORIGINAL ARTICLE

Relationship between A-line Autoregressive Index, Spectral Entropy and steady state predicted site-effect effective concentrations at 05-50-95 of propofol at different clinical endpoints

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ABSTRACT

Aim. Target controlled infusion intravenous anesthesia is a growing phenomenon. Nowadays, many anesthesiologists feel the need to monitor depth of anesthesia during total intravenous anesthesia, even though it is not a standard technique worldwide. Spectral Entropy (SE) is a relatively new depth of anesthesia index. The aim of this study was to investigate whether predicted site-effect propofol concentrations, A-line Autoregressive Index (AAI) and SE values are useful for predicting loss of verbal contact (LVC) and loss of consciousness (LOC) during steady-state conditions.

Methods. Forty-four patients scheduled for elective major abdominal surgery were recruited. All patients were unpremedicated. A target controlled infusion of propofol was administered using Schnider's pharmacokinetic model. The initial propofol infusion provided a site-effect concentration of 1.0 mcg mL^{-1}, and was increased stepwise by 1.0 mcg mL^{-1} every 4 minutes until the concentration reached 6.0 mcg mL^{-1}. A 4 minute interval was chosen to assure that steady state site-effect concentrations were obtained. AAI, SE and propofol site-effect concentrations were recorded when LVC occurred and also when LOC occurred. Population values for predicted site-effect concentrations at the clinical endpoints were estimated and correlated with AAI and SE values.

Results. In our study for LOC the effect-site concentration to include 90% of patients was 5.85 ?mcg mL^{-1} (5.70-5.90) and 3.4 mcg mL^{-1} (3.24-3.60) for LVC. In this study, 90% of patients lost verbal contact at an AAI value of 68 (64.6-71.4) and an SE value of 68.2 (66.2-70.2). LOC occurred in 90% of patients at an AAI value of 39.2 (37.2-41.1) and an SE value of 40.2 (38.1-41.3).

Conclusion. LOC and LVC occur within a defined range of predicted site-effect concentrations. More emphasis should be given to site-effect concentrations. SE and AAI have similar values at different endpoints and similar correlation with Ceprop. AAI and SE are both useful tools in predicting both LVC and LOC.

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Key words: Propofol - Anesthesia, intravenous - Unconsciousness.

Nowadays many anesthesiologists feel the need to monitor depth of anesthesia during total intravenous anesthesia, even though it is not a standard technique worldwide. The A-line Autoregressive Index (AAI) and the Spectral Entropy (SE) are two commercially available indexes of anesthetic depth widely used in clinical practice. The A-line ARX Index (AAI) is an adaptive

method for extracting MLAEP from the electroencephalogram using an autoregressive model with exogenous input. This technology is incorporated in the A-line System (A-line Monitor; Alaris Medical System Inc., San Diego, CA, USA). SE is an alternative approach for assessing depth of anesthesia that quantifies the degree of spatial and temporal integration of cerebral neuronal activity using entropy principles.

The time-honored concept of minimum alveolar concentration (MAC) for volatile anesthetics is widely used to clinically ensure that patients are receiving sufficient anesthesia to prevent awareness.[1]

A similar concept exists for intravenous anesthetic agents and is referred to as the effective concentration 50 or EC50.[2] It is defined as the concentration of an *i.v.* anesthetic at which 50% of patients will not respond to skin incision. This concept 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 the study was to determine which value of predicted site-effect propofol concentrations, AAI or SE, best predicts two different clinical endpoints: loss of verbal contact (LVC) and loss of consciousness (LOC) during steady-state conditions.

Materials and methods

Forty-four patients undergoing elective major thoraco-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, recent administration of sedative or opioid drugs, and renal, hepatic, cardiac or respiratory function impairment. No sedative or opioid drugs were administered before induction of anesthesia. All patients had a 16 G and an 18 G venous cannula inserted in the forearm for fluid infusion and anesthetic drug administration, respectively. Standard monitoring was established. Monitoring for AAI and EEG State Entropy was established before drug administration, and sensors were positioned according to the manufacturer's instructions.

The AAI (AEP/2 version) from the MLAEP was calculated using the A-line® monitor (Danmeter A/S, Odense, Denmark). The AAI value ranges from 100 to 0. The MLAEPs were elicited with a bilateral click stimulus of 70-dB intensity and 2-ms duration. Three electrodes (A-line® AEP electrodes; Danmeter A/S) were positioned at the mid forehead (+), left forehead (reference), and left mastoid (-). The MLAEP are automatically extracted using a short moving-time average technique together with an ARX model.

SE was calculated using the M-ENTROPY module (Datex-Ohmeda Inc., Madison, WI, USA). The SE value ranges from 91 to 0. Entropy values were derived from the frontal electroencephalogram and electromyogram using three electrodes. SE is computed over the frequency range from 0.8 to 32 Hz. It includes the electroencephalogram-dominant part of the spectrum. The time windows for SE are chosen optimally for each particular frequency component and range from 60 to 15 s.

The SE is a relatively new approach for assessing depth of anesthesia that quantifies the degree of spatial and temporal integration of cerebral neuronal activity using entropy principles.[5]

A target controlled infusion of propofol was administered using the Base Primea Infusion System (Fresenius-Vial) according to Schnider's pharmacokinetic model.[6] This system displays predicted site-effect concentrations (estimates of the drug concentration at its site of action). The target site-effect concentration of propofol was computed to yield a time to peak effect [4] of 1.6 min as published by Schnider [7] and clinically confirmed by Struys.[8] The initial propofol infusion was to provide a site-effect concentration of 1.0 mcg mL^{-1}, and it was increased stepwise by 1.0 mcg mL^{-1} every four minutes until the concentration reached 6.0 mcg mL^{-1}. A four minute interval was chosen to assure that steady state site-effect concentrations were obtained.[9] At each step, the Observer's Assessment of Alertness/Sedation Scale was performed to clinically measure the level of sedation.[10, 11]

AAI, State Entropy and propofol predicted site-effect concentrations were recorded when both loss of verbal contact and LOC occurred. All patients received 100% oxygen during the study.

Statistical analysis

A quantal response model (probit analysis) was used to calculate EC05, EC50, and EC95 at each end-point based on predicted site-effect concentrations, 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 with AAI and SE is the following: $P=C+(1-C)(1/1+e^{-(\beta o+ \beta 1x1)}$ where P is the probability of unconsciousness for predicted site-effect concentration or the probability of consciousness for AAI 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 x^1 (propofol concentration, AAI or SE).[12] The ability of AAI and SE to describe LVC and LOC was evaluated using prediction probability (P_κ). P_κ represents a measure of performance by which an indicator correctly predicts the rank order of an arbitrary pair of distinct observed anesthetic depths. An ideal anesthetic depth indicator is described by a monotonic decreasing or increasing function. The prediction probability P_κ has a value of 1 when the indicator predicts the observed anesthetic depth perfectly and the correlation is positive. P_κ has a value of 0 when the indicator predicts the observed anesthetic depth perfectly and the correlation is negative. P_κ has a value of 0.5 when the indicator predicts the outcome no better than chance. For each electroencephalographic measure of anesthetic drug effect, we calculated the prediction probability (P_κ) developed by Smith *et al.*[13] P_κ was calculated using the P_κ Macro Sheet (Excel-Windows).

A sample size of 44 was determined by a power analysis based on the following assumptions: 1) a five-point variation of SE, AAI would be clinically significant; 2) alpha=0.05; d) beta=0.1.

Data analysis was performed with SPSS Software Version 10.1 Windows XP and GraphPad Prism Software Version 6.0 Windows XP.

Results

Forty-four patients were studied. The demographic data are as follows: 20 male/24 female, 18 ASA I / 26 ASA II, age (years) 48.7±10.6, height (cm) 165.3±7.1, BMI (kg/m^2) 23±2.5.

TABLE I.—*Cardiovascular and respiratory data.*

	Baseline	Loss of verbal contact	Loss of consciousness
Heart rate (bpm^{-1})	77.3 (9.1)	82.2 (8.4)	78.4 (7.2)
Mean arterial pressure (mmHg)	80.5 (9.2)	84.6 (6.4)	76.3 (5.5)*
SaO_2 (%)	98.5 (1.1)	99.0 (1.0)	99.1 (0.8)

Mean (SD) . *P<0.001 (Student's t-test).

Induction of anesthesia was smooth in all cases, although 14 patients (34%) reported burning pain during injection of propofol. Hemodynamic parameters remained stable despite a non-clinically significant decrease in mean arterial pressure; no clinically important hypotension occurred. Heart rate, mean arterial blood pressure and oxygen saturation were recorded at baseline, when LVC occurred and at LOC (Table I).

At baseline before any drug administration, AAI and SE values were 97.2±1.3 (95-98) and 91.00±0.8 (89-92), respectively.

When LVC occurred the site-effect EC05, AAI and SE were 1.2 mcg mL^{-1} (1.1-1.2), 84.2 (81.7-86.7), and 79.5 (76.5-82.5), respectively; the site-effect EC50, AAI and SE were 2.3 mcg mL^{-1} (2.2-2.4), 73.4 (70.0 -76.8), and 71.2 (68.2-74.2), respectively; the site-effect EC90, AAI and SE were 3.4 mcg mL^{-1} (3.2-3.6), 68 (64.6-71.4), 68.2 (66.2-70.2), respectively.

When LOC occurred the site-effect EC05, AAI and SE were 2.95 mcg mL^{-1} (2.8-3.1), 70.4 (67.4-73.8), and 68.4 (64.2-72.6), respectively; the site-effect EC50, AAI and SE were 4.2 mcg mL^{-1} (4.0-4.3), 58.4 (53.4 - 62.4), and 52.3 (49.7-54.8), respectively; the site-effect EC90, AAI and SE were 5.9 mcg mL^{-1} (5.7-5.9), 39.2 (37.2- 41.1) 40.2 (38.1-41.3), respectively. No gender differences were observed in any of the endpoints either for AAI or SE ($\chi^2 \geq 0.05$). The ability of the indicators to predict LVC and LOC are presented as P_κ values. The P_κ's of AAI for LVC and LOC were 0.86 (0.03) and 0.84 (0.01), respectively, while the P_κ values of SE for LVC and LOC were 0.93 (0.04) and 0.91 (0.03), respectively. P_κ values did not differ significantly.

The probabilities of LVC and LOC *versus* pre-

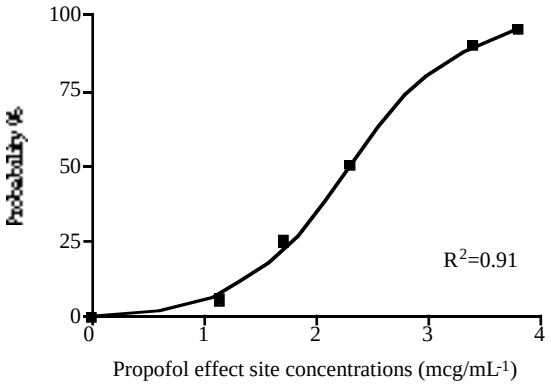

Figure 1.—Predicted site-effect concentrations of propofol (mcg mL^{-1}) *vs.* probability of LVC.

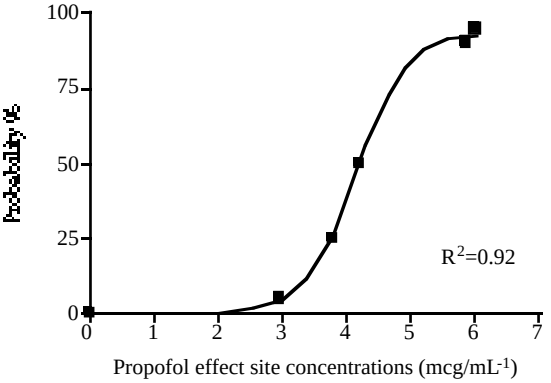

Figure 2.—Predicted site-effect concentrations of propofol (mcg mL^{-1}) *vs.* probability of LOC.

dicted site-effect propofol concentrations are shown in Figures 1, 2.

Good correlation was found between AAI and propofol predicted site-effect concentrations (r^2=0.77) and correlation between SE and propofol predicted site-effect concentrations well (r^2=0.88).

Bland-Altman plot was used to compare the two measurement systems. SE and AAI showed good comparability (mean difference: 2.1). The upper and lower limits of agreement were 26.9 and 31.1, respectively. AAI and SE differed by more than 20% only in eight cases of over 140 measurements (5.7%) (Figure 3).

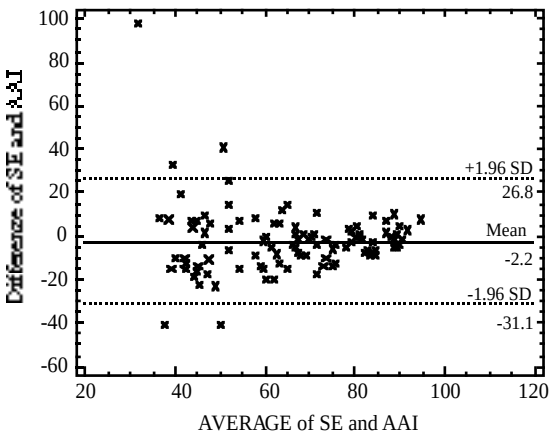

Figure 3.—Bland Altman analysis.

Discussion

The aim of the study was to investigate whether predicted site-effect propofol concentrations and values of SE and AAI are useful in 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. Anesthesiologists have used the concept of MAC to ensure they are delivering sufficient volatile anesthetic to ensure patient unconsciousness. The EC50 is a concept analogous to MAC and can be an estimate of how much intravenous 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 they can be predicted by using pharmacokinetic models. Equilibration of the site-effect with the 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 Schnider'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 a site-effect steady state concentration in approximately four minutes.[9] A pharmacokinetic model widely used in target controlled infusion anesthesia uses a k_{eo} of 0.2 min^{-1} and would take approximately 15 minutes for blood and site-effect concentrations to equilibrate.[15]

We believe that the ability to clearly display site-effect concentration should be an integral part of any TCI system and that during induction and recovery predicted site-effect concentrations are clinically more useful than predicted blood concentrations.

For LVC the value of site-effect concentrations to include 90% of patients was 3.4 mcg mL^{-1} and 5.9 mcg mL^{-1} for LOC . Although the range of predicted blood concentrations is useful in the assessment whether a patient is unconscious, neither the MAC nor the predicted concentration range guarantees lack of awareness. A previous study [16] compared the behavior of two calculations of electroencephalographic spectral entropy, SE and response entropy (RE) with the AAI and the Bispectral Index (BIS) as measures of anesthetic drug effects. They compared the measures for baseline variability, burst suppression, and prediction probability. They also developed pharmacodynamic models relating SE, RE, AAI, and BIS to the calculated propofol site-effect concentration (Ceprop). Although all within the acceptable range, prediction probability and individualized Spearman's rank correlation were highest for BIS, lower for AAI and the lowest for SE.

In our study, we tried to achieve a steady-state concentration of propofol in the site-effect, which was not reached in the previous study, to better determine the pharmacodynamic effects in the individual. We believe that in our study higher EC90 values for LOC are due to the fact that our study was conducted in steady state conditions, while previous data [12, 17] were collected in non-steady state conditions. Furthermore, in our study Schnider's pharmacokinetic model was used, while other authors have used Marsh's pharmacokinetic model. For a cerebral monitor to be reliable in assessing the depth of anesthesia, it should display a strong correlation between the observed variable (*e.g.*, SE, AAI) and the patient's state of consciousness, with no correlation with the anesthetic drugs and with minimal patient intervariability. In a recent editorial, Kalkmann and Drummon [18] suggested that these conditions have not yet been achieved with any of the available cerebral monitoring devices.

In our study for LOC the value of effect-site concentrations to include 90% of patients was 5.85 mcg mL^{-1} (5.70-5.90) and 3.4 mcg mL^{-1} (3.24-3.60) for LVC. In this study 90% of patients lost verbal contact at an AAI value of 68.2 (64.6.-71.4) and an SE value of 68.2 (66.2-70.2). LOC occurred in 90 % of patients at an AAI value of 39.2 (37.2-41.1) and at an SE value 40.2 (38.1-41.3). The range of SE is similar to the range of AAI, but SE showed a higher correlation with propofol predicted-site concentrations; thus AAI and SE are both useful in predicting LVC and LOC.

This study has some limitations: it was done on a small specific population and uses a specific anesthetic technique and pharmacokinetic model that do not reproduce the general anesthesia population. SE and AAI appeared to be comparable 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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