Ability of the Bispectral Index, Autoregressive Modelling with Exogenous Input–derived Auditory Evoked Potentials, and Predicted Propofol Concentrations to Measure Patient Responsiveness during Anesthesia with Propofol and Remifentanil

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Background: This study was conducted to compare the performance accuracy of the independent variables Bispectral Index (BIS), A-Line ARX index (AAI), and predicted propofol effect-site concentration (CePROP) to measure the dependent variables of loss of responses to different stimulation defined as loss of response to verbal command (LOR_{verbal}), eyelash reflex (LOR_{lash}), and noxious stimulus ($LOR_{noxious}$) during stepwise increased levels of propofol infusion with and without remifentanil.

Methods: Forty-five patients were randomly allocated to one of three groups (0, 2, and 4 ng/ml remifentanil) to receive graded CePROP and predicted effect compartment controlled remifentanil (CeREMI). At every step, the ability to respond to verbal command using the Observer's Assessment of Alertness/Sedation Scale (OAA/S), eyelash reflex, and electrical tetanic noxious stimulus were compared against BIS, AAI, and CePROP. Prediction probability and sensitivity/specificity were calculated.

Results: Increasing CeREMI increased BIS and AAI values at LOR_{verbal} and LOR_{lash} and decreased CePROP. Similar findings were found for $LOR_{noxious}$. The overall prediction probability to measure the hypnotic component of anesthesia remained accurate in the three groups for BIS, AAI, and CePROP. Combined information from CePROP, CeREMI, and BIS or AAI increased the overall prediction probability for predicting the OAA/S scale and LOR_{lash}. Less accuracy to $LOR_{noxious}$ was found in all independent variables.

Conclusions: Although BIS, AAI, and CePROP were influenced by remifentanil during propofol administration, their ability to detect OAA/S and LOR_{lash} remained accurate. Improved performance is obtained when BIS and AAI are measured in conjunction with drug targeted effect-site concentrations. Remifentanil decreases the ability of these independent variables to detect $LOR_{noxious}$.

BOTH electroencephalography- and midlatency auditory evoked potential (MLAEP)– derived variables have been proposed as measures of the hypnotic state during anesthesia.[1] For the electroencephalography, the Bispectral Index (BIS) incorporated in the A-2000 BIS® monitor (Aspect Medical Systems, Inc., Newton, MA) has been proven to have a high sensitivity and specificity to measure anesthetic drug effect, compared with other processed electroencephalographic variables.[2–4] Previously, MLAEP has been used by various investigators to study anesthetic depth.[5] Recently, Jensen *et al.*[6,7] developed a new method for extracting the MLAEP from the electroencephalographic signal by using an autoregressive model with an exogenous input (ARX) adaptive model. This method allows extraction of the MLAEP signal within 15–25 sweeps of 110 milliseconds' duration each, resulting in only a 6- to 15-s response delay time. A new monitoring variable, called the A-Line ARX index (AAI), is then calculated from this fast extracted MLAEP wave. This new technology is incorporated in a recently commercialized system called A-Line® (Danmeter A/S, Odense, Denmark). Recently, Struys *et al.*[8] compared the accuracy of both BIS and AAI for measuring loss of responses to different stimulation defined as loss of verbal command (LOR_{verbal}), loss of eyelash reflex (LOR_{lash}), and loss of response to noxious stimulus ($LOR_{noxious}$) during steady state propofol administration. We found that BIS, AAI, and predicted effect-site concentration of propofol (CePROP) revealed a similar level of information on LOR_{verbal} and LOR_{lash} but did not predict $LOR_{noxious}$. Also, AAI has recently been shown to reliably assess the level of consciousness during propofol,[8,9] sevoflurane,[10] and midazolam[11] anesthesia. The BIS correlated better to propofol plasma concentrations than AAI, but AAI correlated better than BIS to the clinical signs during recovery from propofol anesthesia.[11]

In previous work done with the AAI, propofol was administered solely. Although a clear pharmacodynamic interaction between remifentanil and propofol has been described,[12] controversy still exists on the influence of opiates on the accuracy of both BIS and MLAEP to measure loss of response to different stimulation.[13–16] During remifentanil monoinfusion, AAI measured changes in patients' level of arousal better than BIS.[17] However, in this study, a different electrode position was used, where the AEP was recorded between a frontal (+) and an occipital electrode (−). It is possible that a change in

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montage such as this could lead to significantly different results compared with those from the current study.

A fundamental question is whether the electroencephalograph- or AEP-derived variables can be used to optimize drug delivery. A first step to answer this question is to examine the performance and accuracy of these monitors under various conditions and to compare them with the accuracy and usefulness of on-line calculated drug effect-site concentration. A secondary question is how opiates affect these performance parameters. This study was conducted to assess the performance accuracy of the AAI to reflect the hypnotic component of anesthesia and to measure loss of responses to different stimulation defined as LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ during stepwise increased levels of propofol infusion with and without remifentanil. The performance of AAI was compared with that of BIS and CePROP.

Materials and Methods

After Institutional Ethics Committee (Ghent University Hospital, Gent, Belgium) approval, informed consent was obtained from 45 female patients with American Society of Anesthesiologists class I, aged 18–60 yr, who were scheduled to undergo ambulatory gynecologic surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and recent use of psychoactive medication, including alcohol. They were randomly allocated to one of the three groups. In all groups, patients received a "staircase" computer-controlled infusion of propofol targeting the effect compartment. Initially, an effect-site concentration of 1.5 μg/ml was targeted in the group without remifentanil, and 1 μg/ml was targeted in the two other groups; this was increased every 4 min by 0.5 μg/ml until loss of response to all relevant clinical measures of anesthetic depth was observed. In the 0 ng/ml remifentanil group, no remifentanil was given. In the 2 ng/ml and 4 ng/ml remifentanil groups, an effect compartment controlled infusion of remifentanil was started 4 min before the start of propofol. Calculated remifentanil effect-site concentrations (CeREMI) of 2 and 4 ng/ml were targeted, respectively.

Propofol and remifentanil were administered *via* a computer-assisted continuous infusion device to a target effect-site concentration (RUGLOOP**) using a three-compartment model enlarged with an effect-site compartment. For propofol, the pharmacokinetic–dynamic model previously published by Schnider *et al.*[18,19] was used. For remifentanil, the pharmacokinetic–dynamic model previously published by Minto *et al.*[20,21] was

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale[24]

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

used. CePROP was computed to yield a time-to-peak effect[22] of 1.6 min after bolus injection, as also published by Schnider *et al.*[18,19] and clinically confirmed by Struys *et al.*[23] For remifentanil, a $t_{1/2}k_{e0}$ of 1.020619 min was applied as published by Minto *et al.*[20,21] Propofol and remifentanil infusion were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). RUGLOOP steers the pump at infusion rates between 0 and 1,200 ml/h *via* an RS-232 interface. By using this infusion technique, we were able to obtain a steady state condition for both propofol and remifentanil at every target level after 4 min of infusion. Hereby, steady state is defined as the equilibration between the calculated plasma and effect-site concentration of the drug. Remifentanil and propofol were infused *via* a large left forearm vein. Every patient received approximately 200 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation *via* a facemask delivering 6 l/min O_2.

Heart rate and noninvasive blood pressure, oxygen saturation measured by pulse oximetry (Spo_2), and capnography were recorded at 1-min intervals using an AS3 monitor (Datex, Helsinki, Finland). BIS (version 3.4) was derived from the frontal electroencephalogram (At-Fpzt) and calculated by the A-2000 BIS® monitor using a BIS-Sensor® (Aspect Medical Systems, Inc.). The smoothening time of the BIS® monitor was set at 15 s. The AAI from the MLAEP was calculated using the A-Line® monitor. The MLAEPs were elicited with a bilateral click stimulus of 70 dB in intensity and 2 ms in duration. Three electrodes (A-Line AEP electrodes; Danmeter A/S) were positioned at the mid forehead (+), left forehead (reference), and left mastoid (−). The extraction of the MLAEP using a short moving time average technique together with an ARX model and the calculations of the AAI are described elsewhere.[8]

Ten seconds before each increase in CePROP (after 4 min of infusion at the specific target effect-site concentration), the independent variables of response (BIS, AAI, and CePROP) were recorded. Immediately after that, patient responsiveness to different stimuli was tested using the dependent variables eyelash reflex, Observer's

Assessment of Alertness/Sedation Scale (OAA/S[24]; table 1), and response to electrical tetanus (at 100 Hz and 50 mA for 2 s; applied to the volar forearm level) assessments, in that order. Verbal stimulation proceeded noxious stimulus. Patients were considered responsive to verbal stimulus if their OAA/S value was 3, 4, or 5 and were considered unresponsive to verbal command at OAA/S values of 0, 1, and 2. Transition between a responsive and an unresponsive state was defined as loss of response to verbal command (LOR_{verbal}). Loss of response of eyelash reflex was defined as LOR_{lash}. Patients were considered responsive to noxious stimulus if they responded to the tetanic electrical stimulation, regardless of whether they responded to trapezius squeeze during the OAA/S assessment. Loss of response to tetanic stimulus was defined as $LOR_{noxious}$.

Both BIS and AAI indices were also logged automatically. RUGLOOP digitally recorded the BIS index every 10 s, and the A-Line monitor recorded AAI index values nominally every 6 s. The time marks of both systems were synchronized with the manual timing for stimulus and manually recorded events to within ±1 s.

Statistical Analysis

The significance level was set at 5% unless otherwise reported. The ability of the independent variables (BIS, AAI, and CePROP) to detect the level of OAA/S, LOR_{lash}, and $LOR_{noxious}$ was evaluated using prediction probability (P_K), which compares the performance of independent variables with different units of measure, as developed by Smith *et al.*[25,26] Consider a variable such as BIS or AAI and a "definitive standard" measure of anesthetic depth such as the multilevel OAA/S score or the two-level responsiveness (yes/no) to eyelash reflex or noxious stimulus. Then, a P_K of 1 for the BIS or AAI variable would mean that BIS or AAI always increases (decreases) as the anesthesia gets lighter (deeper) according to the definitive standard depth measure. Such an independent variable can perfectly measure anesthetic depth. Alternatively, a P_K value of 0.5 would mean that the independent variable is useless for measuring anesthetic depth. For the OAA/S score, a P_K was computed for all OAA/S levels combined. Similarly, P_K values for LOR_{lash} and $LOR_{noxious}$ were determined. The jackknife method was used to compute the SE of the estimate, based on the assumption that all assessments were independent.[25,26] A Student *t* test with Bonferroni correction was used to evaluate whether the P_K for one variable was different from another one. Significance level was set at 0.0167. Prediction probability was calculated using a custom spreadsheet macro, P_KMACRO, developed by Smith *et al.*[25,26] The P_K value was calculated for each independent variable in each group. A P_K analysis for each independent variable with the three groups pooled was performed.

To study whether the combined information from BIS and AAI together with the drug effect-site concentrations offers more accurate information than the independent variables alone, two new composite variables have been designed based on the combined information from BIS + CePROP + CeREMI and AAI + CePROP + CeREMI, and a P_K analysis was performed on both composite variables. The OAA/S score was used as clinical comparator. The P_K on the combined information was calculated using ordinal logistic regression, as described in the Appendix.

The power on the P_K values was calculated using a *t* statistic defined as the difference considered of clinical importance divided by the SE of the difference between two independent variables. Assuming a P_K difference of 0.05 as being of significant with an SE of 0.02, 15 patients should be included to find significant differences with $P < 0.025$ (Bonferroni correction for two *t* tests). Previous assumption were based on previous results of the AAI and other AEP-independent variables.[27]

By applying Probit analyses, the effective concentration or index at which 50% (ED_{50}) and 95% (ED_{95}) of the patients reached LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ were calculated for all independent variables. For all independent variables, ED_{50} and ED_{95} values were compared between groups using one-way analysis of variance statistics. If significant, an unpaired two-sided Student *t* test with Bonferroni correction was used ($P < 0.0167$).

We calculated cutoff (threshold) values for the ability of the BIS, AAI, and CePROP to detect LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$ in each group. For these calculations, we used "positive" to denote a test result that suggested responsiveness and "negative" to denote a test result that suggested nonresponsiveness. We assumed that increases in the BIS and AAI and a decrease in CePROP corresponded to an increased likelihood of responsiveness. We computed sensitivity as the proportion of responsive patients with positive test results (value higher than cutoff value for BIS and AAI and lower than cutoff value for CePROP). Similarly, we computed specificity as the proportion of nonresponsive patients with negative test results (value lower than cutoff value for BIS and AAI and higher than cutoff value for CePROP). We computed the cutoff values for each independent variable and specificity at a level of 100% sensitivity and at which the sum of sensitivity and specificity were highest. The same sensitivity/specificity analyses were performed for composite variables.

Results

The demographics (mean ± SD) of the 45 female patients in the three groups are shown in table 2. No significant demographic differences were found between groups.
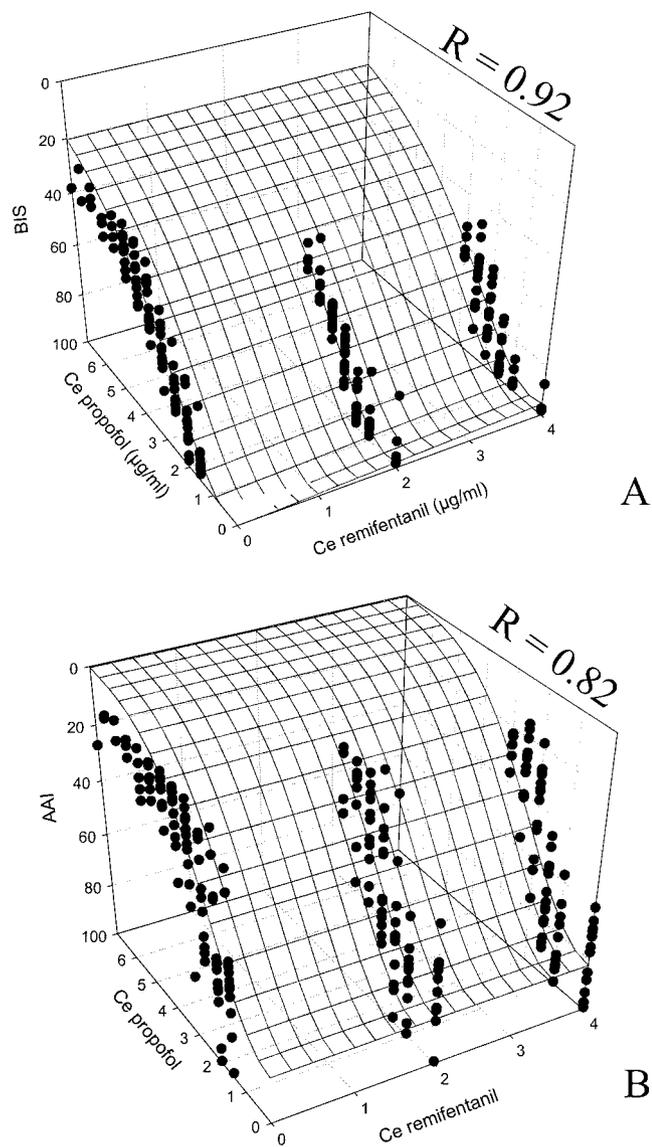
Figures 1A and B show the behavior of BIS and AAI
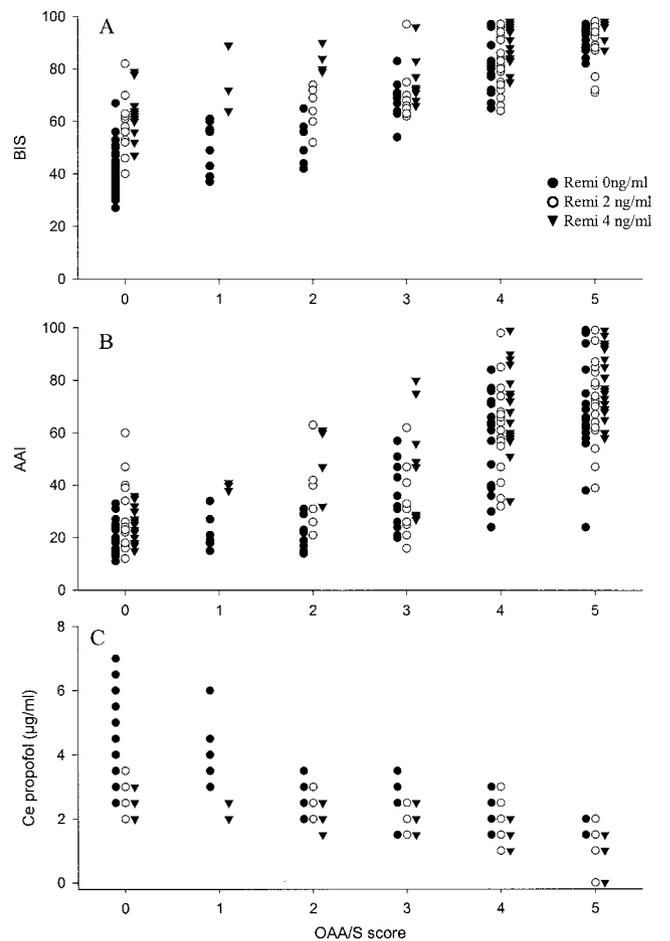
Table 2. Antropometry

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil
Age, yr	33 ± 5	33 ± 5	34 ± 4
Weight, kg	63 ± 10	66 ± 11	65 ± 9
Height, cm	167 ± 6	168 ± 6	167 ± 6

versus CePROP and CeREMI. The correlation coefficient between BIS and the drug effect-site concentrations ($r = 0.92$) was significantly higher than for AAI ($r = 0.82$). In all groups, a stepwise increase in CePROP resulted in a monotonic decrease in the OAA/S score. BIS and AAI decreased in all groups with decreasing OAA/S scores, as shown in figure 2.

Figures 3A–C show the behavior of BIS, AAI, and

Fig. 2. Raw data at every Observer's Assessment of Alertness/ Sedation Scale (OAA/S) score for Bispectral Index (BIS; *A*), A-Line ARX index (AAI; *B*), and propofol effect-site concentration (Ce; *C*). Data from the 0 ng/ml remifentanil (Remi) group are presented as *black circles*, data from the 2 ng/ml remifentanil group as *white circles*, and data from the 4 ng/ml remifentanil group as *black triangles*.

CePROP at LOR$_{lash}$. For all independent variables, a significant decrease of the variable values between the responsive and unresponsive state was observed in all groups. The BIS, AAI, and CePROP values at LOR$_{noxious}$ are plotted in figures 3D–F. In all groups, all independent variables changed significantly.

By applying Probit analyses, the effective BIS, AAI, or CePROP at which 50% (ED$_{50}$) and 95% (ED$_{95}$) of the patients produced a LOR$_{verbal}$, LOR$_{lash}$, and LOR$_{noxious}$ were calculated and are shown in table 3. For all three groups, the probability curves for the observations at LOR$_{verbal}$, LOR$_{lash}$, and LOR$_{noxious}$ are shown in figures 4A–C for BIS, in figures 4D–F for AAI, and in figures 5A–C for CePROP.

The ability of the BIS, AAI, and CePROP to predict the level of the OAA/S, LOR$_{lash}$, and LOR$_{noxious}$ as presented by the P$_K$ values is shown in table 4. Overall, similar performances were found for BIS, AAI, and CePROP. A P$_K$ analysis for each independent variable with the three groups pooled revealed similar ability to detect both the

Fig. 1. Nonlinear regression analysis from the raw data from all groups (0, 2, and 4 ng/ml remifentanil effect-site concentration [Ce]) at different propofol effect-site concentrations. (*A*) Correlation with the Bispectral Index (BIS); (*B*) correlation with the A-Line ARX index (AAI).
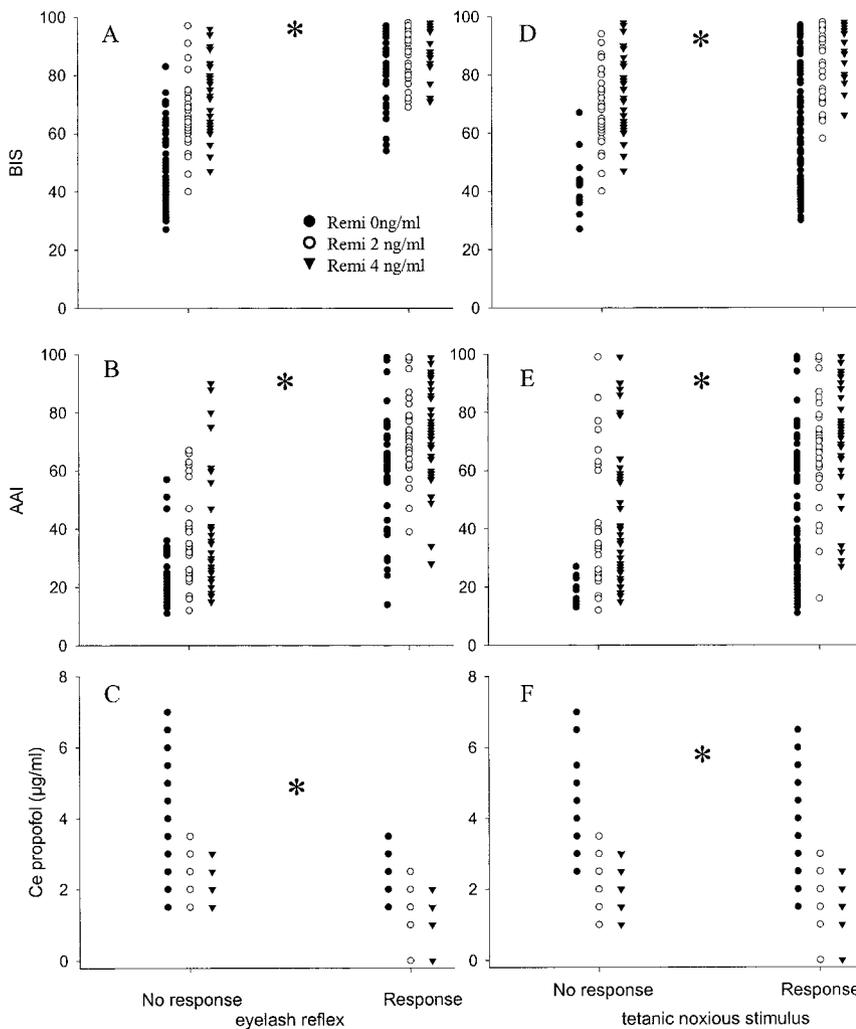
Fig. 3. (*A–C*) Raw data for (no) response to eyelash reflex for Bispectral Index (BIS), A-Line ARX index (AAI), and propofol effect-site concentration (Ce). (*D–F*) Raw data for (no) response to noxious stimulus for BIS, AAI, and propofol effect-site concentration. *$P < 0.05$ for each group between the responsive and non-responsive states. Data from the 0 ng/ml remifentanil (Remi) group are presented as *black circles*, data from the 2 ng/ml remifentanil group as *white circles*, and data from the 4 ng/ml remifentanil group as *black triangles*.

OAA/S levels and LOR_{lash}. In contrast, the overall ability for detection of $LOR_{noxious}$ was lower when pooling the groups together.

By calculating the *t* statistic, we found that this study including 15 patients for each group had the power to determine significant differences between independent variables to predict OAA/S larger than 0.052, which is in accordance with our initial assumption that only differences larger than 0.05 would be considered significantly different.

The P_K values to detect the OAA/S level using the combinations of input variables were better compared to the P_K values of pooled data for BIS, AAI, and CePROP alone. For the composite index using the combination BIS + CePROP + CeREMI, the P_K value was 0.91 (SE = 0.01), and for the composite index using the combination AAI + CePROP + CeREMI, it was 0.93 (SE = 0.01) to detect the OAA/S level.

We also performed more in-depth sensitivity/specificity analysis. Within the three groups, table 5 shows the cutoff values for each independent variable at which the sum of the sensitivity and specificity was the highest, representing the independent variable value where the

Table 3. ED_{50} (95% CI)/ED_{95} Values of BIS, AAI, and EC_{50} (95% CI)/EC_{95} Propofol for All Groups at LOR_{verbal}, LOR_{lash}, and $LOR_{noxious}$

	Group I: 0 ng/ml Remifentanil	Group II: 2 ng/ml Remifentanil	Group III: 4 ng/ml Remifentanil
LOR_{verbal}			
AAI	26 (25–28)/20*§	33 (31–34)/18*§	40 (39–42)/25*§
BIS	61 (60–62)/55*§	66 (65–68)/58*§	77 (75–78)/65*§
CePROP	2.9 (2.7–3.1)/3.8*‖	2.4 (2.2–2.6)/3.1*‖	2.0 (1.8–2.2)/2.7*‖
LOR_{lash}			
AAI	34 (33–36)/21†‡	56 (55–58)/44†‡	56 (54–58)/32†‡
BIS	67 (65–68)/55*‡	80 (79–82)/66*‡	84 (82–85)/71*‡
CePROP	2.8 (2.5–3.0)/3.4†	1.8 (1.7–2.0)/2.6†	1.7 (1.6–1.9)/2.5†
$LOR_{noxious}$			
AAI	16 (15–17)/11*‡	42 (40–44)/23*‡	55 (53–57)/27*‡
BIS	41 (40–43)/29*‡	72 (70–73)/56*‡	85 (84–87)/68*‡
CePROP	4.1 (3.8–4.4)/6.6*#	1.8 (1.4–2.1)/3.8*#	1.3 (1.1–1.5)/3.3*#

* $P < 0.0167$ for ED_{50} levels between all groups. † $P < 0.0167$ for ED_{50} levels between group I *vs.* II and I *vs.* III. ‡ $P < 0.0167$ for ED_{95} levels between all group. § $P < 0.0167$ for ED_{95} levels between group I *vs.* III and II *vs.* III. ‖ $P < 0.0167$ for ED_{95} levels between group I *vs.* III. # $P < 0.0167$ for ED_{95} levels between group I *vs.* II and I *vs.* III.

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; LOR_{lash} = loss of eyelash reflex; $LOR_{noxious}$ = loss of response to electrical tetanic stimulus; LOR_{verbal} = loss of response to verbal command.
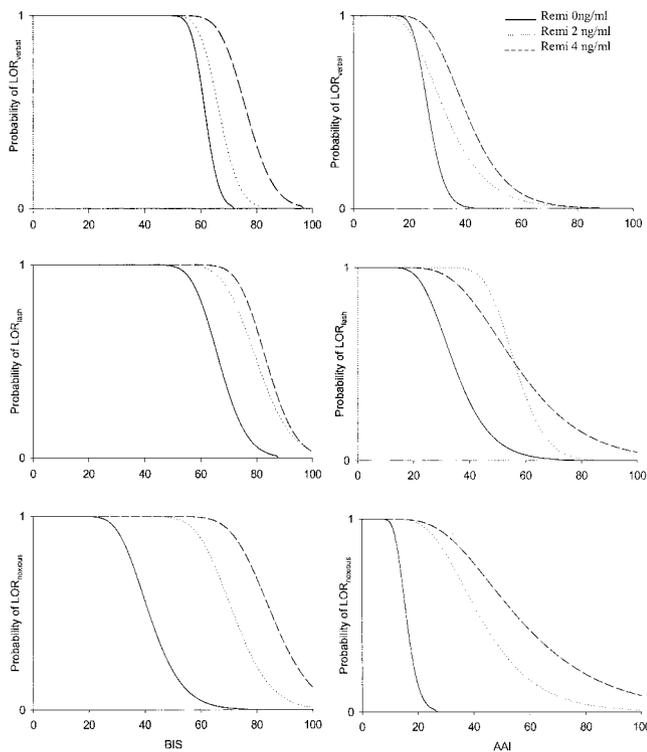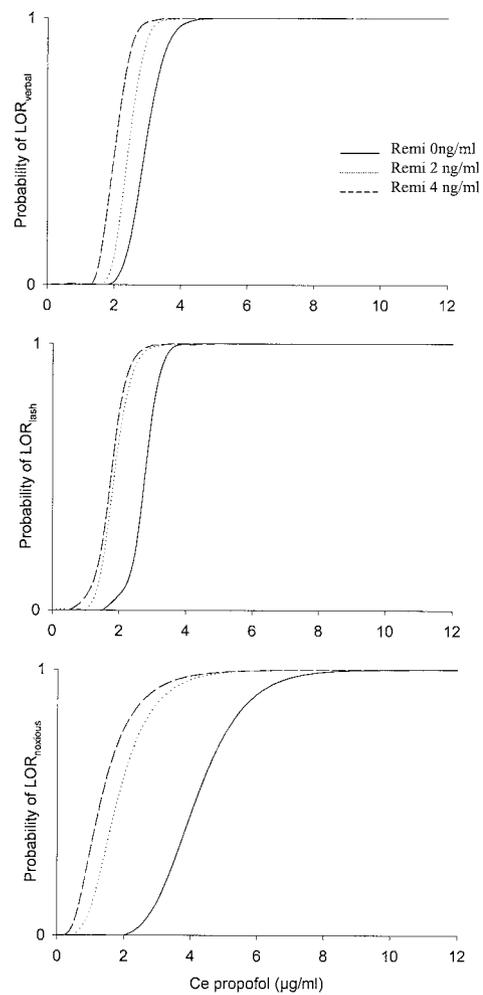
Fig. 4. Probability of loss of response to verbal commend (LOR$_{verbal}$), eyelash reflex (LOR$_{lash}$) and a tetanic electrical stimulus (LOR$_{noxious}$) as a function of Bispectral Index (BIS) and A-Line ARX index (AAI). Data from the 0 ng/ml remifentanil (Remi) group are presented as a *solid line*, data from the 2 ng/ml remifentanil group as a *dotted line*, and data from the 4 ng/ml remifentanil group as a *dashed line*.

overall "errors" are minimized.[28] Table 6 shows the different cutoff values and their specificity at level of 100% sensitivity. When using the combined information of BIS or AAI together with CePROP and CeREMI, the sensitivity/specificity profiles were more accurate. For both combinations, the best sensitivity-*versus*-specificity combinations were found at 100% sensitivity for 82% specificity.

Table 7 shows at which average OAA/S score at LOR$_{lash}$ and LOR$_{noxious}$ occurred in each of the three groups. The OAA/S is an ordinal scale, but it was considered continuous to be able calculate an average of OAA/S score with a decimal value.

Discussion

This study was conducted to compare the performance accuracy of the independent variables BIS, AAI, and CePROP to measure anesthetic depth and how opiates quantitatively influence this information. Therefore, we observed the influence of remifentanil on the accuracy of the AAI, a new index calculated from the MLAEP, to reflect the hypnotic component of anesthesia (measured by the different levels of the OAA/S) and to measure loss of responses to different stimulation defined as

Fig. 5. Probability of loss of response to verbal commend (LOR$_{verbal}$), eyelash reflex (LOR$_{lash}$), and a tetanic electrical stimulus (LOR$_{noxious}$) as a function of the propofol effect-site concentration (Ce). Data from the 0 ng/ml remifentanil (Remi) group are presented as a *solid line*, data from the 2 ng/ml remifentanil group as a *dotted line*, and data from the 4 ng/ml remifentanil group as a *dashed line*.

LOR$_{verbal}$, LOR$_{lash}$, and LOR$_{noxious}$ during stepwise increased levels of propofol infusion with and without remifentanil. The performance of AAI was compared with that of BIS and CePROP.

In previous work, our group concluded that, during propofol anesthesia (without opiates) under steady state conditions, BIS, AAI, and CePROP were accurate independent variables to measure the hypnotic component of anesthesia and loss of responsiveness to different stimuli. Hemodynamic variables did not perform accurately enough to measure the hypnotic–anesthetic status of the patient. BIS correlated best with CePROP, followed by the AAI. Hemodynamics did not correlate well.[8] To study the hypnotic component of anesthesia, two clinical measures (also called dependent variables) were used. We selected the OAA/S score because it provides a good correlation with a clinical reflection of the hypnotic component of anesthesia and has been

Table 4. Prediction Probability (P_K) Described as Mean (SE) for Each Independent Variable (BIS, AAI, and CePROP) Using OAA/S, LOR$_{lash}$, and LOR$_{noxious}$

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil	Pooled Data
OAA/S				
AAI	0.88 (0.02)	0.87 (0.02)	0.88 (0.02)	0.87 (0.01)
BIS	0.93 (0.01)	0.90 (0.02)	0.88 (0.02)	0.90 (0.01)
CePROP	0.92 (0.02)	0.92 (0.03)	0.92 (0.02)	0.90 (0.01)
LOR$_{lash}$				
AAI	0.94 (0.02)	0.96 (0.02)	0.87 (0.04)	0.94 (0.01)
BIS	0.96 (0.02)	0.92 (0.03)	0.94 (0.04)	0.95 (0.01)
CePROP	0.94 (0.02)	0.95 (0.02)	0.94 (0.02)	0.93 (0.01)
LOR$_{noxious}$				
AAI	0.87 (0.04)*	0.86 (0.04)*	0.81 (0.05)*	0.72 (0.03)
BIS	0.88 (0.05)*	0.86 (0.05)	0.86 (0.04)*	0.75 (0.03)
CePROP	0.83 (0.06)	0.86 (0.04)*	0.87 (0.04)*	0.72 (0.03)

* $P < 0.05$ compared to pooled data P_K.

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; OAA/S = Observer's Assessment of Alertness/Sedation Scale; LOR$_{lash}$ = loss of eyelash reflex; LOR$_{noxious}$ = loss of response to electrical tetanic stimulus.

tested prospectively.[29] Also, loss of eyelash reflex was used because it is a simple binary variable and commonly applied by anesthesiologists in clinical practice to detect loss of consciousness.[14]

In all groups, a stepwise increase in CePROP resulted in a monotonic decrease in BIS and AAI as shown in figure 1. Similar to our previous work using propofol alone,[8] the correlation between BIS and the combined drug effect-site concentrations was higher than for the AAI. In all groups, a monotonic decrease in both BIS and AAI was observed at decreasing OAA/S levels as shown in figure 2. Similar findings were found for LOR$_{lash}$, as seen in figures 3A–C.

LOR$_{verbal}$ and LOR$_{lash}$ were reached at higher independent variable values in a dose-dependent manner when adding remifentanil. This can be concluded from the Probit analyses shown in figure 4 and the extracted ED$_{50}$ and ED$_{95}$ as seen in table 3. Although some differences between groups for the ED$_{50}$ and ED$_{95}$ did not reach the

level of significance, a clear trend could be observed. Our results are in contrast with the findings from Iselin-Chaves *et al.*,[30] who reported no significant influence of opiates on the BIS and MLAEP to detect the probability of loss of consciousness and lack of recall by using the OAA/S score. However, they used lower concentrations of opiates (50 and 100 ng/ml alfentanil; potency ratio alfentanil:remifentanil around 40:1). Recently, Mi *et al.*[14] also found that when applying fentanyl pretreatment during propofol administration, the hypnotic endpoints were achieved at higher BIS values. The addition of remifentanil potentiates the effect of propofol. LOR$_{verbal}$ and LOR$_{lash}$ were detected at lower CePROP in the 2 and 4 ng/ml remifentanil groups compared to the 0 ng/ml remifentanil group, as shown in figure 5. Also, EC$_{50}$ and EC$_{95}$ propofol decreased significantly or tended to decrease in a remifentanil dose-dependent matter, as also described previously by others.[31]

A possible bias might have been caused by the influence of opiates on the clinical dependent variables. Both

Table 5. Cutoff Values (Sensitivity [%]–Specificity [%]; Sum of Sensitivity + Specificity [%]) at Maximum Level of Sensitivity + Specificity whereby Sensitivity > Specificity

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil
LOR$_{verbal}$			
AAI	29 (91–91; 182)	42 (82–81; 163)	41 (93–86; 179)
BIS	61 (99–94; 193)	64 (95–76; 171)	79 (85–82; 167)
CePROP	3.5 (99–76; 175)	3.0 (98–57; 155)	2.5 (96–64; 160)
LOR$_{lash}$			
AAI	34 (90–88; 178)	47 (96–82; 178)	47 (96–77; 173)
BIS	67 (90–88; 178)	75 (89–85; 174)	84 (89–87; 176)
CePROP	3.0 (92–85; 177)	2.5 (98–68; 166)	2.0 (87–83; 170)
LOR$_{noxious}$			
AAI	20 (76–64; 140)	40 (92–71; 163)	59 (84–67; 151)
BIS	44 (84–71; 155)	75 (76–71; 147)	90 (77–73; 150)
CePROP	4.0 (80–71; 151)	2.5 (88–50; 138)	2.5 (95–40; 135)

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; LOR$_{lash}$ = loss of eyelash reflex; LOR$_{noxious}$ = loss of response to electrical tetanic stimulus; LOR$_{verbal}$ = loss of response to verbal command.

Table 6. Cutoff Values (Specificity) at Level of 100% Sensitivity

	0 ng/ml Remifentanil	2 ng/ml Remifentanil	4 ng/ml Remifentanil
LOR$_{verbal}$			
AAI	19 (58%)	15 (5%)	26 (41%)
BIS	53 (58%)	61 (52%)	65 (55%)
CePROP	4.0 (39%)	3.5 (14%)	3.0 (23%)
LOR$_{lash}$			
AAI	23 (63%)	38 (59%)	27 (37%)
BIS	53 (46%)	68 (65%)	70 (53%)
CePROP	3.5 (63%)	3.0 (32%)	2.5 (53%)
LOR$_{noxious}$			
AAI	13 (14%)*	15 (7%)	26 (27%)
BIS	29 (7%)	57 (21%)	65 (27%)
CePROP	7.0 (7%)	3.5 (21%)	3.0 (13%)

* At the 98% sensitivity level.

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; LOR$_{lash}$ = loss of eyelash reflex; LOR$_{noxious}$ = loss of response to electrical tetanic stimulus; LOR$_{verbal}$ = loss of response to verbal command.

Table 7. Averaged OAA/S Score at LOR_lash and LOR_noxious

Group	OAA/S Level at LOR$_{lash}$	OAA/S Level at LOR$_{noxious}$
0 ng/ml Remifentanil	3.6	0.87
2 ng/ml Remifentanil	4.2	3.4
4 ng/ml Remifentanil	4.1	4.0

* Average of 15 patients.

LOR$_{lash}$ = loss of eyelash reflex; LOR$_{noxious}$ = loss of response to electrical tetanic stimulus; OAA/S = Observer's Assessment of Alertness/Sedation scale.

OAA/S (from level 2 to 0) and eyelash reflex use tactile stimuli, which might have been lost earlier when adding remifentanil. To demonstrate this, the averaged OAA/S scores at LOR$_{lash}$ and LOR$_{noxious}$ were calculated and are shown in table 7. LOR$_{lash}$ results showed some increase. A clear increase in the OAA/S value is observed when remifentanil is added. In the 2 and 4 ng/ml remifentanil groups, several patients were still responsive at LOR$_{noxious}$. This resulted in larger transitions when the transition between the response and the unresponsive state, for example, from OAA/S 3 to OAA/S 0 without passing through OAA/S levels 2 or 1, causing an increase in averages. This finding obviously confirms that remifentanil blocks the response to pain, without causing LOR$_{verbal}$ and LOR$_{lash}$, but proves also that it might be difficult to quantify the dependence of the electronic independent variables such as BIS and AAI to opiates because the definitive standard to which they were compared changed its behavior through the groups. This fact highlights that care should be taken when validating loss of response to different stimuli by using OAA/S score or eyelash reflex when opioids are administered. However, because no better validated clinical scoring techniques exist at this moment, we have to accept this possible bias.

Skepticism still exists in the literature regarding the accuracy of cerebrally derived parameters to measure anesthetic depth when adding opiates. Several articles suggested a weaker correlation between BIS and CePROP in the presence of opiates.[14,32,33] Although they state that this might reveal the importance of an analgesic component on the efficacy of depth-of-anesthesia electronic monitors, these studies did not apply specific statistical techniques such as prediction probability[25] or specificity/sensitivity calculations.[1] Also, one should clearly differentiate the phenomenon of the influence of opiates on the changes in cutoff values for LOR$_{verbal}$, LOR$_{lash}$, and LOR$_{noxious}$ and the overall change in accuracy of these anesthetic depth independent variables when adding opiates.

The prediction probability, P$_K$, provides a good alternative to investigate the overall relative performance of the different independent variables to measure the hypnotic component of anesthesia and loss of responsiveness to different stimuli.[25] For BIS, Lysakowski et al.[34] found no decrease in P$_K$ when adding clinical dosages of fentanyl, alfentanil, remifentanil, or sufentanil versus placebo during propofol administration. Iselin-Chaves et al.[16] studied the influence of different dosages of alfentanil on the accuracy of both BIS and nonprocessed MLAEP during propofol administration and found no differences in P$_K$ between groups. In their study, BIS performed better than MLAEP. In our study, as indicated in table 4, the performance results indicate that both BIS and AAI are reliable independent variables for assessing the level of OAA/S and LOR$_{lash}$ and did not decrease by the addition of remifentanil. Before being able to conclude that the ability to measure the hypnotic component remained intact, a P$_K$ analysis with the three groups pooled was needed. As seen in table 4, the P$_K$ remained similar to the group-based P$_K$ for both OAA/S and LOR$_{lash}$, indicating an overall equal accuracy of the independent variables with and without the addition of opiates.

At the level of significance used in our study, BIS and AAI were found to be comparable in performance to the estimated steady state propofol concentration, CePROP. When drug effect-site concentrations are known, one might argue that it only make sense to measure BIS or AAI if the combined information offers more accuracy in measuring depth of anesthesia than a single measure alone. *Vice versa*, it might be asked whether drug effect-site concentrations offer additional information for the clinician when BIS or AAI is used. However, it must be stated that electroencephalographic and MLAEP monitors can be attached to the patient at any random time, whereas calculation of drug effect-site concentration requires knowledge of the complete administration history. As none of the independent variables in the present study gave a P$_K$ larger than 0.9, when pooling the data from the three groups into one, it could be interesting to explore whether a new independent variable defined as a composite of the electronic independent variables and the anesthetics concentrations would produce a larger P$_K$ when predicting the OAA/S. Therefore, we calculated the P$_K$ value for the combined information from both BIS + CePROP + CeREMI and AAI + CePROP + CeREMI using ordinal logistic regression to develop a predicted OAA/S score (see Appendix). For both combinations, the overall prediction probability for predicting the levels of OAA/S increased (or tended to increase) compared to the pooled P$_K$ data.

Because the P$_K$ concept was developed to generalize nonparametric receiver operating characteristic curves area to polytomous ordinal patient state,[26] we thought it was interesting to observe some specific sensitivity/specificity characteristics for BIS, AAI, and CePROP. Statistically speaking, the most frequently applied combined sensitivity/specificity lies at the elbow of the receiver operating characteristic curve, where the sum of both sensitivity and specificity is the highest.[28] However, as defined by J. Drummond[35] recently, a depth of anesthe-

sia–independent variable should have, at a minimum, a 100% sensitivity (no false negatives) if what the clinicians seek is a specific numeric threshold (cutoff value) that can be interpreted to mean "not aware." Therefore, we observed the influence of remifentanil on the cutoff value for LOR_{verbal} and LOR_{lash} and the corresponding sensitivity/specificity profiles for BIS, AAI, and CePROP at the two important points of the receiver operating characteristic curves: (1) highest sum of sensitivity and specificity and (2) level of 100% sensitivity. For both BIS and AAI, the cutoff values at LOR_{verbal} and LOR_{lash} revealing the highest sum of sensitivity/specificity clearly increased in a dose-dependent manner during remifentanil addition. However, the changes in the values of the highest sum were minimal and similar between the different anesthetic depth–independent variables, as observed in table 5. This means that the addition of remifentanil did not decrease the overall sensitivity/specificity profiles of the tested independent variables when observing the cutoff value at the level of maximum combined sensitivity and specificity. As shown in table 6, the cutoff values detecting LOR_{verbal} and LOR_{lash} at the 100% sensitivity level were influenced by the addition of remifentanil. For BIS, a trend toward higher cutoff values at the 100% sensitivity level was observed at LOR_{verbal} and LOR_{lash}. For AAI, the cutoff value only increased in the 4 ng/ml remifentanil group when observing LOR_{verbal} and slightly increased between the 0 and 2 ng/ml remifentanil groups, between the 0 and 4 ng/ml remifentanil groups, and when observing LOR_{lash}. The CePROP cutoff values decreased at this 100% sensitivity level when adding remifentanil. For all independent variables, the influence of remifentanil on the specificity at a level of 100% sensitivity was calculated. For the AAI, a clear decrease in specificity was observed in the 2 ng/ml remifentanil group when observing LOR_{verbal}, and a decrease between the 2 and 4 ng/ml remifentanil groups was seen when observing LOR_{lash}. This might be caused by the severity of the used statistical criterion, where one outlier might cause a dramatic decrease in specificity at the 100% sensitivity level. No decrease in specificity was observed between groups for BIS when observing LOR_{verbal} and LOR_{lash}. Inconsistencies are found in the data for CePROP when comparing the specificity results obtained by LOR_{verbal} with these obtained by using LOR_{lash}. Better sensitivity/specificity profiles were obtained when the information from drug concentrations and BIS or AAI were used together.

This study also tested the influence of opiates on the performance of the independent variables to predict $LOR_{noxious}$. The supramaximal tetanic stimulus used in this study was previously used by others as a substitute for conventional forms of stimulation in humans.[36] In previous work, when only using propofol without opiates, we observed that measures from the cerebral cortex such as BIS and AAI were poor predictors for

$LOR_{noxious}$.[8] The overall accuracy for $LOR_{noxious}$ tended to be lower for all independent variables compared with their hypnotic prediction accuracy. The P_K values were lower, however, because of the larger SE, not statistically significant at the level of significance used in our study. Sensitivity/specificity profiles for all independent variables in the three groups were calculated at the two classic points. As seen in table 5, the values of the highest sum of sensitivity and specificity to $LOR_{noxious}$ were lower compared with the values for the detection of LOR_{verbal} and LOR_{lash}. Also, the cutoff values at the point of highest sensitivity/specificity were clearly influenced by the addition of remifentanil in a dose-dependent manner. At the level of 100% sensitivity to detect $LOR_{noxious}$, a very low specificity and a clear influence of remifentanil on the cutoff values was observed (table 6).

A strong interaction between propofol and remifentanil is observed at the ED_{50} and ED_{95} levels when studying the analgesic component of this interaction at $LOR_{noxious}$, as plotted in figure 5 and table 3. This interaction is more pronounced than the hypnotic interaction between remifentanil and propofol, resulting in the fact that in this "staircase study," patients in the 2 and 4 ng/ml remifentanil groups might reach $LOR_{noxious}$ before reaching LOR_{verbal} and LOR_{lash}, as shown in table 7. Similar findings were observed for fentanyl and propofol by Smith *et al.*[37] and by Katoh *et al.*[38] for fentanyl and sevoflurane.

In conclusion, we found that although BIS, AAI, and CePROP were increased by remifentanil during propofol administration, their ability to detect OAA/S and LOR_{lash} remained accurate. Improved performance is obtained when BIS and AAI are measured in conjunction with drug effect-site concentrations. Remifentanil decreases the ability of these independent variables to detect $LOR_{noxious}$.

References

1. Drummond J: Monitoring depth of anesthesia. ANESTHESIOLOGY 2000; 93: 876–82

2. Sleigh JW, Donovan J: Comparison of Bispectral Index, 95% spectral edge frequency, and approximate entropy of the EEG, with changes in heart rate variability during induction of general anaesthesia. Br J Anaesth 1999; 82:666–71

3. Bruhn J, Ropcke H, Hoeft A: Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. ANESTHESIOLOGY 2000; 92:715–26

4. Bruhn J, Lehmann LE, Ropcke H, Bouillon TW, Hoeft A: Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. ANESTHESIOLOGY 2001; 95:30–5

5. Thornton C, Sharpe RM: Evoked responses in anaesthesia. Br J Anaesth 1998; 81:771–81

6. Jensen EW, Nygaard M, Henneberg SW: On-line analysis of middle latency auditory evoked potentials (MLAEP) for monitoring depth of anaesthesia in laboratory rats. Med Eng Phys 1998; 20:722–8

7. Urhonen E, Jensen EW, Lund J: Changes in rapidly extracted auditory

evoked potentials during tracheal intubation. Acta Anaesthesiol Scand 2000; 44:743–8

8. Struys MMRF, Jensen EW, Smith W, Smith NT, Rampil I, Dumortier FJE, Mestach C, Mortier EP: Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: A comparison with Bispectral Index and hemodynamic measures during propofol administration. ANESTHESIOLOGY 2002; 96:803–16

9. Litvan H, Jensen EW, Revuelta M, Henneberg SW, Paniagua P, Campos JM, Martinez P, Caminal P, Villar Landeira JM: Comparison of auditory evoked potentials and the A-line ARX Index for monitoring the hypnotic level during sevoflurane and propofol induction. Acta Anaesthesiol Scand 2002; 46:245–51

10. Alpiger S, Helbo-Hansen HS, Jensen EW: Effect of sevoflurane on the mid-latency auditory evoked potentials measured by a new fast extracting monitor. Acta Anaesthesiol Scand 2002; 46:252–6

11. Ge SJ, Zhuang XL, Wang YT, Wang ZD, Li HT: Changes in the rapidly extracted auditory evoked potentials index and the Bispectral Index during sedation induced by propofol or midazolam under epidural block. Br J Anaesth 2002; 89:260–4

12. Vuyk J: Pharmacokinetic and pharmacodynamic interactions between opioids and propofol. J Clin Anesth 1997; 9:23S–26S

13. Mi WD, Sakai T, Takahashi S, Matsuki A: Haemodynamic and electroencephalograph responses to intubation during induction with propofol or propofol/fentanyl. Can J Anaesth 1998; 45:19–22

14. Mi WD, Sakai T, Singh H, Kudo T, Kudo M, Matsuki A: Hypnotic endpoints vs. the Bispectral Index, 95% spectral edge frequency and median frequency during propofol infusion with or without fentanyl. Eur J Anaesthesiol 1999; 16:47–52

15. Iselin-Chaves IA, Flaishon R, Sebel PS, Howell S, Gan TJ, Sigl J, Ginsberg B, Glass PS: The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the Bispectral Index. Anesth Analg 1998; 87:949–55

16. Iselin-Chaves IA, El Moalem HE, Gan TJ, Ginsberg B, Glass PS: Changes in the auditory evoked potentials and the Bispectral Index following propofol or propofol and alfentanil. ANESTHESIOLOGY 2000; 92:1300–10

17. Jensen E, Litvan H: Monitoring of auditory evoked potentials and bispectral analysis of the EEG during remifentanil infusion. Journal für Anästhesie und Intensivbehandlung 2001; 3:88–9

18. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502–16

19. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82

20. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil: I. Model development. ANESTHESIOLOGY 1997; 86:10–23

21. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil: II. Model application. ANESTHESIOLOGY 1997; 86:24–33

22. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. J Pharmacokinet Biopharm 1992; 20:147–69

23. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment versus two methods for effect compartment–controlled target-controlled infusion for propofol. ANESTHESIOLOGY 2000; 92:399–406

24. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51

25. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38–51

26. Smith WD, Dutton RC, Smith NT: A measure of association for assessing prediction accuracy that is a generalization of non-parametric ROC area. Stat Med 1996; 15:1199–215

27. Dutton RC, Smith WD, Rampil IJ, Chortkoff BS, Eger EI II: Forty-hertz midlatency auditory evoked potential activity predicts wakeful response during desflurane and propofol anesthesia in volunteers. ANESTHESIOLOGY 1999; 91:1209–20

28. Altman DG, Bland JM: Diagnostic tests 3: Receiver operating characteristic plots (statistical communications). BMJ 1994; 309:188

29. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. ANESTHESIOLOGY 1997; 86:836–47

30. Glass PS, Iselin-Chaves IA, Goodman D, Delong E, Hermann DJ: Determination of the potency of remifentanil compared with alfentanil using ventilatory depression as the measure of opioid effect. ANESTHESIOLOGY 1999; 90:1556–63

31. Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG: Propofol anesthesia and rational opioid selection: Determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. ANESTHESIOLOGY 1997; 87:1549–62

32. Barr G, Anderson RE, Owall A, Jakobsson JG: Effects on the Bispectral

Index during medium-high dose fentanyl induction with or without propofol supplement. Acta Anaesthesiol Scand 2000; 44:807–11

33. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, Smith NT, Glass PS, Manberg P: A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg 1997; 84:891–9

34. Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E: Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and Bispectral Index during propofol induction of anaesthesia. Br J Anaesth 2001; 86:523–7

35. Drummond JC: Monitoring depth of anesthesia: With emphasis on the application of the Bispectral Index and the middle latency auditory evoked response to the prevention of recall. ANESTHESIOLOGY 2000; 93:876–82

36. Leslie K, Sessler DI, Smith WD, Larson MD, Ozaki M, Blanchard D, Crankshaw DP: Prediction of movement during propofol/nitrous oxide anesthesia: Performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. ANESTHESIOLOGY 1996; 84:52–63

37. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PS: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. ANESTHESIOLOGY 1994; 81:820–8

38. Katoh T, Ikeda K: The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. ANESTHESIOLOGY 1998; 88:18–24

Appendix: Definition of an OAA/S Predictor Based on Combinations of AAI/BIS, Propofol, and Remifentanil Effect Concentrations

Methods

Two composite indexes were defined to study whether the combined information BIS + CePROP + CeREMI or AAI + CePROP + CeREMI offers more accuracy in loss of response to hypnotic stimuli than a single measure alone (BIS, AAI, CeREMI, and CePROP). The composite index was defined as an OAA/S predictor based on combined information from the data set BIS + CePROP + CeREMI or AAI + CePROP + CeREMI. The method of choice for designing a composite index was the ordinal logistic regression. The ordinal logistic regression has the advantage, as compared with multiple linear regression, that the output variable is ordinal. An ordinal variable is a categorical variable that has three or more levels of natural ordering, such as awake, drowsy, asleep, and deep asleep. This is suitable for the kind of data from this study because the OAA/S scale is ordinal and not linear. Two models were proposed: model A, where the input variables are BIS, CePROP, and CeREMI; and model B, where the input variables are AAI, CePROP, and CeREMI. The composite index is the output variable that in both models is a prediction of the OAA/S as shown in figures 6 and 7. The composite index is therefore ordinal in the 0–5 range as the OAA/S.

An ordinal logistic regression model was calculated by using SPSS software (SPSS Inc., Chicago, IL), which also provides a more detailed description of the method. The model is composed of constants, θ_i, factors, β_n, and a link function, here the "logit." The constants are associated with the ith event, which in the current study refers to the level of OAA/S.

The factors are obtained from each covariable (input), which here are BIS, AAI, CePROP, and CeREMI at every jth sample in time. Hence, the two models are defined in equations 1 and 2
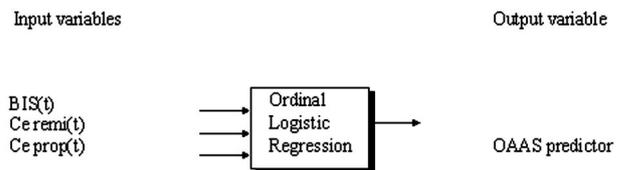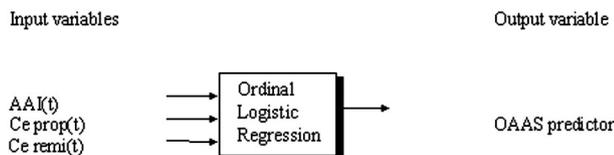

Fig. 6. Model A for calculating the Observer's Assessment of Alertness/Sedation Scale (OAA/S) predictor from the combined information Bispectral Index (BIS) + propofol effect-site concentration (CePROP) + remifentanil effect-site concentration (CeREMI).

Input variables Output variable

Fig. 7. Model B for calculating the Observer's Assessment of Alertness/Sedation Scale (OAA/S) predictor from the combined information A-Line ARX index (AAI) + propofol effect-site concentration (CePROP) + remifentanil effect-site concentration (CeREMI).

$$g(\text{OAAS ij}) = \theta i + \beta_{\text{remi}}\text{Ce Remi}_i + \beta_{\text{Ceprop}}\text{Ceprop}_j + \beta_{\text{bis}}\text{BIS}_j \quad (1)$$

$$g(\text{OAAS ij}) = \theta i + \beta_{\text{remi}}\text{Ce Remi}_j + \beta_{\text{Ceprop}}\text{Ceprop}_j + \beta_{\text{AII}}\text{AAI}_j. \quad (2)$$

The accumulated probability of being at or lower than the ith level of OAA/S at the jth sample in time, γ_{ij}, is now calculated as

$$\gamma_{ij} = \frac{e^{g(\text{OAASi})}}{1 + e^{g(\text{OAASi})}} \quad (3)$$

Example: The following state has been recorded: remifentanil = 0 ng/ml, propofol = 4 μg/ml, AAI = 25. When using these data as input to model B, the corresponding probabilities for OAA/S 0, 1, 2, 3, 4, and 5 are 0.7944, 0.8867, 0.9620, 0.9935, 0.9998, and 1. The model

Table 8. Ordinal Logistic Regression of Model A (BIS)

Predictor	Value	SD	Z	P
θ_1	−3.718	1.851	−2.01	0.045
θ_2	−2.995	1.850	−1.62	0.105
θ_3	−1.832	1.853	−0.99	0.323
θ_4	−0.109	1.868	−0.06	0.954
θ_5	3.228	1.896	1.70	0.089
βremi	0.9548	0.1163	8.21	0.000
βprop	2.6277	0.3395	7.74	0.000
βbis	−0.10034	0.01779	−5.64	0.000

Test that all slopes are zero: *P* value < 0.001.

θ_{1-5} = constants of the ordinal logistic regression model used in the prediction of the OAA/S levels 1 to 5; βremi = coefficient of the ordinal logistic regression model multiplied with the remifentanil (remi) effect-site concentration in the prediction equation; βprop = coefficient of the ordinal logistic regression model multiplied with the propofol (prop) effect-site concentration in the prediction equation; βbis = coefficient of the ordinal logistic regression model multiplied with the BIS in the prediction equation; SD = standard deviation.

Table 9. Ordinal Logistic Regression of Model B (AAI)

Predictor	Value	SD	Z	P
θ_1	−9.265	1.117	−8.29	0.000
θ_2	−8.559	1.094	−7.83	0.000
θ_3	−7.386	1.057	−6.99	0.000
θ_4	−5.583	1.009	−5.53	0.000
θ_5	−1.9793	0.9563	−2.07	0.038
βremi	1.0143	0.1194	8.50	0.000
βprop	3.0479	0.3091	9.86	0.000
βAAI	−0.064	0.0097	−6.61	0.000

Test that all slopes are zero: *P* value < 0.001.

θ_{1-5} = constants of the ordinal logistic regression model used in the prediction of the OAA/S levels 1 to 5; βremi = coefficient of the ordinal logistic regression model multiplied with the remifentanil (remi) effect-site concentration in the prediction equation; βprop = coefficient of the ordinal logistic regression model multiplied with the propofol (prop) effect-site concentration in the predication equation; βAAI = coefficient of the ordinal logistic regression model multiplied with the AAI in the prediction equation; SD = standard deviation.

output is always the OAA/S level, where the accumulated probability exceeds 0.67. In this example, the predicted OAA/S is 0 because the first probability (0.7944) is larger than 0.67.

Results

Tables 8 and 9 show the parameters of the ordinal logistic regression for models A and B, with the corresponding levels of significance for each constant and factor as well as the *P* value for the whole model. A *P* value less than 0.05 means that the parameter is significant in the model. Both models were statistically significant. The OAA/S values predicted by the two models were compared with the measured OAA/S and evaluated using the P_K analysis, shown in table 10.

Table 10. Prediction Probability (P_K of the Indices

Model	P_K (SE)
Model A (BIS + CePROP + CeREMI)	0.91 (0.01)
Model B (AAI + CePROP + CeREMI)	0.93 (0.01)

AAI = A-Line ARX index; BIS = Bispectral Index; CePROP = calculated propofol effect-site concentration; CeREMI = calculated remifentanil effect-site concentration.