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Prediction of depth of sedation and anaesthesia by the Narcotrend™ EEG monitor

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Background. The Narcotrend™ (Monitor Technik, Bad Bramstedt, Germany) assesses sedation by automatic classification of EEG signals, using a scale first used for visual evaluation of the EEG. Limited information is available on its value, and only a few studies of the method exist. We set out to study the performance of the Narcotrend™ during propofol sedation.

Methods. In 23 ASA I–II patients, aged 18–65 yr, about to have general anaesthesia, we induced anaesthesia in steps using a target-controlled infusion of propofol. After equilibration for 8 min at each predicted propofol concentration (0.5, 1.0, 2.0, 3.0 and 4.0 μg ml^{-1}), sedation was assessed clinically with the modified Observer's Assessment of Alertness/Sedation Scale and the Narcotrend™ stage was noted. The prediction performance of the Narcotrend™ was assessed with the prediction probability P_K. A P_K value of 1.0 means an exact prediction on every occasion, while a P_K of 0.5 is no better than a 50:50 chance of being correct.

Results. In 12 women and 11 men (age 42 (SD 11) yr), a total of 138 measurements were made; 129 were analysed and nine were of poor signal quality. The prediction probability for the corresponding level of sedation was P_K=0.92 (SE 0.01); for the different target concentrations of propofol it was P_K = 0.91 (SE 0.01).

Conclusions. The Narcotrend™ can monitor sedation with propofol. Other sedatives, anaesthetics and opioids should be used to test this monitor.

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As depth of sedation cannot be reliably judged by cardiovascular measurements alone, especially during total i.v. anaesthesia,[1] a reliable method is needed to measure the hypnotic component of sedation and anaesthesia. Hypnotic effects are associated with a slowing of the EEG signal, and processed EEG variables such as the Bispectral Index (BIS) or the spectral edge frequency were developed to ease EEG interpretation, which is time-consuming and requires special knowledge.[2]

The Narcotrend™ (Monitor Technik, Bad Bramstedt, Germany) is an EEG monitor. It was developed by a research group at the Hannover University Medical School (Germany) and uses algorithms for automatic assessment of the raw EEG during anaesthesia and sedation.[2 3] Two EEG channels are recorded comparing signals from the two hemispheres of the brain. After artefact detection, the EEG signals are automatically classified, using multivariate statistical procedures, using a scale with six stages from A (awake) to F (general anaesthesia/coma) and 14 substages.[4] The stages are displayed on a computer monitor that also shows the raw signal EEG, the median frequency, the spectral edge frequency and a trend analysis.

We set out to test the ability of the Narcotrend™ to assess sedation obtained with different propofol doses.

Materials and methods

After ethics committee (Medizinische Fakultät der Universität Würzburg) approval and with written informed consent from the patients, we prospectively studied ASA I–II patients aged from 18 to 65 yr who were about to have anaesthesia for ophthalmic or urological surgery. We

excluded patients with central nervous or cerebrovascular diseases, including poor hearing, those taking benzodiazepines or other centrally acting agents, those with a history of oesophageal reflux or a body mass index over 30. No premedication was given.

In the induction room we applied blood pressure, ECG and pulse oximeter monitors. The three EEG electrodes for the Narcotrend™ (Version 2.0 AF; Monitor Technik) were applied to the forehead as recommended by the manufacturer. A full description of the Narcotrend™ algorithm has been published.[5] Impedance was automatically checked and the electrodes repositioned if the value was greater than 6 kΩ. The range of the Narcotrend™ stages and substages shown by the monitor are given in Table 1. After recording the heart rate and blood pressure and the Narcotrend™ stage, we set up a propofol infusion using a target-controlled infusion system (BD Pilot Anaesthesia; Becton Dickinson and Fresenius VIAL Medical, Brezins, France), with an initial target concentration of 0.5 μg ml^{-1}. Considering the plasma effect–site equilibration half-time for propofol,[6–8] we took measurements 8 min after the target level of propofol had been set. The Narcotrend™ stage was then recorded by one person and a clinical assessment of sedation, using the modified Observer's Assessment of Alertness/Sedation Scale (OAA/S) (Table 2), was made by another person who was not aware of the monitor output. Of the four components of the OAA/S score, responsiveness was the chief characteristic used for assessing the sedation level.[9 10] The set concentration of propofol was increased incrementally to 1.0, 2.0, 3.0 and 4.0 μg ml^{-1} and the sedation score and cardiovascular measurements were recorded at each stage.

At greater degrees of sedation, when the OAA/S scale failed, a noxious stimulus was applied with a peripheral nerve stimulator (NS 252; Fisher & Paykel, Auckland, New Zealand) using a tetanic stimulus with 50 Hz/50 mA for 10 s via ECG electrodes mounted over the tibia.[11]

Table 1 Kugler's[4] classification of stages of sedation

Awake	A_0
Subvigilance	A_1/A_2
Very slight sleep (sedation)	$B_0/B_1/B_2$
Light sleep (light anaesthesia)	$C_0/C_1/C_2$
Moderately deep sleep (general anaesthesia)	$D_0/D_1/D_2$
Very deep sleep (general anaesthesia with deep hypnosis)	E
Coma	F

Statistics

Statistical analysis was performed with SPSS 11.0 (SPSS, Chicago, IL, USA). The prediction probability P_K was calculated to show the relationship between the anaesthetic depth indicator value (Narcotrend™ stages) and the observed anaesthetic depth (OAA/S levels). The prediction probability P_K is independent of scale units, it does not require knowledge of underlying distributions or efforts to linearize or transform scales, and is recommended as an appropriate measure for evaluating and comparing the performance of anaesthetic depth indicators.[12] We determined the P_K and compared P_K values with special software (PK/PKD MACRO™; California State University, Sacramento, CA, USA) based on a standard calculation program (Excel™, Microsoft). To describe the precision of the estimated prediction probability P_K, the standard deviation of the estimate of P_K was calculated, which in this statistical approach is called the standard error (SE) of the estimate of P_K (personal communication, W. Smith, California State University, Sacramento, CA, USA). Spearman rank correlation analysis was performed with SPSS.

Results

Patients characteristics are shown in Table 3. A total of 138 measurements were obtained, of which nine could not be interpreted because the signal quality was poor. The Narcotrend™ failed to analyse the EEG of seven patients

Table 3 Patient characteristics

No. of patients	23
Mean age: yr (SD)	42 (11)
Age range: yr	20–64
Sex: female/male	12/11
Mean weight: kg (SD)	73 (14)
Min/max: kg	52/100
Mean body mass index	24.2 (3.3)
Min/max	19/30
ASA classification I/II	7/16

Table 2 Modified Observer's Assessment of Alertness/Sedation Scale (OAA/S). In assessing the OAA/S score the main criterion was responsiveness

Score	Responsiveness	Speech	Facial expression	Eyes
5 (alert)	Responds readily to voice with normal tone	Normal	Normal	Clear, no ptosis
4	Responds slowly to voice with normal tone	Mild slowing	Mild relaxation	Mild ptosis (less than half the eye)
3	Responds after calling loudly or repeatedly	Prominent slowing or slurring	Marked relaxation (slack jaw)	Marked ptosis (half the eye or more)
2	Responds after mild prodding or shaking	Few recognizable words	–	–
1	Does not respond to mild prodding or shaking	–	–	–
0	Does not respond to pain	–	–	–

at target propofol concentrations of 0.0, 0.5, 1.0, and 2.0 μg ml^{-1}. With all these measurements the OAA/S score was 4 or 5. In these lightly sedated patients, the signal could have been contaminated by electrical activity from muscles.

Narcotrend™ and OAA/S scale

With increasing sedation indicated by the Narcotrend™ levels, the OAA/S scores decreased significantly ($P<0.05$). The Narcotrend™ levels and the corresponding values of the OAA/S score for each patient and the median response are shown in Figure 1. The prediction probability (P_K) value for the OAA/S scores in each patient ranged from 0.86 to 1.00. The overall value was 0.92 (SE 0.01), indicating a strong relationship between the Narcotrend™ and OAA/S stages. This was supported by the Spearman correlation coefficient (ρ=0.91). In addition, if the sedation scale is treated as an interval variable, linear regression analysis showed a positive correlation (R^2=0.83, $P<0.001$), with the following relationship:

OAA/S=–0.51[Narcotrend™ level]+5.35

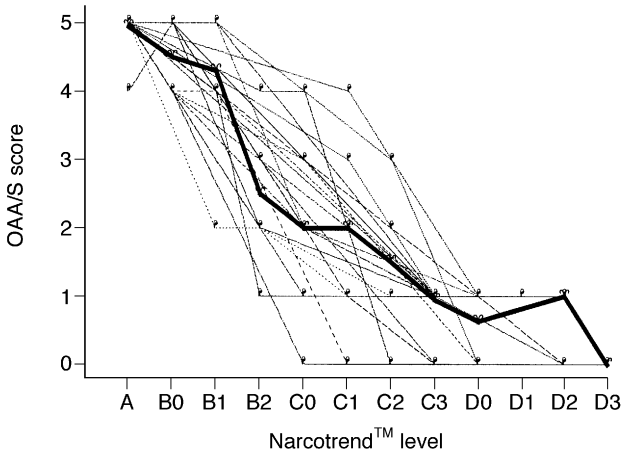

Fig 1 OAA/S *vs* Narcotrend™. OAA/S score and corresponding Narcotrend™ level for each patient. The bold curve represents the median response.

Greater diversion of the OAA/S levels was seen at the Narcotrend™ levels C (C0 to C2), indicating the light sleep phase that corresponded to target propofol concentrations 2.0 and 3.0 μg ml^{-1}. In this range the prediction probability was fair, with a P_K of 0.79 (SE 0.04) and a Spearman correlation coefficient of ρ=0.66.

Table 4 compares the Narcotrend™ levels and the corresponding OAA/S levels. Considering patients with an OAA/S score of 1 or less as unconscious, 44 out of 129 observations indicated deep sedation or unconsciousness. Of these, 37 measurements matched the Narcotrend™ levels D or E. Only in two measurements, a Narcotrend™ level of D or E did not correspond with OAA/S scores of 1 or 0.

Considering awake patients, there were 68 OAA/S scores of 4 or 5, which indicate the awake state, and 66 of these corresponded to A or B levels of the Narcotrend™. In eight out of 74 cases, Narcotrend™ levels of A or B were not associated with an OAA/S score of 4 or 5.

Sedation scales and target concentration of propofol

The prediction probability (P_K) values of the Narcotrend™ levels for the target propofol concentration in each patient ranged from 0.80 to 1.00 with a mean P_K of 0.92 (SE 0.01) and a Spearman correlation coefficient of ρ=0.92. Figure 2 shows the Narcotrend™ levels and the corresponding values of the target propofol concentration for each patient and the median response.

We found an almost linear relationship between the mean target concentrations of propofol and the Narcotrend™. Treating the propofol concentration as an interval variable, linear regression analysis gave a positive correlation (R^2=0.87, $P< 0.001$), with the following equation:

Target propofol concentration =
0.38[Narcotrend™ level]+0.10

The P_K calculated to reflect the predictive performance of target propofol concentrations for the OAA/S levels was P_K=0.93 (SE 0.01). The Spearman correlation coefficient was ρ=0.91.

Table 4 Assessment of OAA/S and Narcotrend™ levels in all patients (number of patients). Cells shaded light grey show the numbers of patients in whom Narcotrend™ and OAA/S both indicated unconsciousness or being awake. An OAA/S score of ≤1 and a Narcotrend™ level ≤D0 were considered as unconscious. Cells shaded dark grey indicate disagreement; for example, when the Narcotrend™ indicated an awake patient with a level of B2 whereas the OAA/S indicated a score of 1 (unconscious)

OAA/S score	Narcotrend™ level												Total
	A	B0	B1	B2	C0	C1	C2	D0	D1	D2	E0	E1	
0					1	1	1	5	3	0	3	2	16
1				1	1	1	1	10	5	7	2		28
2			1	3	3	1	1						9
3				3	1	1	1	2					8
4	2	7	4	1	1	1							16
5	40	7	5										52
Total	42	14	10	8	7	5	4	17	8	7	5	2	129

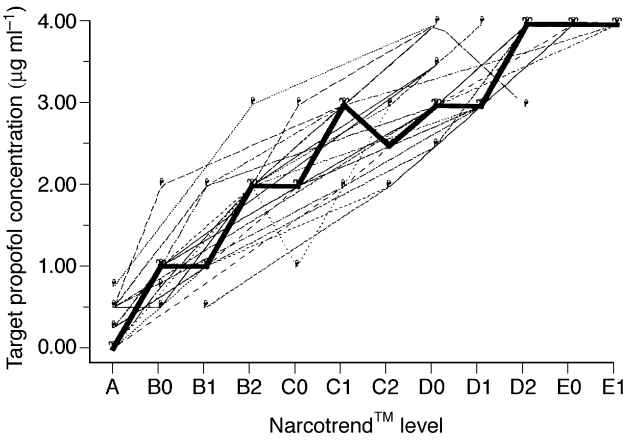

Fig 2 Target propofol concentration *vs* Narcotrend™. Target propofol concentration (μg ml^{-1}) and corresponding Narcotrend™ level for each patient. The bold curve represents the median response.

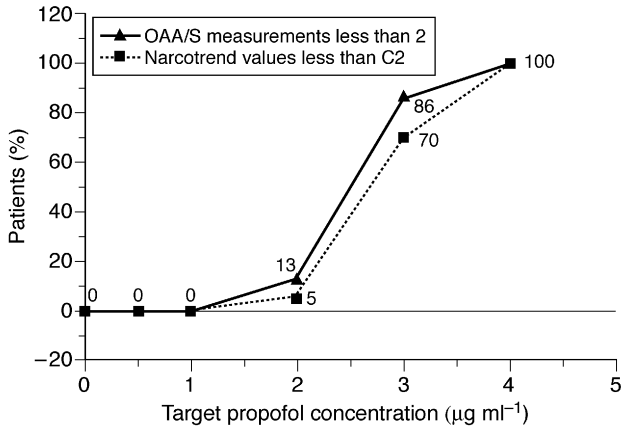

Fig 3 Number of patients who were unconscious at specific target propofol concentrations. OAA/S measurements less than 2 and Narcotrend™ values less than C2.

Figure 3 shows the percentage of patients who were unconscious (OAA/S score <2) at given target concentrations of propofol. When the mean target concentration of propofol exceeded 3 μg ml^{-1}, 86% of the patients were unconscious, while at 4 μg ml^{-1} all patients were unconscious. Figure 3 shows that at target concentrations of propofol between 1 and 4 μg ml^{-1}, the Narcotrend™ identifies fewer patients as unconscious than the OAA/S score.

Mean arterial pressure, heart rate and OAA/S scale

To compare cardiovascular measurements, which are often used to detect light stages of anaesthesia, with the OAA/S score we estimated the prediction probability (P_K) for mean arterial pressure (MAP) and heart rate. The P_K value for the MAP was 0.69 (SE 0.04) and for the heart rate it was 0.51 (SE 0.04). Direct comparison of the P_K values for Narcotrend™ levels, MAP and heart rate showed that the Narcotrend™ levels gave a significantly higher prediction probability.

Discussion

Devices to estimate anaesthetic depth from EEG signals are currently of interest. They may help prevent underdosage and awareness, and also avoid overdosage and allow faster recovery.[13] The bispectral index and other measures have been studied frequently but only a few studies have been published so far on the Narcotrend™, a monitor recently available in Europe.[2 14 –16]

We tested if the Narcotrend™ could correctly assess the depth of propofol sedation and anaesthesia. Depth of anaesthesia can be assessed clinically using measures such as heart rate, blood pressure, sweating, tear formation and pupil size,[17] but these do not indicate the level of consciousness directly. Because measures of anaesthetic depth such as the BIS lack the required validity to be used as a gold standard, we used clinical judgement as a measure, with the OAA/S scale, which is reliable and valid.[9]

We found that the Narcotrend™ level was a good predictor of the patient's state of clinical sedation and correlated well with the responsiveness score. Narcotrend™ levels also predicted specific target concentrations of propofol (P_K=0.916) and correlated well with these. There was no difference in the ability of the Narcotrend™ levels and the target concentrations of propofol to predict the clinical sedation. This was not found in other studies,[10 18] in which the responsiveness score correlated significantly better with the BIS score (r=0.883) than the targeted or measured concentration of propofol (r=–0.778).

Ordinal values from a responsiveness rating scale may not give a linear relation between the observed effect and other measures of anaesthetic depth.[12] To account for this difficulty, prediction probability has been proposed as a measure of the performance of such depth measurements. The good correlation between the Narcotrend™ levels and the responsiveness score and the excellent prediction probability values indicate that the Narcotrend™ is a good measure of sedation and loss of consciousness. The Narcotrend™ predicted the responsiveness of the patient with a mean probability of 92%.

Some studies have already compared the predictive performance of the Narcotrend™ and BIS monitoring. Liu and colleagues reported good correlation between BIS and clinical criteria of sedation.[19] Narcotrend™ and BIS monitoring corresponded well during increasing depth of anaesthesia with propofol and remifentanil.[14] Both Narcotrend™ and BIS monitoring can reduce recovery times and propofol dosage during general anaesthesia.[5] During emergence from anaesthesia, both Narcotrend™ and BIS monitoring correlated significantly with a target concentration of propofol, but failed to assess the level of consciousness when a remifentanil infusion was given simultaneously.[15]

Because monitoring devices for anaesthetic depth may not always be available, we also analysed the relationship between traditional markers for the responsiveness of anaesthetized patients. P_K values for mean arterial pressure and heart rate were less than 0.70 and failed to predict the level of sedation. As well as anaesthetic depth, other factors, such as blood volume and cardiac contractility, will affect the autonomic responses to stimuli,[1] so the autonomic effects of propofol are likely to vary widely during sedation.

We found that a target propofol concentration of 4 μg ml^{-1} is needed to obtain unconsciousness reliably in all patients. At given concentrations of propofol, the Narcotrend™ identified fewer patients as unconscious than the responsiveness score. This suggests high specificity for adequate depth of anaesthesia, but our data do not allow such an analysis. Assessment of the level of sedation by the OAAS/S score and the Narcotrend™ levels diverges at low target concentrations of propofol, because at 2.0 and 3.0 μg ml^{-1} we observed the greatest differences in the prediction probability values. In this range, the averaged predictive performance was only 79%. Clinically unrecognizable excitation during initial sedation by propofol could cause these differences, and these could vary between patients depending on age, weight and other factors. More studies of EEG-derived measures, such as BIS and Narcotrend™ levels, are needed for the lighter levels of anaesthesia.

By reducing anaesthetic dosage to the minimum required to provide adequate anaesthetic depth, overdosage can be prevented and a decrease in cost is possible. By monitoring the depth of remifentanil-supplemented propofol anaesthesia with BIS or Narcotrend™, emergence from anaesthesia was speeded up by 60% and consumption of propofol was reduced by 30%.[5] In a multicentre comparison of 4630 patients with and without the Narcotrend™, the Narcotrend™ speeded emergence from total i.v. anaesthesia when compared with patients managed without Narcotrend™ analysis.[16]

The Narcotrend™ can reliably distinguish between wakefulness and anaesthesia but lacks accuracy in assessing the intermediate stages. Possible advantages compared with other devices, such as the BIS, remain to be demonstrated. Better understanding of EEG patterns in relation to anaesthetic agents and the effects of opioids and other anaesthetics may indicate the value of the Narcotrend™ monitor.

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