Application of Bispectral Index® and Narcotrend® Index to the Measurement of the Electroencephalographic Effects of Isoflurane with and without Burst Suppression

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Background: The Narcotrend® monitor (MonitorTechnik, Bad Bramstedt, Germany) has recently been introduced as an intraoperative monitor of anesthetic state, based on a classification scheme originally developed for visual assessment of the electroencephalogram. The authors compared the performance of the Narcotrend® index (software version 4.0) to the Bispectral Index® (BIS®, version XP; Aspect Medical Systems, Natick, MA) as electroencephalographic measures of isoflurane drug effect during general anesthesia.

Methods: The authors observed 15 adult patients scheduled to undergo radical prostatectomy with a combined epidural–isoflurane general anesthesia technique. At least 45 min after induction of general anesthesia, during a phase of constant surgical stimulation, end-tidal isoflurane concentrations were varied between 0.5 and 2.0 multiples of minimum alveolar concentration, and the BIS® and the Narcotrend® index were recorded. The prediction probability (P_K) was calculated for the BIS® and the Narcotrend® index to predict isoflurane effect compartment concentration for each measure. The correlation analysis of the BIS® and the Narcotrend® index with the isoflurane effect compartment concentration was obtained by pharmacodynamic modeling based on two sigmoidal curves to account for the discontinuity in both indices with the onset of burst suppression.

Results: The prediction probabilities were indistinguishable (BIS® P_K = 0.72 ± 0.07 (mean ± SD); range, 0.61–0.84; Narcotrend® index P_K = 0.72 ± 0.10; range, 0.51–0.87), as were the correlations between the electroencephalographic measures and isoflurane effect compartment concentrations (BIS® R^2 = 0.82 ± 0.12; Narcotrend® index R^2 = 0.85 ± 0.09). The pharmacodynamic models for the BIS® and the Narcotrend® index yielded nearly identical results.

Conclusions: The BIS® and the Narcotrend® index detected the electroencephalographic effects of isoflurane equally. Combining two fractional sigmoid E_{max} models adequately described the data before and after the onset of burst suppression.

THE Bispectral Index® scale (BIS®; Aspect Medical Systems, Natick, MA) was introduced into anesthesia practice nearly a decade ago, and its relations to anesthetic drugs and the anesthetized state have been well characterized. The BIS® is a multiparameter electroencephalogram index that integrates bispectral, spectral, quasi-suppression, and time domain (burst suppression ratio) parameters into a value from 100 (awake) to 0.[1] More recently, the Narcotrend® index (MonitorTechnik, Bad Bramstedt, Germany) has been certified for clinical use in Europe. The Narcotrend® monitor (version 4.0) uses a classification developed for visual assessment of the electroencephalogram, based on a six-letter ordinal scale ranging from A (awake) to F (general anesthesia with increasing burst suppression). The Narcotrend® analysis integrates this scale using a multivariate statistical algorithm[2] that yields a value from 99 (awake) to 0, called the Narcotrend® index. Comparative studies between the BIS® and the Narcotrend® index have shown similar values with both monitors during propofol–remifentanil anesthesia.[3,4]

Besides its clinical use for estimating anesthetic depth,[5] the electroencephalogram is an important tool for the quantification of anesthetic drug effect.[6] Pharmacodynamic E_{max} modeling using the Hill equation enables the determination of the parameters E_0, E_{max}, C_{50}, λ, and k_{e0}.[7] The E_0 and E_{max} values describe the minimum and maximum drug effect, whereas the drug concentration that causes 50% of the maximum effect is given by the C_{50} value. The λ assigns the steepness of the concentration–response curve, and the k_{e0} value is the first-order rate constant determining the efflux from the effect compartment. These parameters have been used to estimate relative potencies of opioids[8] and volatile anesthetics,[9,10] as well as the time course of anesthetic drug effect.

In the current investigation, we compared the applicability of the BIS® and the Narcotrend® index for quantification of the pharmacodynamic effects of isoflurane. We developed a new model with two connected sigmoidal curves, with the first sigmoidal curve describing the electroencephalographic response before the onset of burst suppression and the second sigmoidal curve describing the electroencephalographic response with burst suppression.

Materials and Methods

Patients and Anesthesia

With local ethics committee approval (Ärztekammer des Saarlandes, Saarbrücken, Saarland, Germany) and

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written informed consent, 15 men scheduled to undergo radical prostatectomy were studied. Exclusion criteria were a history of any disabling central nervous or cerebrovascular disease, substance abuse, or a treatment with opioids or any psychoactive medication.

All patients were premedicated with 7.5 mg midazolam orally on the morning before surgery. In the operating room, an intravenous catheter was inserted into a larger forearm vein, and standard monitors were applied. An epidural catheter was inserted in the lumbar space, and a test dose of 3 ml bupivacaine, 0.5%, was given. The electroencephalogram was recorded continuously using an Aspect A-2000 BIS® monitor (version XP) and the Narcotrend® monitor (version 4.0). After the skin of the forehead had been degreased with 70% isopropanol, the BIS® (BIS-XP® sensor; Aspect Medical Systems) and the Narcotrend® (Blue Sensor; Medicotest, Olstykke, Denmark) electrodes were positioned as recommended by the manufacturers. For the Narcotrend®, two electrodes were placed on the patients' foreheads with a minimum distance of 8 cm, and a third electrode was positioned laterally, serving as a reference electrode. Impedances were measured for each set of electrodes to ensure adequate electrode contact defined as 6 kΩ or less for the Narcotrend® and 7.5 kΩ or less for the BIS® as required by the manufacturers.

While 10 l/min oxygen was given *via* a facemask for preoxygenation, induction of anesthesia was started with a remifentanil infusion at 0.4 μg · kg^{-1} · min^{-1}. Five minutes later, the patients received 2.0 mg/kg propofol. After loss of consciousness occurred, oxygen was given *via* facemask ventilation, and patients received 0.5 mg/kg atracurium. Three minutes later, the trachea was intubated, and the lungs were ventilated to an end-tidal carbon dioxide concentration of 35 mmHg. Immediately after intubation, the remifentanil infusion was stopped, and isoflurane in 1.5-l/min fresh gas flow (0.5 l/min O_2 and 1 l/min air) was given for hypnosis. End-tidal isoflurane concentrations were measured using infrared absorption technology (PM 8050; Dräger, Lübeck, Schleswig-Holstein, Germany).

After induction of anesthesia had been completed, patients received 12 ml bupivacaine, 0.5%, epidurally for intraoperative analgesia. Complete neuromuscular blockade during the investigation was ensured by repeated injections of 0.25 mg/kg atracurium and by neuromuscular monitoring, *i.e.*, train-of-four and double burst stimulation monitoring. All patients were visited in the postanesthesia care unit and on the first and third postoperative days and were interviewed about intraoperative recall.

Study Measurements

To rule out residual propofol or remifentanil effects and to ensure a condition of constant surgical stimula-

tion, study measurements were performed during dissection of the prostate, a minimum of 45 min after induction of anesthesia. To obtain concentration–response curves, isoflurane end-tidal concentrations were subsequently increased and decreased two times: Starting at an end-tidal isoflurane concentration of 0.5 vol%, the vaporizer was opened to the maximum of 5 vol% isoflurane concentration until the end-tidal isoflurane concentration reached 2.3 vol%. Thereafter, the vaporizer was closed (0 vol% isoflurane concentration) until the end-tidal isoflurane concentration had decreased to 0.5 vol% or a BIS® value of 60 had been reached. Fifteen minutes later, this procedure was repeated. BIS®, Narcotrend® index, and end-tidal isoflurane concentration were gathered every 5 s. The precision of the end-tidal isoflurane measurements was 0.1 vol%.

An additional set of measurements were taken on emergence from anesthesia. After the final suture was placed, the isoflurane was discontinued, and patients were allowed to awaken from anesthesia. The BIS® and the Narcotrend® index were recorded. These measurements were not used in building the pharmacodynamic model (see Materials and Methods, Pharmacodynamic Model) but were examined to demonstrate the performance of each monitor in tracking effect site isoflurane concentrations during emergence from anesthesia.

Study data were automatically recorded at intervals of 5 s using the software programs Proto 99 (version 1.0.2.0; Dräger) for the end-tidal isoflurane concentrations and Hyperterminal (Microsoft, Redmond, VA) for BIS® values. The Narcotrend® index was recorded using a modified research laptop version with Narcotrend® software version 4.0. The synchronization of the data were performed automatically by the software Access® 2000 (Microsoft). After the assessment of study parameters had been finished, subsequent anesthesia was administered according to individual clinical needs.

Prediction Probability

Prediction probability (P_K) was assessed as described by Smith *et al.*.[11] We calculated P_K using the Somer d cross-tabulation statistic on SPSS (version 12; SPSS Inc., Chicago, IL), which was then transformed from the −1 to 1 scale of the Somer d to the 0 to 1 scale of P_K as $P_K = 1 - (1 - |\text{Somer d}|)/2$. The BIS® or Narcotrend® index was set as the dependent variable for the Somer d calculation, and the calculated isoflurane effect compartment concentration was set as the independent variable. The prediction probability was calculated on the full set of measurements, including the up and down ramps used to estimate the pharmacodynamic model, and the measures gathered through emergence from anesthesia.
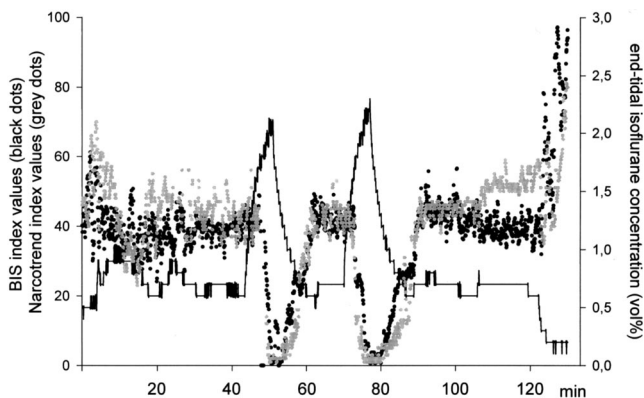
Fig. 1. Bispectral Index® (BIS®; *black dots*), Narcotrend® index (*gray dots*), and end-tidal isoflurane concentration data *versus* time for one representative patient. Each *dot* represents the electroencephalogram parameter value of a 5-s epoch.

Pharmacodynamic Model

The BIS® and the Narcotrend® index were related to isoflurane effect compartment concentration using a classic first-order effect site:

$$\frac{dC_{eff}}{dt} = (C_{ET} - C_{eff}) \times k_{e0},$$

where C_{et} is the end-tidal isoflurane concentration, C_{eff} is the effect compartment concentration of the isoflurane, and k_{e0} is the first-order rate constant determining the equilibration between the two. One individual k_{e0} value was calculated for each patient on the basis of the two ramps. Isoflurane effect site concentrations during emergence from anesthesia were calculated with the individual k_{e0} values of each patient.

We used a variation of the classic fractional sigmoid E_{max} model (Hill equation)[12] with two linked sigmoidal curves describing the electroencephalographic effect at isoflurane concentrations without burst suppression (no BSR) and after the onset of burst suppression (BSR):

For $C_{eff} \leq C_{plateau}$:

$$E = 99 - (99 - E_{plateau})\left(\frac{C_{eff}^{\lambda_{no\ BSR}}}{C_{50\ no\ BSR}^{\lambda_{no\ BSR}} + C_{eff}^{\lambda_{no\ BSR}}}\right).$$

For $C_{eff} > C_{plateau}$:

$$E = E_{plateau} - E_{plateau}\left(\frac{(C_{eff} - C_{plateau})^{\lambda_{BSR}}}{C_{50\ BSR}^{\lambda_{BSR}} + (C_{eff} - C_{plateau})^{\lambda_{BSR}}}\right).$$

Both sigmoidal curves have their own parameter. The first curve goes from 99, the presumed value in the absence of isoflurane, to $E_{plateau}$, where a transition occurs to the second curve, which extends from $E_{plateau}$ to 0, the presumed maximum drug effect. $C_{plateau}$ is the isoflurane concentration at $E_{plateau}$. C_{eff} is the apparent effect site concentration. $C_{50\ no\ BSR}$ is the isoflurane concentration associated with 50% decrease from E_0 to $E_{plateau}$, and $\lambda_{no\ BSR}$ is the steepness of that relation. $C_{50\ BSR}$ is the isoflurane concentration associated with 50% decrease from $E_{plateau}$ to E_{max}, and λ_{BSR} is the steepness of that relation.

The parameters of the model including $C_{plateau}$ and $E_{plateau}$ for each individual were estimated separately using nonlinear regression with ordinary least squares.

The computations were performed on a spreadsheet using the Excel 2000 software program (Microsoft), and the parameters were optimized with the Solver tool within Excel.

Statistical Analysis

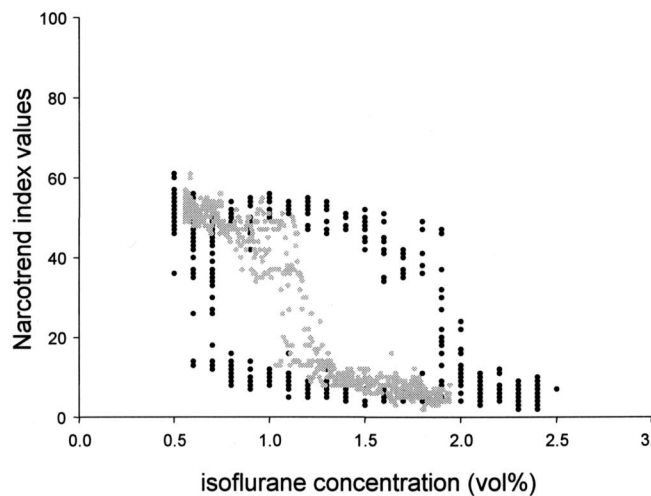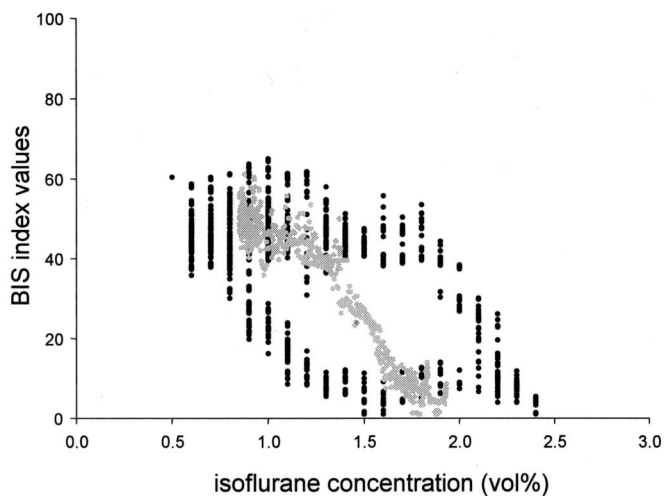Minimizing the squared error between the measured and predicted concentration necessarily maximizes the

Fig. 2. Relation between Bispectral Index® (BIS®; *left graph*) or Narcotrend® index (*right graph*) and the respective end-tidal (*black dots*) or effect site (*gray dots*) isoflurane concentrations for one representative patient. Each *dot* represents the electroencephalogram parameter value of a 5-s epoch.
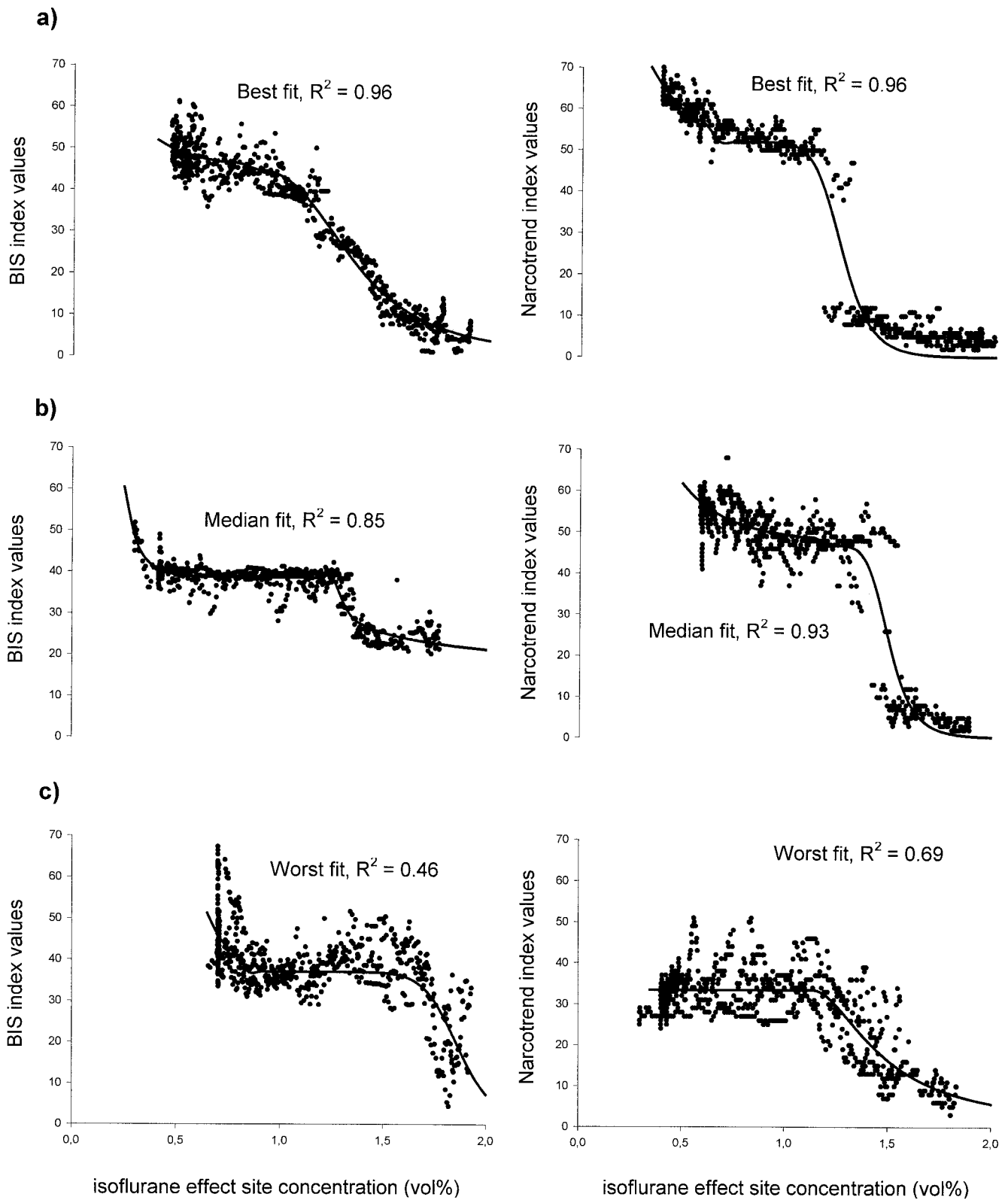
a)

Fig. 3. Dose–response curves between Bispectral Index® (BIS®; *left graphs*) or Narcotrend® index (*right graphs*) and the isoflurane effect site concentrations for best fit (*A*), median fit (*B*), and worst fit (*C*). *Dots* are the respective electroencephalogram parameter values of a 5-s epoch.

coefficient of determination (R^2), which we therefore report as our objective function[13]:

$$R^2 = 1 - \frac{\text{SSE}}{\text{SST}} = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (y_i - \bar{y}_i)^2},$$

where SSE (sum of squared errors) represents the sum of the squares of the differences between the observed measurements y_i for a given time and the corresponding model prediction, $\hat{y}_i$, and SST, the total sum of squares, stands for the sum of the squares of the differences between each actual measurement and the average of all the measurements, $\bar{y}_i$.

A value of R^2 close to 1 means that changes in the electroencephalographic measurement can be entirely explained by changes in the effect compartment isoflurane concentrations. A value of R^2 close to zero means that there is no relation between effect compartment isoflurane concentration and electroencephalographic effect.[13]

The correlations of the BIS® or the Narcotrend® index with the isoflurane effect compartment concentrations indicated by the R^2 values were tested with the Wilcoxon test. Pharmacodynamic parameters were compared between the two indices using the Student t test. All tests were two tailed, with statistical significance defined as $P < 0.05$. Data are presented as mean ± SD. Statistical calculations were performed using SigmaStat 2.03, SigmaPlot 2000 (both SPSS GmbH, Erkrath, Germany), and SPSS (version 12) computer software.

Results

Fifteen men with American Society of Anesthesiologists physical status II (age, 64 ± 5 yr; weight, 81 ± 9 kg; height, 175 ± 6 cm) were enrolled in this study. There were no problems with skin adherence of the electrodes. No patient reported postoperative recall of intraoperative awareness. The isoflurane concentration was systematically varied to characterize the electroencephalographic response for 69.8 ± 6.2 min.

The end-tidal isoflurane concentration ranged from 0.44 ± 0.07 to 2.34 ± 0.19 vol%. With increasing end-tidal isoflurane concentrations, the BIS® and the Narcotrend® index (fig. 1) decreased adequately with a time delay in all patients.

Plotting the BIS® *versus* end-tidal isoflurane concentrations or the Narcotrend® index *versus* end-tidal isoflurane concentrations revealed hysteresis (fig. 2, black dots), which collapsed by introduction of the isoflurane effect site concentration (fig. 2, gray dots). Figure 3 shows the best fit (A), median fit (B), and worst fit (C) relations between the BIS® or the Narcotrend® index and the effect site isoflurane concentration for individual patients.

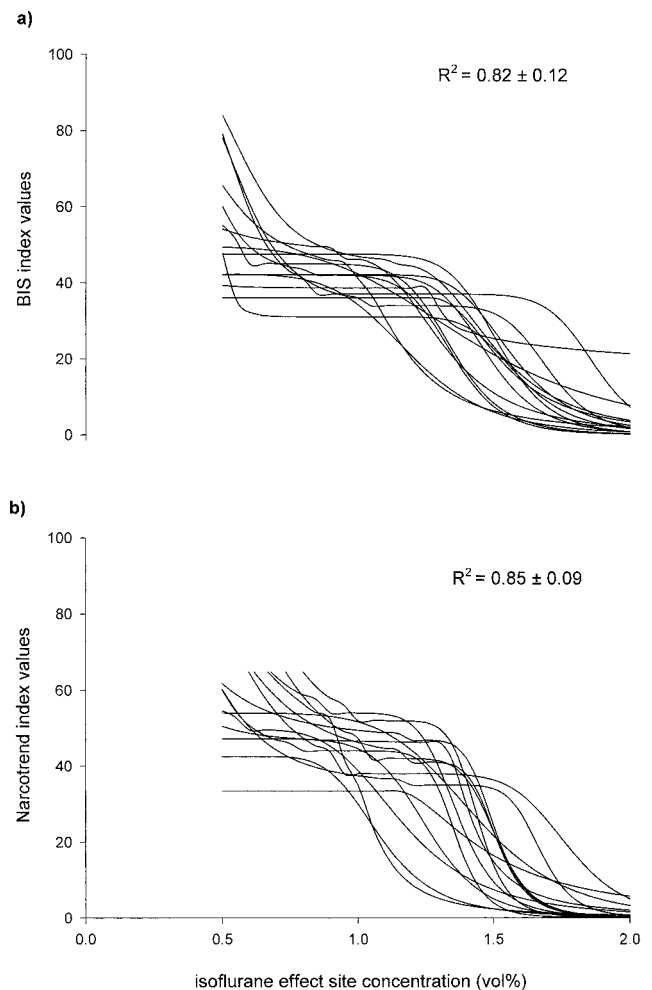In all patients, increasing BIS® and Narcotrend® values

Fig. 4. **Individual dose–response curves of the isoflurane effect site concentration *versus* Bispectral Index® (BIS®; *A*) or Narcotrend® index (*B*). Each *line* represents one individual patient. In seven patients for the BIS® and in four patients for the Narcotrend® index, only the pharmacodynamic plateau and the second sigmoidal curve with burst suppression were observed. Because of the study design, the decrease of isoflurane was limited to 0.5 vol%.**

adequately reflected a decrease in isoflurane effect compartment concentrations. The correlation of the BIS® to effect site isoflurane concentration ($R^2 = 0.82 \pm 0.12$; fig. 4A) was no better than the correlation of the Narcotrend® index to effect site isoflurane concentration ($R^2 = 0.85 \pm 0.09$; fig. 4B). As shown in figures 4A and B, a pharmacodynamic plateau, *i.e.*, unchanged electroencephalographic parameter values despite changing isoflurane concentrations, was observed in some patients with both electroencephalographic measures of isoflurane effect, necessitating the use of the linked sigmoidal curves.

The pharmacodynamic parameters are displayed in table 1. The k_{e0} value derived from the BIS® data was 0.16 ± 0.03 min^{−1}, and that from the Narcotrend® index was 0.18 ± 0.05 min^{−1}. The change between the first and the second sigmoidal curve was positioned at a BIS® value of 41.3 ± 5.2 and a Narcotrend® index of 44.5 ±

Table 1. Pharmacodynamic Parameters

	Bispectral Index®	Narcotrend® Index
k_{e0}	0.16 ± 0.03	0.18 ± 0.05
$E_{plateau}$	41.3 ± 5.2	44.5 ± 6.1
$C_{plateau}$	0.96 ± 0.20	0.99 ± 0.21
$C_{50\ no\ BSR}$	$0.46 \pm 0.11*$	$0.50 \pm 0.14*$
$\lambda_{no\ BSR}$	$10.5 \pm 7.2*$	$10.6 \pm 10.0*$
$C_{50\ BSR}$	1.55 ± 0.33	1.41 ± 0.19
λ_{BSR}	5.73 ± 3.18	6.25 ± 2.88

Values are presented as mean $\pm$ SD.

* $P < 0.05$ for $C_{50\ no\ BSR}$ *vs.* $C_{50\ BSR}$ or $\lambda_{no\ BSR}$ *vs.* λ_{BSR} (*t* test).

$C_{50\ BSR}$ = concentration that causes 50% of the maximum effect of the second sigmoidal curve, which includes the effects of burst suppression; $C_{50\ no\ BSR}$ = concentration that causes 50% of the maximum effect of the first sigmoidal curve before the onset of burst suppression; $C_{plateau}$ = concentration at $E_{plateau}$; $E_{plateau}$ = plateau that is the maximum effect of the first sigmoidal curve and simultaneously the minimum effect of the second sigmoidal curve; λ_{BSR} = steepness of the concentration–response relation of the second sigmoidal curve, which includes the effects of burst suppression; $\lambda_{no\ BSR}$ = steepness of the concentration–response relation of the first sigmoidal curve before the onset of burst suppression; k_{e0} = first-order rate constant determining the efflux from the effect compartment.

6.1. The respective isoflurane effect site concentrations were 0.96 ± 0.20 vol% for the BIS® monitor and 0.99 ± 0.21 vol% for the Narcotrend® monitor. The C_{50} values for the electroencephalographic response before the onset of burst suppression were 0.46 ± 0.11 vol% for the BIS® and 0.50 ± 0.14 vol% for the Narcotrend® index. The C_{50} values with burst suppression were significantly higher than those without burst suppression, *i.e.*, 1.55 ± 0.33 vol% for the BIS® and 1.41 ± 0.19 vol% for the Narcotrend® index.

During emergence from anesthesia, the correlation between isoflurane effect compartment concentration and Narcotrend® index ($R^2 = 0.88 \pm 0.15$) was better than the BIS® ($R^2 = 0.77 \pm 0.19$; fig. 5). Figure 6 shows all BIS® and Narcotrend® index values *versus* effect site isoflurane concentrations. The isoflurane effects site concentrations were calculated with a k_{e0} value of 0.16 for the BIS® data and of 0.18 for the Narcotrend® data. The concentration-*versus*-response relation was calculated from the mean values of the pharmacokinetic-pharmacodynamic parameters of all patients.

The prediction probabilities for the BIS® and the Narcotrend® index to predict isoflurane effect compartment concentration were indistinguishable for the two measurements, with a BIS® P_K of 0.72 ± 0.07 (mean $\pm$ SD; range, 0.61–0.84) and a Narcotrend® P_K of 0.72 ± 0.10 (range, 0.51–0.87).

Figure 7 shows the relation between the BIS® and the Narcotrend® index *versus* burst suppression ratio. When there is no burst suppression, the BIS® is typically approximately 55. However, as the burst suppression ratio increases, the BIS® starts to decrease from around 43 (the transition point in the model), eventually reaching a linear portion. It is clear from the data that at burst suppression ratios greater than 40%, the BIS® is simply a

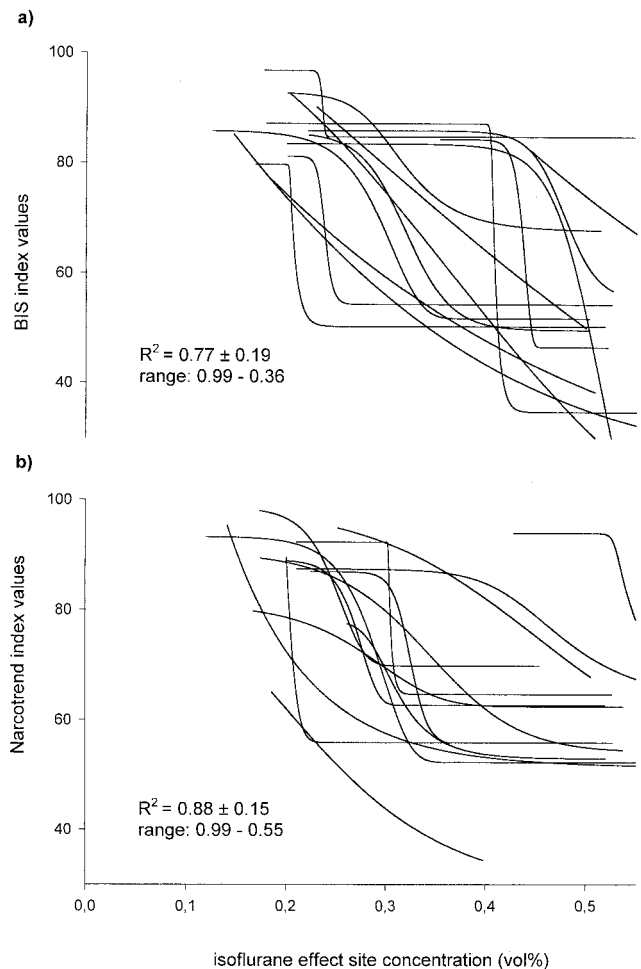**Fig. 5. Individual dose–response curves of the isoflurane effect site concentration *versus* Bispectral Index® (BIS®; *A*) or Narcotrend® index (*B*) during emergence of anesthesia. Each *line* represents one individual patient. The isoflurane effects site concentrations were calculated with the k_{e0} values of each patient.**

linear transformation of the burst suppression ratio, which we calculated to be BIS® $= 42 - 0.42 *$ BSR.

Discussion

We applied a newly developed model with two linked sigmoidal curves to the electroencephalographic effects of 0.5 to 2 multiples of isoflurane minimum alveolar concentration as measured by the BIS® and the Narcotrend® index. The new model adequately described the data, and both electroencephalographic parameters performed equally well as measures of anesthetic drug effect.

Traditionally, a single sigmoidal curve has been used to describe the dose–response relation between anesthetic drugs and electroencephalographic data.[6,10,14] The sigmoidal function *per se* has the advantage of high flexibility, *i.e.*, it is suitable to describe data following nearly a step function as well as data following nearly a linear function. As the basic function of simultaneous pharma-
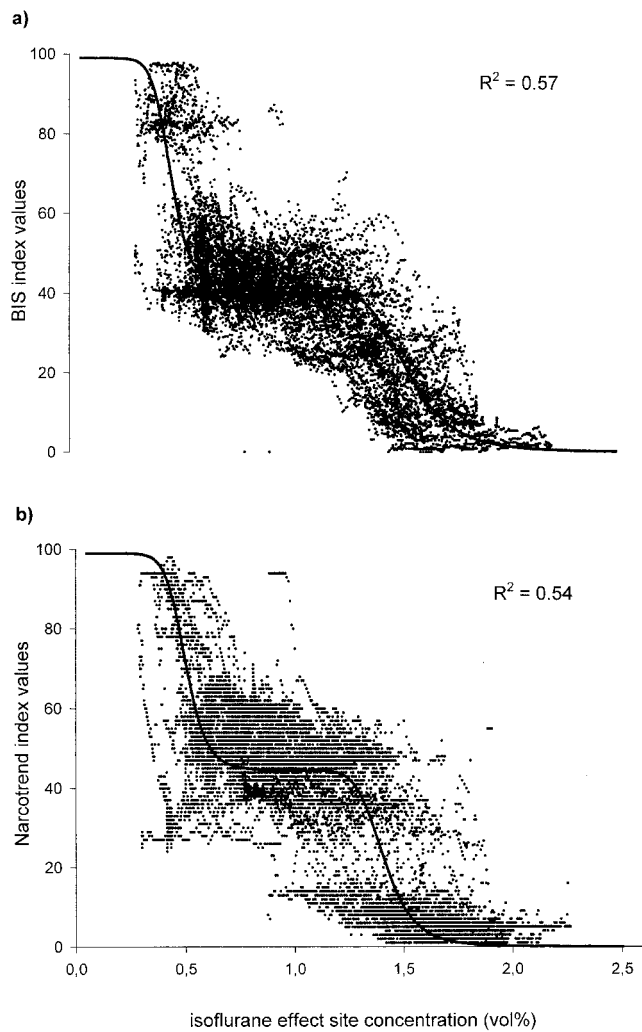
a)

b)

isoflurane effect site concentration (vol%)

Fig. 6. Dose–response curves of the isoflurane effect site concentration *versus* all Bispectral Index® (BIS®; *A*) or all Narcotrend® index data (*B*). The isoflurane effects site concentrations were calculated with a k_{e0} value of 0.16 for BIS® data and of 0.18 for Narcotrend® data. The concentration-*versus*-response relation was calculated from the mean values of the pharmacokinetic–pharmacodynamic parameters of all patients.

a)

Burst suppression ratio (%)

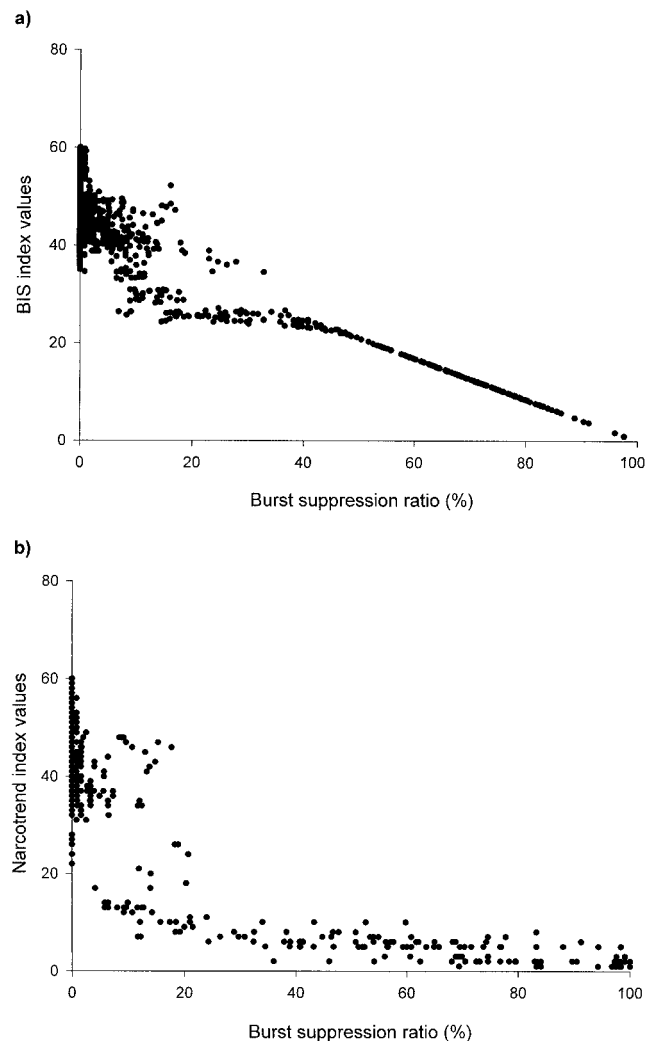b)

Burst suppression ratio (%)

Fig. 7. Relation between the suppression ratio as calculated by the A-2000 BIS® monitor (version XP; Aspect Medical Systems, Natick, MA) and the Bispectral Index® (BIS®; *A*) or the Narcotrend® index (*B*), respectively. Each *dot* represents the parameter values of one epoch with a suppression ratio greater than 5%.

cokinetic–pharmacodynamic modeling,[7] it enables the estimation of meaningful pharmacokinetic and pharmacodynamic parameters. However, until now, the success of applying this model to electroencephalographic data were limited to data without burst suppression.

Recent publications indicated a pharmacodynamic plateau for the BIS® before and at beginning of burst suppression.[10,15] With increasing suppression, a sigmoidal function between isoflurane effect compartment concentrations and burst suppression ratio[15] and a linear function between burst suppression ratio and BIS®, at least for a burst suppression ratio greater than 40%, has been shown.[16] This indicated the adequacy of a sigmoidal function between volatile anesthetic concentrations and the BIS® during burst suppression and led to the development of the new model with two series-connected sigmoidal curves, with the first sigmoidal curve

describing the electroencephalogram data without burst suppression and the second sigmoidal curve describing the data with burst suppression. The good R^2 values for both electroencephalographic parameters, the BIS® and the Narcotrend® index, further supports the new model and the hypothesis that the BIS® and the Narcotrend® index are equally suitable to describe the anesthetic drug effect of isoflurane.

In the current study, the pharmacodynamic plateau, *i.e.*, unchanged electroencephalographic parameter values despite changing isoflurane concentrations, was much broader than expected. For the BIS® in seven patients and for the Narcotrend® index in four patients, only the pharmacodynamic plateau and the second sigmoidal curve with burst suppression were observed. This was in part because of our study design, which limited the decrease of isoflurane to 0.5 vol%. However,

these results are clinically important: For electroencephalographically guided titration of anesthetic drugs, the pharmacodynamic plateau is of disadvantage because changing drug concentrations are not reflected by the electroencephalogram parameter. It remains unclear whether the electroencephalogram pattern in this range is really unchanged or whether the electroencephalogram parameter algorithm is just too insensitive in this range. However, because three patients showed a pharmacodynamic plateau with BIS® monitoring but not with Narcotrend® monitoring, one might speculate that the observed phenomenon is more a problem of the calculation algorithm.

Describing the data without burst suppression, the C_{50} value as well as the slope factor of the first sigmoidal curve must be interpreted with some caution because the lower limit of isoflurane was set as 0.5 vol%, and this prohibited covering a broader range of the first sigmoidal curve. In contrast, the range of the second sigmoidal curve, describing the data with burst suppression, covered the whole range in nearly all patients. The higher values for C_{50} and the slope factor λ of the second sigmoidal curve for the BIS® compared with the Narcotrend® index are in concordance with the behavior of both electroencephalogram parameters during burst suppression.

In conclusion, the BIS® and the Narcotrend® index performed equally in terms of R^2 values as measures of anesthetic drug effect. The newly developed model with two series-connected sigmoidal curves allowed the estimation of meaningful pharmacokinetic and pharmacodynamic parameters in electroencephalographic data series with and without burst suppression pattern.

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