Enhancing a sedation score to include truly noxious stimulation: the Extended Observer’s Assessment of Alertness and Sedation (EOAA/S)

T. K. Kim¹,², P. J. Niklewski³,⁴, J. F. Martin², S. Obara¹,⁵ and T. D. Egan¹,*

¹Department of Anesthesiology SOM 3C444, University of Utah School of Medicine, 30 North 1900 East, Salt Lake City, UT 84132, USA, ²Department of Anesthesia and Pain Medicine, Pusan National University, Busan, Korea, ³Ethicon Endo-Surgery, Inc., 4545 Creek Road, Cincinnati, OH, USA, ⁴Department of Pharmacology and Cell Biophysics, College of Medicine, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267, USA, and ⁵Department of Anesthesiology, Fukushima Medical University School of Medicine, 1 Hikariga-oka, Fukushima 960-1295, Japan

*Corresponding author. E-mail: talmage.egan@hsc.utah.edu

Abstract

Background: Although the Modified Observer’s Assessment of Alertness and Sedation (MOAA/S) is frequently used in sedation-related drug and device studies, a major shortcoming is that it does not differentiate between lighter and deeper levels of general anaesthesia because the only noxious stimulus of the MOAA/S is a trapezius squeeze. The primary aim of this investigation was to expand the MOAA/S score to include truly noxious stimulation, thereby extending the dynamic range of the assessment to include sedation states consistent with deeper levels of general anaesthesia.

Methods: Twenty healthy volunteers received target controlled infusions of fentanyl (target = 0.8 ng ml⁻¹) and propofol (starting at 0.5 µg ml⁻¹ and gradually increasing to 5 µg ml⁻¹). At each propofol concentration, a MOAA/S score was obtained before and after tetanic electrical stimulation. The tetanic electrical stimulation current was gradually increased until the subject responded or until 50 mA was delivered without a response. A pharmacodynamic model was constructed to characterize the concentration–effect relationship between propofol and the MOAA/S scores.

Results: All subjects required a significantly higher propofol concentration to produce unresponsiveness to tetanic electrical stimulation at 50 mA compared with a standardized trapezius squeeze. The pharmacodynamic model adequately characterized the concentration–effect relationship.

Conclusions: The Extended Observer’s Assessment of Alertness and Sedation (EOAA/S) extends the range of the widely used MOAA/S score to include truly noxious stimulation, thereby enabling the identification of drug-induced central nervous system depression representative of surgical anaesthesia.

Key words: anaesthetics i.v., propofol; sedation; sedation scale

In the sedation literature, general anaesthesia is sometimes considered as an all-or-nothing state for the purpose of assessing the patient risk associated with deeper-than-intended sedation.¹ ² However, anaesthetists have long appreciated that general anaesthesia represents a spectrum of central nervous system depression ranging from ‘light’ anaesthesia to much ‘deeper’ levels. In the early days of modern anaesthetic practice, progressively deeper planes of anaesthesia, as reflected in findings on clinical
Editor’s key points
• The MOAA/S is a six-point sedation scale commonly used to assess sedation.
• It has one level corresponding to unconsciousness (absence of response to trapezius squeeze).
• The authors have extended the scale to test responsiveness also to a standardized tetanic stimulus.
• They show that this stimulus can detect a deeper level, more representative of surgical anaesthesia.

examination, were described in association with increasing doses of ether. Since then, numerous other investigators have demonstrated that general anaesthesia is indeed a continuum of central nervous system depression that can be related to the concentration of the anaesthetic agents.

The Modified Observer’s Assessment of Alertness and Sedation (MOAA/S) scale is frequently used in sedation-related drug and device studies to assess a subject’s level of sedation. The MOAA/S scale has been aligned with the ASA continuum of sedation. The MOAA/S ranges from 0 to 5, with a score of 5 defined as awake or minimally sedated, and a score of 0 defined as general anaesthesia. A major shortcoming of the MOAA/S as it has often been implemented is that it does not differentiate between lighter and deeper levels of general anaesthesia. Given that the noxious stimulus of the MOAA/S has typically been a trapezius muscle squeeze, the method can only identify when a subject has become unresponsive to a mildly painful stimulus. The transition to deeper levels of central nervous system depression wherein a subject would be unresponsive to more noxious stimulation (e.g. skin incision, tracheal intubation) cannot be determined.

From a methodological perspective, this is an important limitation of the MOAA/S scale when applied to sedation drug and device development studies because respiratory complications associated with sedation practice, such as airway obstruction and apnoea, are expected to be more likely when deeper levels of anaesthesia are produced (i.e. ‘deeper-than-intended’ sedation states are used as a surrogate safety signal in these studies). Another problem associated with the current MOAA/S methodology is that there is likely to be considerable variability from assessor to assessor in terms of the noxiousness of the trapezius squeeze (i.e. it is a subjective assessment).

A potential solution to this shortcoming of the MOAA/S is to expand the method by including a truly noxious stimulus, thereby increasing the dynamic range of the assessment to include a painful stimulus more typical of surgical procedures. To be useful as an experimental tool, the more noxious stimulus should be non-invasive, objective, and quickly repeatable. Tetanic electrical stimulation (TES) to a level of 50 mA is a suitable candidate for this purpose.

The primary aim of this investigation was to assess the feasibility of expanding the MOAA/S score to include truly noxious stimulation (TES at 50 mA), thereby extending the dynamic range of the assessment to include clinical states more representative of deeper general anaesthesia. We refer to this new sedation score as the Extended Observer’s Assessment of Alertness and Sedation (EOAA/S); this new sedation score is intended for use in sedation-related drug and device development studies; it is not intended as a clinical tool in the care of patients. A secondary aim was to assess the effect of noxious electrical stimulation on the sedation state as assessed by the processed EEG (and the MOAA/S). We hypothesized that producing central nervous system depression with propofol sufficient to render the subject unresponsive to TES at 50 mA would require propofol concentration targets significantly higher than those needed to produce unresponsiveness to trapezius squeeze. In addition, we hypothesized that noxious stimulation would shift the concentration–effect relationship to the right, requiring higher propofol concentrations to produce a given state of sedation.

Methods

Data gathering

After institutional approval and written informed consent, 20 normal healthy (ASA I and II) adult male and female volunteers, as indicated by medical history and a physical examination, were enrolled. Inclusion criteria included BMI between 18 and 29 kg m⁻², age between 18 and 55 yr, uncomplicated airway anatomy, and a negative drug screen.

A 20 gauge venous catheter was placed in an upper extremity vein under local anaesthesia (lidocaine 1%, 0.2 ml) for the purpose of fluid and drug administration. A continuous i.v. infusion of sodium chloride 0.9% was started at 50 ml h⁻¹. Infusions of fentanyl and propofol were given into this peripheral venous line. Subjects were instrumented with physiological safety monitors that included a continuous ECG, automated blood pressure cuff, pulse oximeter, and expired capnograph. Oxygen, beginning at 2 liters min⁻¹, was delivered via nasal cannula as necessary to maintain oxygenation at acceptable levels. Additional instrumentation for pharmacodynamic assessments included a Bispectral Index (BIS; Covidien, Mansfield, MA, USA) electrode on the forehead and two surface ECG electrodes placed 5 cm apart at the posterior tibial nerve immediately posterior to the medial malleolus (after prepping the skin with isopropyl alcohol) to deliver TES. The posterior tibial nerve was selected because it is accessible, out of the way of most procedures, and has an easily visible motor response to verify the flow of current.

Baseline vital signs, safety monitoring signals, BIS and TES values, and MOAA/S measurements were obtained before commencement of the fentanyl and propofol infusions. After recording of the baseline measurements, subjects received a target controlled infusion (TCI) of fentanyl targeting an effect-site concentration of 0.8 ng ml⁻¹ throughout the study using the kinetic model reported by Shafer and colleagues. The fentanyl target concentration was based on pharmacokinetic simulations of typical dosing schemes used for endoscopic procedural sedation when fentanyl is used in combination with propofol (assuming a single bolus dose of 75 µg in a male, age 60 yr, weight 85 kg, and height 180 cm). The TCI was implemented using the Stanpump software (http://www.opentci.org/doku.php?id=code:code accessed November 13, 2014).

A TCI infusion of propofol was then initiated beginning at an effect-site target of 0.5 µg ml⁻¹ and increased in steps of 0.25 µg ml⁻¹ using the kinetic model reported by Schnider and colleagues. At each pseudo-steady-state target concentration pair for propofol and fentanyl, pharmacodynamic assessments were made (see Supplementary data, Figure S1). Observers waited for 5 min after the TCI system had achieved the targeted effect-site concentration before beginning the assessments. The data gathering proceeded in a fixed sequence. First, a resting BIS value was recorded. Next, the MOAA/S score was obtained. Then, TES was initiated, increasing the current until the subject responded (see details below) or until 50 mA was delivered without a response. Finally, to assess the influence of stimulation on the subject’s level of sedation, a ‘post-TES’ BIS and MOAA/S were...
obtained; the post-TES BIS was defined as the maximal BIS in the first 90 s after TES was completed. The escalation in propofol target concentration increased until the subject was unresponsive to 50 mA TES at two consecutive propofol targets.

The continuum of sedation was measured clinically with the MOAA/S. The currently used MOAA/S scale was expanded to include a ‘0e’ score, defined as no response to 50 mA electrical stimulation (in addition to the ‘0e’ score for no response to trapezius squeeze, now referred to as ‘01’). Our Expanded Observer’s Assessment of Alertness and Sedation score (see Table 1) thus ranges from 0e to 5, with 5 defined as being awake or minimally sedated, and 0e defined as being at the deepest level of sedation (unresponsive to electrical stimulation, or ‘deeper’ general anaesthesia). The MOAA/S assessment included a trapezius squeeze and TES only if the patient was non-responsive to verbal anaesthesia. If none of these pain-avoidance behaviours occurred, the current was increased by 5 mA every 5 s. Electrical current was delivered using a Digi-Stim II nerve stimulator device (Neuro Technology, Houston, TX, USA). The current was increased until the subject was aroused and requested that the current be stopped or the subject exhibited pain-avoidance behaviour, such as withdrawal of the extremity, a facial grimace, or a verbal groan. If none of these pain-avoidance behaviours occurred, the current was increased until a maximal value of 50 mA was delivered for 5 s. With each assessment, the specific response to TES was recorded and categorized as purposeful (i.e. attempting to push the stimulus away), non-purposeful (i.e. reflex withdrawal, facial grimace, or groan), or none.

For the TES, starting with a current of 0 mA, the ’tetanus’ current was increased by ∼5 mA every 5 s. Electrical current was delivered using a Digi-Stim II nerve stimulator device (Neuro Technology, Houston, TX, USA). The current was increased until the subject was aroused and requested that the current stop or the subject exhibited pain-avoidance behaviour, such as withdrawal of the extremity, a facial grimace, or a verbal groan. If none of these pain-avoidance behaviours occurred, the current was increased until a maximal value of 50 mA was delivered for 5 s. With each assessment, the specific response to TES was recorded and categorized as purposeful (i.e. attempting to push the stimulus away), non-purposeful (i.e. reflex withdrawal, facial grimace, or groan), or none.

The data were analysed using a naïve pooled data approach implemented with NONMEM version 7.2 (Globomax LLC, Hanover, MD, USA). In standard mixed-effects modeling, the treatment of interindividual variability in C50,s would often be modelled as a log-normal distribution about the typical estimates of C50,s for individuals at each sedation score:

\[ P(\text{sedation score} = s) = P_s = P_{5,s} - P_{0,s} \] (2)

where \( P_s \) is the probability of a given level of EOAA/S score to be equal or less than \( s \) (i.e. ‘deeper’ level of sedation than \( s \)), \( P_{5,s} \) is the predicted concentration of propofol in the effect site, \( C_{50,s} \) is the steady-state effect-site concentration associated with 50% probability, and \( \gamma \) is the steepness of the probability vs concentration curve. The value of \( \gamma \) was considered the same for all the sedation scores. In every step, after checking the tolerable electrical stimulation, the changed \( C_{50,s} \) is modelled as \( C_{50,s} \times STIM \), where STIM is the electrical stimulating effect which can increase the \( C_{50,s} \). The STIM effect is considered constant for all the EOAA/S scores. For the 0e, however, STIM was not modelled because 0e is the last score for which the electrical intensity is maximum.

Applied to the expanded EOAA/S scale, this pharmacodynamic model yields six sigmoid curves, one for each sedation score (4, 3, 2, 1, 0, and 0e) relating the propofol concentration to the probability of having a specified EOAA/S score.

At any given concentration, a certain level of sedation should be achieved only after achieving lighter levels of sedation and before reaching deeper levels of sedation. It is possible to calculate the probability of a particular sedation score equal to 5, 4, 3, 2, 1, 0, and 0e using the following equation:

\[ P(\text{sedation score} = s) = P_s = \frac{C_{50,s}}{C_{50,s} + C_{E50}} \] (1)

where \( P(\text{Effect} = s) = P_s \) is the probability that the EOAA/S score would be equal to or less than \( s \) (i.e. ‘deeper’ level of sedation than \( s \)) a given discrete score (\( s \)), \( C_e \) is the predicted concentration of propofol in the effect site, \( C_{E50} \) is the steady-state effect-site concentration associated with 50% probability, and \( E_{max} \) is the maximal BIS. The investigators delivering the trapezius squeeze to the subject, the investigators pinched the gauge to 10 pounds per square inch as quality control for the level of force applied.

The degree of force applied during the trapezius squeeze was in line with a typical force applied by a female nurse between the ages of 30 and 50 yr (as part of the study planning, 11 nurses were asked to deliver a trapezius squeeze as strongly as they could using a Jamar hydraulic pinch gauge; Patterson Medical, Bolingbrook, IL, USA). The mean force was found to be ∼0.7 kg cm−2 (10 pounds per square inch). The investigators delivering the trapezius squeeze were trained using a pinch gauge to approximate this level of force. During data gathering, before the delivery of each trapezius squeeze to the subject, the investigators pinched the gauge to 10 pounds per square inch as quality control for the level of force applied.

The data were analysed using a naïve pooled data approach implemented with NONMEM version 7.2 (Globomax LLC, Hanover, MD, USA). In standard mixed-effects modeling, the treatment of interindividual variability in C50,s would often be modelled as a log-normal distribution about the typical estimates of C50,s for individuals at each sedation score:

\[ C_{50,s} = C_{50,s}TV \times e^{\eta(i)} \] (3)

where \( C_{50,s}TV \) is the estimate of the concentration associated with 50% probability of a given sedation score, \( s \), in the ith individual, \( C_{50,s}TV \) is the typical value (TV) of the estimate of the concentration associated with 50% probability of a given sedation score in the population, \( \eta(i) \) is the random variable with a mean of 0 and a variance of \( \omega^2 \). When using the naïve pooled data approach, the interindividual variability \( (\omega^2) \) is modelled as 0 (as though the data arose from a single subject).

For the BIS data, a classic inhibitory sigmoidal \( E_{max} \) relationship between \( C_e \) and the BIS was assumed:

\[ \text{Effect} = E_0 - (E_0 - E_{max}) \times \frac{C_{50,s}}{C_{50,s} + C_{E50}} \] (4)

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Table 1

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Level of sedation or anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken</td>
<td>Minimal</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Responds after name called loudly/repeatedly shaking</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>Purposeful response to mild- to-moderate shaking</td>
<td>Moderate</td>
</tr>
<tr>
<td>1</td>
<td>Responds to trapezius squeeze</td>
<td>Deep</td>
</tr>
<tr>
<td>0e</td>
<td>No response to trapezius squeeze*</td>
<td>Light general anaesthesia</td>
</tr>
<tr>
<td>0e</td>
<td>No response to electrical stimulation†</td>
<td>Deeper general anaesthesia</td>
</tr>
</tbody>
</table>

*For the BIS data, a classic inhibitory sigmoidal \( E_{max} \) relationship between \( C_e \) and the BIS was assumed:

\[ \text{Effect} = E_0 - (E_0 - E_{max}) \times \frac{C_{50,s}}{C_{50,s} + C_{E50}} \] (4)

where \( P(\text{Effect} = s) = P_s \) is the probability that the EOAA/S score would be equal to or less than \( s \) (i.e. ‘deeper’ level of sedation than \( s \)) a given discrete score (\( s \)), \( C_e \) is the predicted concentration of propofol in the effect site, \( C_{E50} \) is the steady-state effect-site concentration associated with 50% probability, and \( \gamma \) is the steepness of the probability vs concentration curve. The value of \( \gamma \) was considered the same for all the sedation scores. In every step, after checking the tolerable electrical stimulation, the changed \( C_{50,s} \) is modelled as \( C_{50,s} \times STIM \), where STIM is the electrical stimulating effect which can increase the \( C_{50,s} \). The STIM effect is considered constant for all the EOAA/S scores. For the 0e, however, STIM was not modelled because 0e is the last score for which the electrical intensity is maximum.

The data were analysed using a naïve pooled data approach implemented with NONMEM version 7.2 (Globomax LLC, Hanover, MD, USA). In standard mixed-effects modeling, the treatment of interindividual variability in C50,s would often be modelled as a log-normal distribution about the typical estimates of C50,s for individuals at each sedation score:

\[ C_{50,s} = C_{50,s}TV \times e^{\eta(i)} \] (3)

where \( C_{50,s}TV \) is the estimate of the concentration associated with 50% probability of a given sedation score, \( s \), in the ith individual, \( C_{50,s}TV \) is the typical value (TV) of the estimate of the concentration associated with 50% probability of a given sedation score in the population, \( \eta(i) \) is the random variable with a mean of 0 and a variance of \( \omega^2 \). When using the naïve pooled data approach, the interindividual variability \( (\omega^2) \) is modelled as 0 (as though the data arose from a single subject).

For the BIS data, a classic inhibitory sigmoidal \( E_{max} \) relationship between \( C_e \) and the BIS was assumed:

\[ \text{Effect} = E_0 - (E_0 - E_{max}) \times \frac{C_{50,s}}{C_{50,s} + C_{E50}} \] (4)
where $E_0$ denotes the EEG effect in the absence of propofol (baseline or awake state), $E_{\text{max}}$ is the EEG value corresponding to the maximal propofol effect, $C_{e50}$ describes the propofol effect-site concentration that causes 50% of the maximal EEG effect, and $\gamma$ quantifies the slope of the sigmoid relationship between $C_e$ and Effect.

After the TES was applied, the $C_{e50}$ term was calculated as $\text{STIM} \times C_{e50}$, where STIM denotes the scaled increase in BIS that is caused by the electrical stimulation when the TES is applied to subjects.

For all parameters, interindividual variability was modelled using a log-normal distribution, as follows:

$$P_i = P_{\text{TV}} \times e^{\eta_i}$$

where $P_i$ is the parameter value in the $i$th patient, $P_{\text{TV}}$ is the typical value of the parameter in the population, and $\eta$ is a random variable with a mean of 0 and a variance of $\omega^2$. Individual variability is reported as $\omega$, the standard deviation of $\eta$ in the log domain.

The intraindividual variability was described with an additive error model. This means that for the $j$th observed BIS of the $i$th individual, the relationship ($Y_{ij}$) is described by:

$$Y_{ij} = \text{BIS}_{\text{pred},ij} + \epsilon_{ij}$$

where $\text{BIS}_{\text{pred},ij}$ is the predicted BIS, and $\epsilon_{ij}$ is a random variable with a mean of zero and variance of $\sigma^2$.

Model performance and validation

Classical tools for assessing the goodness of fit for pharmacokinetic models (visual inspection of fits, residual error plots, median performance error, and absolute median performance error) cannot easily be used to assess the goodness of a probability model with a polychotomous response, such as the EOAA/S score. The main problem is that the observations are sedation scores, not the probability of a given sedation score as predicted by the models. We used methods originally described by Smith and colleagues and refined by Somma and colleagues to address this problem.

To assign a prediction to each propofol concentration, we calculated and plotted the probability of each level of sedation according to equation (2) as a function of concentration. We then computed the percentage of accurate predictions (observed sedation score=predicted sedation score) and close predictions (observed sedation score=predicted sedation score +1 or –1). As another performance measurement, the prediction probability ($P_k$) was calculated as described by Smith and colleagues and programmed by Jordan and colleagues.

We used a bootstrap method to perform an internal validation of the model. Model parameters were estimated by NONMEM from 2000 data sets permuted from the original data set as described by Steyerberg and colleagues using Wings for NONMEM (WFN, version 6.16, http://wfn.sourceforge.net/; Nick Holford, University of Auckland, New Zealand). The 2.5–97.5% confidence intervals of the model parameters from the bootstrap procedure were compared with the NONMEM estimates of the standard error of the parameters.

Results

Twenty volunteers (10 women and 10 men) were enrolled. All subjects tolerated the study well; there were no significant adverse events. In particular, there were no adverse respiratory events requiring significant airway interventions (i.e. artificial airway placement or bag-and-mask ventilation). The EOAA/S and BIS data from all 20 patients were available for final data analysis. The predetermined end point of TES at 50 mA with non-response was reached in all patients. Patient characteristics, baseline vital signs, and baseline pharmacodynamic signals are summarized in Supplementary data, Table S1.
The raw data from the study are presented in Fig. 1; each subject’s observed EOAA/S scores are plotted against the corresponding predicted propofol effect-site concentrations. Along with the BIS values, these data constituted the set data for pharmacodynamic model building.

### Pharmacodynamic model building

The pharmacodynamic model parameter estimates are presented in Table 2. The Ce50 of the final model were 1.04, 1.71, 1.86, 2.06, 2.15, and 3.58 for sedation score 4, 3, 2, 1, 0S, and 0E respectively. The steepness, γ, was 6.41. The electrostimulating effect, STIM, was 1.12; that is, brief TES shifted the concentration–effect relationship slightly to the right.

Predicted propofol effect-site concentrations vs observed EOAA/S scores are presented as a bubble plot in Fig. 2; the pharmacodynamic model Ce50 estimates for the EOAA/S scores of less than or equal to four (both before and after TES) are indicated as vertical lines superimposed on the raw data. As the propofol predicted effect-site concentrations increase, the distribution of EOAA/S scores shifts from minimal sedation through the deeper sedation states to general anaesthesia. Higher propofol concentrations are required to produce sufficient central nervous system depression to render subjects unresponsive to TES at 50 mA compared with trapezius squeeze. No subject was unresponsive to TES of 50 mA at predicted propofol concentrations below 2.5 µg ml\(^{-1}\). Unresponsiveness to trapezius squeeze was first encountered at a predicted propofol concentration of 1.75 µg ml\(^{-1}\). At predicted propofol concentrations near or greater than 3.5 µg ml\(^{-1}\), the majority of subjects were unresponsive to TES of 50 mA; all subjects were unresponsive to TES at concentrations approaching 5 µg ml\(^{-1}\). Brief TES stimulation shifted the concentration–effect relationship slightly rightward.

The probabilities of achieving a specified EOAA/S score as a function of predicted propofol effect-site concentration according to the model are presented in Fig. 3. Logistic regression models characterizing the probability of an EOAA/S sedation score of 1, 0S, and 0E are presented in Fig. 4. The predicted propofol concentrations producing a 50% probability of EOAA/S 1 and 0E (i.e. the Ce50) were 2.06 and 2.15 µg ml\(^{-1}\); respectively, the Ce50 for 0S was 3.58 µg ml\(^{-1}\).

### Model performance and validation

Visual inspection of the EOAA/S and BIS model predictions of the raw data as shown in Fig. 2 and Supplementary data, Figure S2 confirm that the models adequately describe the data. The pharmacodynamic model relating predicted propofol concentration to EOAA/S scores provided 63% correct predictions and 86% close predictions (within 1 sedation score). The prediction probability (Pr) and its standard error were 0.84 and 0.001, respectively, indicating excellent model performance. Table 2 presents the NONMEM model parameter estimates with their standard errors, and the bootstrap procedure median parameter estimates with their confidence intervals. All the bootstrap runs converged successfully for the EOAA/S model, and 97% of bootstrap runs converged successfully for the BIS model. The NONMEM standard errors and bootstrap confidence intervals compare favourably.

### Discussion

This study investigated the feasibility of expanding a commonly used sedation score (i.e. MOAA/S) to include a more noxious stimulus, thereby extending the dynamic range of the sedation score to include clinical states more representative of deeper general anaesthesia. We confirmed the hypothesis that significantly higher concentrations of propofol are necessary to prevent response to 50 mA of transcutaneous electrical stimulation compared with a trapezius squeeze. We also confirmed the hypothesis that the application of noxious stimulation (i.e. tetanic electric current) shifts the propofol concentration–effect relationship to the right, requiring higher propofol concentrations to produce a given sedation state, although we observed only a small effect.

The key findings from the study are evident from inspection of the raw data (Fig. 1). All subjects required a higher propofol concentration to produce unresponsiveness to electrical stimulation at 50 mA compared with a standardized trapezius squeeze. For some subjects, rendering them unresponsive to electrical stimulation required propofol concentrations approaching double those required to prevent response to trapezius squeeze. In aggregate, the pharmacodynamic models (Fig. 4) revealed that unresponsiveness to electrical stimulation required a propofol concentration 1.7 times higher than for trapezius squeeze.

The raw data reflect considerable intersubject variability in terms of the concentration–effect relationship; a given propofol concentration target is associated with a wider range of EOAA/S scores. When considered in terms of the pharmacodynamic model predictions (Fig. 3), this means that a propofol concentration of 2 µg ml\(^{-1}\); for example, can be expected to produce an EOAA/S score ranging between 4 and 0S (although not 5 or 0E). This well-known variability underscores the importance of the

| Table 2 | Pharmacodynamic model parameter estimates from NONMEM and the bootstrap procedure (with standard errors and confidence intervals). BIS, bispectral index; CI, 2.5–97.5% confidence interval; EOAA/S, Extended Observer’s Assessment of Alertness and Sedation; RSE, relative standard error. See text for details regarding parameter definitions |
| --- | --- | --- | --- |
| **Model** | **Parameter** | **Result (RSE, %)** | **Bootstrap (CI)** |
| EOAA/S | Ce50,4 | 1.04 (6.9) | 1.04 (0.89, 1.17) |
| | Ce50,3 | 1.71 (6.3) | 1.71 (1.51, 1.92) |
| | Ce50,2 | 1.86 (6.2) | 1.86 (1.65, 2.1) |
| | Ce50,1 | 2.06 (5.1) | 2.06 (1.87, 2.29) |
| | Ce50,GT | 2.15 (4.9) | 2.15 (1.96, 2.37) |
| | Ce50,UC | 3.58 (6.3) | 3.58 (3.17, 4.03) |
| | STIM | 1.12 (1.8) | 1.12 (1.08, 1.16) |
| | γ | 6.41 (14.7) | 6.68 (5.1, 9.16) |
| | E0 | 95.1 (0.6) | 95.2 (94.9, 95.4) |
| | EMAX | 12.4 (19) | 11.9 (6.4, 17.2) |
| | Ce50 | 2.09 (5.1) | 2.09 (1.9, 2.37) |
| | STIM | 1.15 (1.3) | 1.15 (1.12, 1.18) |
| | γ | 3.11 (7.7) | 3.1 (2.58, 3.52) |
careful titration of sedative drugs in the clinical setting; fixed
dosing recipes are expected to have highly variable results in
terms of the clinical sedation state that is produced.

Another important observation from inspection of the raw
data relates to the lack of differentiating resolution in the sed-
ation scores between moderate sedation (scores of 3 and 2) and
lighter states of general anaesthesia (O₁). Small increases in propofol concentration can result in a significant change in the sedation score in the parts of the sedation scale corresponding to moderate sedation, deep sedation, and light general anaesthesia. This is reflected in the uncertainty of the pharmacodynamic model predictions for propofol concentrations around 2 µg ml⁻¹ (Figs 2 and 3). Although the estimated propofol Ce₅₀ values for EOAA/S scores between 3 and 0ₑ are appreciably different, they are close to one another. In particular, the difference in propofol Ce₅₀ between a deep sedation score (EOAA/S=1) and light general anaesthesia (EOAA/S=0ₑ) is very small (2.06 vs 2.15 µg ml⁻¹). Applied to the clinical realm, this means that patients in the state of deep sedation are likely to be very near light planes of general anaesthesia in terms of the associated propofol concentrations and thus require special vigilance to prevent the airway obstruction and ventilatory depression often associated with general anaesthesia. An extension of this concept is that patients in the lightest planes of general anaesthesia can probably be returned (‘rescued’) to states consistent with moderate sedation with relatively small decreases in target drug concentrations.

Demonstrating that deeper planes of general anaesthesia (EOAA/S=0ₑ) require significantly higher propofol concentrations than lighter planes of general anaesthesia (EOAA/S=O₁) is perhaps the most important practically applicable finding of the study. Although this finding may perhaps be self-evident, studies addressing this issue in the context of sedation practice using sophisticated, high-resolution methods (e.g. TCI, finely graded propofol concentration targets) are lacking.

The ASA sedation continuum suggests that as a patient’s clinical state moves toward general anaesthesia, there is an increasing likelihood of adverse respiratory and circulatory effects. It is therefore critical for sedation practitioners (and sedation drug and device investigators) to identify accurately and reproducibly when a patient (or research subject) has entered the clinical state of general anaesthesia so that rescue manoeuvres can be initiated before serious adverse events occur. This study has confirmed that lighter planes of general anaesthesia can be differentiated from deeper planes of general anaesthesia in terms of the propofol concentrations required. Assuming that the patient’s clinical sedation state is assessed frequently, the implication is that when a patient begins to exhibit clinical states consistent with deep sedation or the lighter planes of general anaesthesia (EOAA/S=1 or 0ₑ), it should be possible to adjust the propofol (or other sedative) dosage to prevent the development of deeper planes of general anaesthesia and the associated risk of adverse respiratory and circulatory effects.

The existing MOAA/S score has considerable limitations in assessing the full range of clinical states on the sedation continuum. To differentiate levels of sedation and anaesthesia, a range of noxious stimuli must be applied. This study suggests that a trapezius squeeze, the noxious stimulus classically included with the MOAA/S assessment, is not sufficiently noxious to identify clinical states consistent with typical surgical anaesthesia. Viewed in terms of the propofol concentrations required, rendering a subject unresponsive to TES at 50 mA represents considerable central nervous system depression that is clearly indicative of deeper planes of general anaesthesia compared with the central nervous system depression associated with unresponsiveness to trapezius squeeze.

Another important clinical implication of this study relates to the possibility of adverse respiratory effects when combining propofol and fentanyl for procedural sedation/analgesia. Although respiratory effects were not a primary pharmacodynamic end point of this study, there were no respiratory events requiring invasive interventions, such as artificial airway placement or bag-and-mask ventilation. The apparent utter lack of respiratory toxicity is likely to be a function of the experimental design, which was not intended to emulate the clinical setting in terms...
of the drug administration scheme. When administered exclusively by infusion, propofol (and fentanyl) has less impact on respiratory physiology compared with bolus administration. It is likely that had we achieved our specified propofol targets using bolus injections, we would have observed more respiratory adverse effects.

A secondary aim of the study was to examine the influence of noxious stimulation on the concentration–effect relationship of sedative drugs. We confirmed a small effect for both the clinical sedation score and the electroencephalographic surrogate for sedation (Fig. 2 and Supplementary data, Figure S2). Given that the application of TES was brief (sustained for 5 s) and was at low current levels when the subject was at clinical states consistent with minimal to moderate sedation, the small effect we observed is perhaps to be expected. Had we allowed the current to be sustained for a longer period, or had we carried out a sub-analysis of only the assessments where TES was delivered at 50 mA, we might have found a greater effect.

It is important to emphasize that the pharmacodynamic drug interaction between the sedative (e.g. propofol) and the opioid (e.g. fentanyl) has important implications on the clinical sedation state and thus the study findings. Understood in terms of a response surface drug-interaction framework, the propofol C50 values for various sedation end points are known to change as a function of the opioid concentration. At lower opioid concentrations, the propofol C50 values for the continuum of sedation scores are expected to be more divergent than at higher opioid concentrations, where the C50 values are expected to converge somewhat. The fentanyl target selected for this study can be considered a moderate opioid dosing regimen that would be typical of many sedation practices. Of course, different sedative–opioid target concentration ratios would be expected to yield somewhat different pharmacodynamic model parameter estimates.

A nuance of the pharmacodynamic modeling approach deserves highlighting. When fitting ‘maximal effect’ equations to experimental data, it is optimal that maximal effect is achieved or very nearly achieved. Without reaching maximal effect, there may be insufficient raw data on which to base the maximal effect parameter estimate. In this experiment, although maximal effect was achieved for the EOAA/S score (the clinical sedation assessment), maximal effect (i.e. a flat electroencephalogram) for the BIS (the surrogate sedation assessment) was not, although very considerable central nervous system depression was evident on the BIS recordings (i.e. BIS values in the high teens and twenties). The pharmacodynamic parameter estimates relating to BIS were certainly influenced by this limitation to some degree.

The analysis of the BIS data was also adversely impacted by the method of data gathering. For a ‘noisy’ signal, such as the processed EEG, a single sample or a median/mean value over some specified period will almost always be lower than the maximal signal value over some other period; therefore, at least part of the increased BIS values observed after electrical stimulation may be an artifact of comparing a single sample or median/mean to a signal maximum (i.e. the increase in BIS values after stimulation may be overestimated).

Another important limitation of the study in terms of its clinical application is a function of the propofol and fentanyl administration regimens. Given that this was a pharmacodynamic study, it was critical to control the pharmacokinetic aspects of the experiment; that is, it was important to establish pseudo-steady-state drug levels at or near specified targets before the pharmacodynamic assessments were made. The necessary accuracy and precision in drug administration was accomplished using TCI technology and techniques. Although these TCI techniques are widely used for experiments like this one, there is of course some error introduced into the analysis because the models for propofol and fentanyl we used are imperfect. Using measured drug concentrations from arterial blood samples (instead of predicted concentrations from TCI technology) is a means of addressing this shortcoming, although there is also error associated with these measurements (and some minor safety considerations regarding the use of arterial catheters in volunteer subjects).

Another potential limitation of the study relates to the use of TES as a non-invasive, objective, quickly repeatable, noxious stimulus. For TES to be useful in this context (i.e. as an experimental pain assessment that extends the traditional OAA/S score to include noxious stimulation approximating a surgical stimulus), TES must clearly be more noxious than a trapezius squeeze. Numerous investigators have produced data suggesting that TES at a current around 50 mA is indeed a significantly noxious stimulus. For example, Yasuda and colleagues reported that desflurane at 1.66 MAC (minimal alveolar concentration) was required to attenuate haemodynamic responses to TES in volunteers. Zbinden and colleagues published very similar findings for haemodynamic end points in patients. Using motor responses in patients, Petersen-Felix and colleagues showed that ~1 MAC of isoflurane was required to produce a 50% probability of no movement response to TES (they introduced the concept of MACtetanus). Applying response surface methods in volunteers, other investigators have drawn similar conclusions regarding the noxiously of TES, studying the interaction between propofol and remifentanil; Kern and colleagues found that abolishing the response to TES required considerably higher propofol concentrations than were required to abolish the response to ‘shout and shake’. However, some investigations have yielded contrary findings. For example, Heyse and colleagues, also using response surface methods, reported that elimination of responses to TES using sevoflurane did not require appreciably higher concentration targets than those required to produce a lack of response to ‘shout and shake’.

In terms of the next steps in this line of investigation, the present study must be regarded as preliminary. Confirmation of the experimental utility of the EOAA/S will require application of the method by other investigators as part of a variety of study paradigms. Reproduction of our results would help to solidify the validity of the EOAA/S as an experimental tool.

In conclusion, this study has provided the beginning of the scientific foundation for a new method to assess the clinical sedation state. Called the Extended Observer’s Assessment of Alertness and Sedation (EOAA/S), the new sedation score is intended for use in sedation-related drug and device development studies (i.e. not as a clinical assessment in the care of patients). The EOAA/S extends the range of the widely used MOAA/S score to include truly noxious stimulation, thereby enabling the identification of drug-induced central nervous system depression representative of surgical anaesthesia. Use of the EOAA/S in the present study clearly demonstrated that substantially higher propofol concentrations are necessary to produce unresponsive-ness to 50 mA of electrical current (tetanus) compared with a standardized trapezius squeeze.

Authors’ contributions

Data gathering: S.O., T.D.E., T.K.K.
Data analysis and data interpretation: T.D.E., T.K.K., P.J.N.
Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

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Declaration of interest

T.K.K. and S.O. have no competing interests. From time to time, T.D.E. has been a paid consultant to Ethicon Endo-Surgery, although not in connection with this study. P.J.N. and J.F.M. are employees of Ethicon Endo-Surgery.

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