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Comparison between Bispectral Index and Patient State Index as Measures of the Electroencephalographic Effects of Sevoflurane

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Background: **The Bispectral Index (BIS) and the Patient State Index (PSI) quantify depth of anesthesia by analyzing the electroencephalogram. The authors examined the response of BIS and PSI to sevoflurane anesthesia.**

Methods: **In 22 patients, sevoflurane anesthesia was induced by inhalation with a tight-fitting facemask and was maintained *via* a laryngeal mask. Sevoflurane concentrations were increased until burst suppression occurred and subsequently decreased until BIS recovered to values above 60. This procedure was repeated twice until patients underwent intubation for subsequent surgery. End-tidal sevoflurane concentrations, BIS, and PSI were recorded simultaneously. The performance of PSI and BIS to predict the estimated sevoflurane effect site concentration, as derived from simultaneous pharmacokinetic and pharmacodynamic modeling, was compared by determination coefficients (ρ^2) and prediction probabilities (P_K).**

Results: **A significant ($P < 0.001$) correlation between BIS and PSI was found ($r^2 = 0.75$), and a close sigmoid relation between sevoflurane effect site concentration and both BIS ($\rho^2 = 0.84 \pm 0.09$) and PSI ($\rho^2 = 0.85 \pm 0.15$) was observed. The maximum sevoflurane electroencephalographic effect resulted in PSI values (1.3 ± 4.3) that were significantly ($P = 0.019$) lower than BIS values (7.9 ± 12.1), and the effect site efflux constant k_{e0} was significantly smaller ($P = 0.001$) for PSI (0.13 ± 0.08 min^{-1}) than for BIS (0.24 ± 0.15 min^{-1}). The probability of BIS ($P_K = 0.80 \pm 0.11$) to predict sevoflurane effect site concentration did not differ ($P = 0.76$) from that of PSI ($P_K = 0.79 \pm 0.09$).**

Conclusions: **The BIS reacted faster to changes in sevoflurane concentrations, whereas the PSI made better use of the predefined index range. However, despite major differences in their algorithms and minor differences in their dose–response relations, both PSI and BIS predicted depth of sevoflurane anesthesia equally well.**

DEPTH of anesthesia is commonly estimated based on indirect signs such as heart rate, blood pressure, or movement in response to noxious stimuli. However, these parameters have been shown to be unreliable in assessing depth of anesthesia and preventing intraoperative awareness.[1,2] The electroencephalogram is affected in a characteristic manner by both volatile and intravenous anesthetics and may therefore be analyzed with respect to depth of anesthesia. Meanwhile, half a dozen different depth-of-anesthesia monitors that are based on the electroencephalogram and express depth of anesthesia as a numerical index are commercially available.[3]

In this study, we compared two such indices, the Bispectral Index (BIS) and the Patient State Index (PSI), to assess the depth of sevoflurane anesthesia. Both indices range between 100 (awake state) and 0 (deep anesthesia) but differ in their recommended range for general anesthesia, which is 40–60 for the BIS# and 25–50 for the PSI.[4] Both indices are based on the spectral analysis of the raw electroencephalogram and the detection of a burst suppression pattern within the raw electroencephalogram, but apply different algorithms. Calculation of BIS and PSI are based on proprietary empirical algorithms that are unknown to the clinical community. So far, only the basic principles of the algorithms are published.[5,6] Furthermore, the BIS calculation especially has been modified repeatedly during recent years.

The BIS monitor analyzes a single-channel electroencephalogram and performs a fast Fourier transformation, which reveals—among others—two parameters, namely power and phase in dependence of the frequency. Whereas most depth-of-anesthesia monitors analyze only the power of distinct electroencephalographic frequency bands (α, β, δ, and θ), the BIS monitor in addition uses the phase information to calculate the phase coupling between frequencies, a process called *bispectral analysis*.[6]

The PSI monitor is based on a quantitative analysis of the α, β, δ, and θ frequency bands as revealed by fast Fourier transformation. The power distribution between such frequency bands is characteristically affected by anesthetics in a dose-dependent manner. In addition, both temporal and spatial gradients occur within the frequency bands during induction and emergence of anesthesia. The analysis of such gradients separates the PSI monitor from other electroencephalographic monitors. Four channels are recorded by the PSI monitor to assess such spatial gradients.[7]

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According to Aspect Medical Systems: BIS range guidelines. Available at: http://www.aspectmedical.com/assets/Documents/pdf/OR_ChainCards_r5.pdf. Accessed June 13, 2008.

To measure and compare the performance of anesthetic-depth monitors, the prediction probability P_K has been developed.[8] It is a nonparametric measure ranging between 0 and 1. An anesthetic-depth monitor that always predicts depth of anesthesia correctly will obtain a P_K value of 1, whereas a monitor that is performing no better than by chance (50:50) will be characterized by a P_K of 0.5.[8]

The aim of this study was to analyze the pharmacodynamic effects of sevoflurane on BIS and PSI and to compare BIS and PSI in their ability to predict depth of sevoflurane anesthesia. A monitor was regarded as superior to the other if its P_K value was significantly higher as compared with the other monitor.

Materials and Methods

With approval of the institutional review board (Ethik-Kommission der Medizinischen Fakultät, Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany; No. 203/03) and written informed consent, 22 patients scheduled to undergo otorhinolaryngologic surgery were studied. Only participants with an American Society of Anesthesiologist physical status of I or II and an age between 18 and 65 yr were included. Exclusion criteria were pregnancy, history of disabling stroke, and treatment with any central nervous system–acting drugs.

After arrival in the induction room, standard monitoring was applied. The electroencephalogram was recorded simultaneously and continuously using the Aspect A-2000® BIS monitor (version XP; Aspect Medical Systems, Newton, MA) and the Hospira (formerly Physiometrix) PSA 4000® monitor (Hospira Inc., Lake Forest, IL). The forehead skin was cleaned with 70% isopropanol to improve skin conductance. Subsequently, both electroencephalographic electrodes (BIS XP-Sensor® and Physiometrix PSArray2 Sensor®) were applied as recommended by the manufacturers.

After preoxygenation with 100% oxygen, anesthesia was induced solely by sevoflurane inhalation *via* a tight-fitting facemask. With a fresh air flow of 4 l pure oxygen/min and the sevoflurane vapor set to 8 vol%, patients breathed slowly increasing concentrations of sevoflurane. As spontaneous breathing diminished, respiration was manually assisted, and when breathing ceased, patients were mechanically ventilated *via* the facemask to maintain an end-tidal carbon dioxide partial pressure of 35 mmHg. Upon occurrence of a burst suppression electroencephalographic pattern, a laryngeal mask (*LMA Classic*™; Laryngeal Mask Company Ltd., Oxon, United Kingdom) was inserted, and the sevoflurane vapor was closed. End-tidal sevoflurane concentration decreased thereafter, and patients recovered from deep sevoflurane anesthesia. When BIS reached a value of 60, the vapor was opened and set to 8 vol% until burst suppression was reached again. This procedure was repeated until the patients recovered from the second burst suppression period (fig. 1). Finally, the patients underwent intubation for subsequent otorhinolaryngologic surgery.

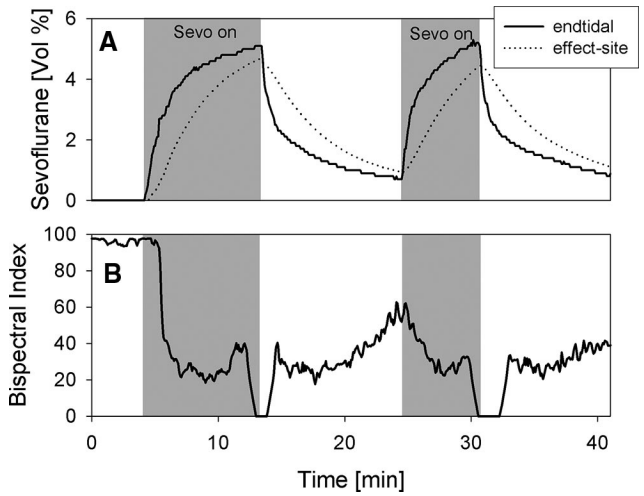

Fig. 1. Example of the time course of sevoflurane end-tidal and effect site concentrations (*A*) as well as the Bispectral Index (*B*) as obtained in a 21-yr-old patient. Periods during which the sevoflurane vapor was opened are *shaded*.

During the study period, BIS (version 4.0, smoothing time 15 s, BIS value updated every second), PSI (release 3.00.09, averaging time 25 s, PSI value updated every 1.25 s), and end-tidal sevoflurane concentration (C_{et}) (Datex Ohmeda S/5® monitor; Helsinki, Finland) were stored simultaneously every 5 s using software supplied by the manufacturer (Aspect: Winlog software; Datex Ohmeda: S/5 Collect software version 4.0).

The sevoflurane effect site concentration (C_{eff}) was obtained by simultaneous pharmacokinetic–pharmacodynamic (PK-PD) modeling.[9] First, C_{eff} was estimated using the differential equation:

$$dC_{eff}/dt = \left(C_{et} - C_{eff}\right) \times k_{e0},$$

where k_{e0} is the first-order rate constant determining the efflux from the effect site. To do so, the hysteresis between the electroencephalographic variable (BIS, PSI) and the sevoflurane effect site concentration was collapsed. Second, a classic fractional sigmoid relation between C_{eff} and the electroencephalographic effect E (BIS, PSI) was assumed[10]:

$$E = E_0 + \left(E_{max} - E_0\right)\left(\frac{C_{eff}^{\lambda}}{C_{50}^{\lambda} + C_{eff}^{\lambda}}\right),$$

where E_0 is the electroencephalographic parameter in the absence of sevoflurane (= baseline or awake state), and E_{max} is the electroencephalographic value corresponding to the maximum drug effect. C_{50} describes the sevoflurane effect site concentration that causes 50% of the maximum electroencephalographic effect, and λ quantifies the slope of the sigmoid relation between C_{eff} and E.

Pharmacokinetic–pharmacodynamic parameters were calculated offline using two different approaches. First,

parameters were obtained for each individual patient (individual fit) applying the solver tool in Excel 2000 software (Microsoft, Redmond, WA). This tool was used to perform a sigmoid regression of the electroencephalographic effect based on C_{eff}. To quantify the goodness of the sigmoid fit, the coefficient of determination ρ^2 was calculated as

$$\rho^2 = 1 - \frac{\sum \left(E_{measured} - E_{calculated}\right)^2}{\sum \left(E_{measured} - \bar{E}_{measured}\right)^2},$$

where $\bar{E}_{measured}$ is the averaged measured electroencephalographic effect. The pharmacokinetic parameter k_{e0} as well as the pharmacodynamic parameters E_0, E_{max}, C_{50}, and λ were simultaneously optimized. To do so, ordinary least squares—resulting from the difference between observed and estimated electroencephalographic effect—were minimized, which produced a collapse of the aforementioned hysteresis loop. For statistical analysis, parameters were averaged among all patients.

In a second analysis, NONMEM (Nonlinear Mixed Effects Modeling) software[11] (version V; GloboMax, Hanover, MD) was used to estimate PK-PD parameters applying a population-based approach (population fit) and mixed effect modeling. NONMEM takes into account that intraindividual as well as interindividual variability exists in PK-PD parameters among a patient population.[12] The software optimized the PK-PD parameters to obtain a close agreement between observed and estimated electroencephalographic effect. That is, in a statistical meaning, NONMEM maximizes the likelihood that the observed electroencephalographic effect would have been observed based on the sevoflurane C_{et} data if the PK-PD parameters were chosen and the intraindividual and interindividual variability were estimated as suggested by NONMEM assuming a certain (here: sigmoid) electroencephalographic effect model.[11] k_{e0} and the pharmacodynamic parameters itself were estimated directly without fitting the pharmacokinetic model itself. Interindividual variability was calculated for C_{50} and k_{e0}, and the intraindividual variability σ (residual error) of the electroencephalographic effect (BIS, PSI) was estimated using an additive error model:

$$E_{observed} = E_{expected} + \varepsilon,$$

where $E_{observed}$ and $E_{expected}$ refer to the observed and predicted electroencephalographic effect, respectively, and ε is a normally distributed random variable with mean zero and variance σ.[2]

Finally, the prediction probability P_K by which the electroencephalographic variable (BIS, PSI) correctly predicts the sevoflurane effect site concentration was calculated according to Smith *et al.*[8] by applying his Excel (Microsoft Corporation) software program PKMACRO.

Statistics

Statistical analysis was performed using SigmaStat software (Jandel Scientific, Erkrath, Germany) applying the Student *t* test or Mann–Whitney test. A power analysis ($\alpha = 0.05$, power = 0.80) aiming at detecting a difference in P_K means of 0.09 at an estimated SD in P_K of 0.1 revealed a study population size of at least 21 patients. Statistical significance was assumed at $P < 0.05$. Wherever applicable, data are presented as mean ± SD.

Results

The 22 patients consisted of 8 women and 14 men with an age of 37 ± 13 yr (mean ± SD). Their body weight was 77 ± 14 kg, resulting in a body mass index of 24.8 ± 3.2 kg/m^2.

Individual PK-PD Fitting

Individual fits were in close agreement with a sigmoid relation between C_{eff} and BIS ($\rho^2 = 0.84 \pm 0.09$) or PSI ($\rho^2 = 0.85 \pm 0.15$) (figs. 2 and 3). The values of the PK-PD parameters are shown in table 1. E_{max} was significantly lower ($P = 0.019$) for PSI (1.3 ± 4.3) than for BIS (7.9 ± 12.1), and k_{e0} was significantly smaller ($P = 0.001$) for PSI (0.13 ± 0.08/min) than for BIS (0.24 ± 0.15/min). The prediction probability of BIS ($P_K = 0.80 \pm 0.11$) to predict sevoflurane effect site concentration did not differ statistically from that of PSI ($P_K = 0.79 \pm 0.09$).

Population-based PK-PD Fitting

The NONMEM analysis revealed intraindividual variabilities (residual error σ) for BIS and PSI of 9.8 and 9.7, respectively. PSI showed a lower E_{max} (0), a smaller C_{50} (0.77 ± 0.20 vol%), and a lower k_{e0} (0.10 ± 0.28/min) as compared with BIS ($E_{max} = 6.9$, $C_{50} = 1.08 \pm 0.22$ vol%, $k_{e0} = 0.20 \pm 0.47$/min; table 1), whereas E_0 and λ were

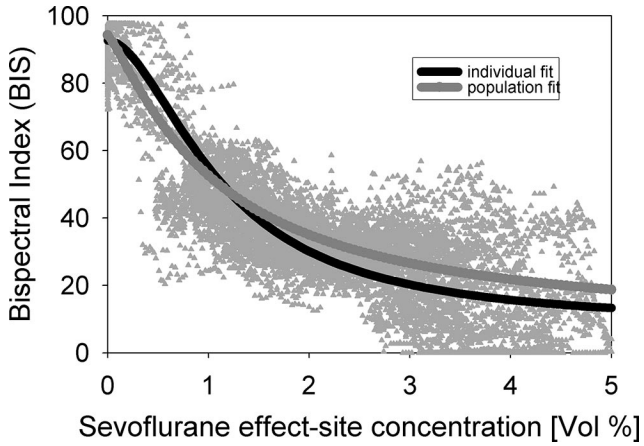

Fig. 2. Response of the Bispectral Index to changes in sevoflurane effect site concentrations. Individual data (n = 11,000 values from 22 patients) are indicated by *triangles*, whereas the data obtained by individual or population-based pharmacokinetic–pharmacodynamic modeling are shown as *black* and *gray lines*, respectively.

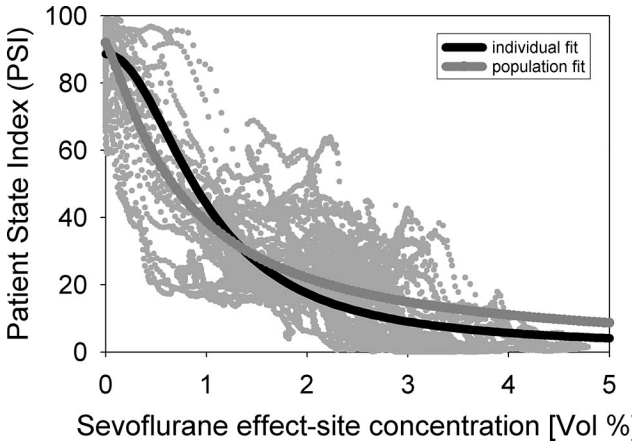

Fig. 3. Relation between Patient State Index and sevoflurane effect site concentrations. Individual data (n = 11,000 values from 22 patients) are illustrated by *circles*, whereas the data obtained by individual or population-based pharmacokinetic–pharmacodynamic modeling are indicated as *black* and *gray lines*, respectively.

similar for both electroencephalographic monitors. Therefore, the recommended intraoperative range for BIS (60–40) and PSI (50–25) corresponded to sevoflurane effect site concentrations of 0.75–1.63 and 0.65–1.73 vol%, respectively (fig. 4).

Correlation between BIS and PSI

A close and significant correlation between BIS and PSI was found ($r^2 = 0.75$, $P < 0.001$). However, for BIS values between 40 and 60—the recommended range for general anesthesia—only 49% of corresponding PSIs were within the recommended range of 25–50. *Vice versa*, for PSI values between 25 and 50, only 36% of corresponding BIS data were within the range of 40–60.

Table 1. Comparison of Pharmacokinetic and Pharmacodynamic Parameters between BIS and PSI

	BIS		PSI	
Fit	Individual	Population	Individual	Population
E_0	92.7 ± 7.5	94.3	88.6 ± 11.4	92.0
E_{max}	7.9 ± 12.1	6.9	1.3 ± 4.3*	0
C_{50}, vol%	1.13 ± 0.45	1.08 ± 0.22	0.98 ± 0.58	0.77 ± 0.20
λ	1.82 ± 0.77	1.21	2.07 ± 1.40	1.21
k_{e0}, min^{-1}	0.24 ± 0.15	0.20 ± 0.47	0.13 ± 0.08*	0.10 ± 0.28
P_K	0.80 ± 0.11		0.79 ± 0.09	
σ		9.8		9.7

Parameters were obtained by individual and population-based fitting. A sigmoid relation between sevoflurane effect site concentration and electroencephalographic effect (Bispectral Index [BIS], Patient State Index [PSI]) was assumed. Data are expressed as mean ± SD.

* $P < 0.05$ *vs* BIS.

C_{50} = sevoflurane effect site concentration that causes 50% of the maximum electroencephalographic effect; E_0 = electroencephalographic effect without anesthesia; E_{max} = electroencephalographic effect corresponding to maximum drug effect; k_{e0} = effect site efflux constant; λ = slope of the sigmoid relation; σ = intraindividual electroencephalogram variability (residual error); P_K = prediction probability by which the electroencephalogram variable (BIS, PSI) correctly predicts the sevoflurane effect site concentration.

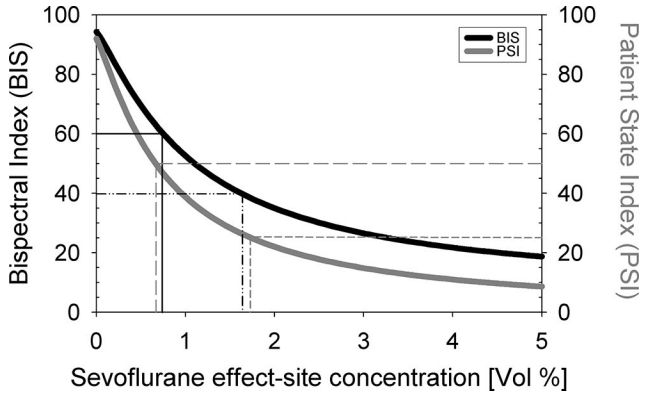

Fig. 4. Correlation between sevoflurane effect site concentration and Bispectral Index or Patient State Index, as obtained by population-based fitting. The sevoflurane concentrations that are related to the recommended index range (Bispectral Index: 40–60, shown in *black*; Patient State Index: 25–50, shown in *gray*) are highlighted.

As shown by the Bland–Altman plot (fig. 5), the difference between BIS and PSI increased with rising anesthetic depth, *i.e.*, decreasing index values.

Discussion

This is the first study to investigate the correlation between sevoflurane effect site concentration and PSI. We observed a relation in close agreement to the sigmoid E_{max} model[10], which assumes in the first place a baseline drug effect E_0 that is maintained until a threshold concentration is reached, and in the second place a saturable maximum effect E_{max} despite increasing drug concentrations. The sigmoid shape is thought to reflect the laws of mass action describing the interaction between drug and receptor,[13] or rather between drug and site of action, because no "sevoflurane receptor" has

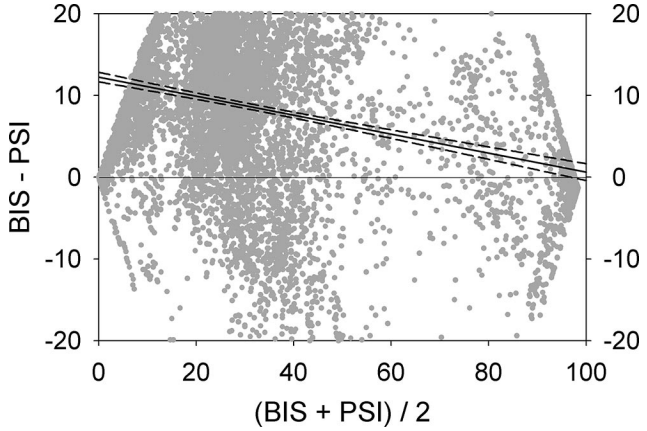

Fig. 5. Bland–Altman plot displaying the difference between Bispectral Index (BIS) and Patient State Index (PSI) *versus* their arithmetic mean, based on 11,000 values obtained in 22 patients. The linear regression line between difference and arithmetic mean is shown as a *solid line*, and its 99% confidence interval is shown as *dashed lines*. For illustrational reasons, the ordinate was scaled from −20 to +20 even though some data points were outside this range.

Table 2. Pharmacokinetic and Pharmacodynamic Parameters of BIS during Sevoflurane Anesthesia as Obtained by Different Authors

Authors	E_0	E_{max}	C_{50}, vol%	λ	k_{e0}, min^{-1}	ρ^2
Olofsen *et al.*[18]	94.9 ± 2.1	23.0 ± 9.4	1.12 ± 0.17	3.24 ± 1.28	0.22	0.95
Ellerkmann *et al.*[14]	86.7 ± 17.7	32.6 ± 22.0	1.45 ± 0.59	3.64 ± 2.96	0.31 ± 0.16	0.85 ± 0.12
Mourisse *et al.*[17]	95.3 ± 2.8	25.6 ± 3.0	1.29 ± 0.19	2.37 (1.94–2.90)	0.48 (0.38–0.60)	0.87 ± 0.06
Current study	92.7 ± 7.5	7.9 ± 12.1	1.13 ± 0.45	1.82 ± 0.77	0.24 ± 0.15	0.84 ± 0.09

Data are presented as mean ± SD or mean (95% confidence interval).

BIS = Bispectral Index; C_{50} = sevoflurane effect site concentration that causes 50% of the maximum electroencephalographic effect; E_0 = electroencephalographic effect without anesthesia; E_{max} = electroencephalographic effect corresponding to maximum drug effect; k_{e0} = effect site efflux constant; λ = slope of the sigmoid relation; ρ^2 = coefficient of determination.

been identified so far. Because the maximum electroencephalographic effect is restricted to zero by design in the majority of depth-of-anesthesia monitors, a saturable C_{eff} electroencephalographic effect kinetic results that is very similar to the saturable drug–receptor interaction. Consequently, a close sigmoid drug–electroencephalographic effect correlation has been described for other depth-of-anesthesia indices, such as the BIS, spectral entropy, and Narcotrend index,[14–16] even though a true drug–receptor interaction does not seem to exist.

The observed PK-PD values of BIS during sevoflurane anesthesia were in close agreement with those previously published,[14,17,18] (table 2) except for two parameters: E_{max} was smaller in our study because deeper levels of sevoflurane anesthesia were reached, and the slope λ of the sigmoid curve was lower in our study.

Between BIS and PSI, significant PK-PD differences were remarkable. First, the effect site constant k_{e0} was significantly higher for the BIS monitor; hence, the BIS reacted faster to changes in sevoflurane concentration than the PSI did. At first sight, it may seem unlikely that a pharmacokinetic parameter such as k_{e0} differs for the same given anesthetic when using different electroencephalographic monitors. At second sight, it might be explained as follows: First, k_{e0} is determined by the time delay between blood and effect site concentration, which is not affected by the chosen electroencephalographic monitor. Second, k_{e0} is influenced by the time delay for a particular neurophysiologic electroencephalographic effect to occur at that particular effect site concentration. This electroencephalographic effect to be analyzed is different for BIS and PSI monitors. The BIS is mainly determined by three parameters, which are SyncFastSlow, a subparameter derived from the analysis of the bispectrum; relative β ratio; and burst suppression ratio.[6] In contrast, the PSI assesses purely quantitative electroencephalographic changes, which are—among others—absolute power changes in α and β between electrodes, and total spectral power in the frontopolar region.[5] Different electroencephalographic effects, *e.g.*, SyncFastSlow and absolute power changes in α, are not necessarily characterized by the same PK-PD parameters. Just recently, Kennedy *et al.*[19] reported different k_{e0} values for a BIS greater than 30 (which is mainly determined by SyncFastSlow) and burst suppression ratio. Third, k_{e0} is modified by the time delay between the electroencephalographic effect and its corresponding BIS or PSI effect (time lag). Fourth, k_{e0} is affected by the time it takes the algorithm to calculate a particular BIS or PSI value (calculation time). Fifth, both BIS and PSI monitors average their index values over 15 and 25 s, respectively, to smooth their time course (averaging or smoothing time). The existing difference in averaging time of 10 s between monitors could at least partially explain the lower k_{e0} associated with the PSI monitor. Hence, time lag, calculation time, and averaging time are different entities that may affect the overall response time of the monitor and therefore influence k_{e0}: The larger these temporal parameters are, the smaller k_{e0} is. Furthermore, these parameters may depend on the depth of anesthesia and occurrence of electroencephalogram artifacts. For example, Pilge *et al.*[20] showed a large variability in the time delay for calculation of BIS as well as other indices and reported different results for increasing and decreasing anesthetic concentrations.

The second significant PK-PD difference between the monitors refers to the maximum sevoflurane electroencephalographic effect E_{max}, which was significantly lower for the PSI than for the BIS, by approximately 7 index points. Therefore, the predefined electroencephalographic effect range (100 to 0 for both monitors) was used more extensively by the PSI monitor. As a consequence, the PSI was smaller than the BIS during maintenance of sevoflurane anesthesia, which confirms previous findings by White *et al.*[21] Because of the lower E_{max} value, the PSI differentiates high sevoflurane concentrations worse than the BIS does. However, this is relevant for sevoflurane effect site concentrations higher than 3 vol%, which are not worth striving for during general anesthesia. The recommended electroencephalographic indices during general anesthesia are on a lower level for the PSI (25–50) as compared with the BIS (40–60). Notably, this range is broader for the PSI (25 index points) than for the BIS (20 index points), which translates to a wider range of sevoflurane effect site concentrations when considering PSI recommendations (0.65–1.73 vol%) as compared with BIS recommendations (0.75–1.63 vol%) (fig. 4). We observed only a weak

agreement between the recommended index ranges as expressed by our finding that for advised BIS values between 40 and 60, only 49% of corresponding PSI values were within the recommended range of 25–50. Because the desired sevoflurane concentration range is smaller for BIS monitoring, a smaller percentage (36%) of corresponding BIS data were within the recommended PSI range of 25–50. A similar poor agreement between advised BIS and PSI ranges was previously noted by Schneider *et al.*[22]

In contrast, we obtained a strong linear correlation between BIS and PSI during sevoflurane anesthesia (r^2 = 0.75), which was higher as reported by White *et al.*[21] ($0.55 < r^2 < 0.72$) or by Schneider *et al.*[22] ($r^2 = 0.44$). However, both applied a different anesthetic regimen, and Schneider *et al.* used a previous version of the BIS monitor (A-1000®) and PSI electrodes. Hence, relative changes of BIS and PSI correlate well during sevoflurane induction and emergence; however, absolute indices agree poorly during maintenance.

As with previous investigators,[14–18] we observed an interindividual difference in PK-PD parameters. Hence, we applied the NONMEM software, which was designed to deal with these differences and to perform a population-based fitting of PK-PD parameters.[11,12] The results thus obtained differed slightly from those calculated by individual fitting (table 1). The population-based approach revealed an intraindividual electroencephalographic variability (residual error) of almost 10 index points (σ_{BIS} = 9.8, σ_{PSI} = 9.7), which is thought to reflect biologic electroencephalographic variability rather than insufficiency of the BIS or the PSI algorithm.

We observed a high prediction probability of both BIS (P_K = 0.80 ± 0.11) and PSI (P_K = 0.79 ± 0.09) to predict sevoflurane effect site concentration. This means that if we change depth of anesthesia a hundred times (regardless of whether we increase or decrease), BIS would correctly indicate this change (a BIS decrease in the case of increasing anesthetic depth and *vice versa*) in 80 cases and PSI would correctly indicate this change in 79 cases. These values seem reasonably high from a clinical standpoint, although no accepted threshold exists above which an electroencephalographic monitor is deemed accurate or valid. In contrast, there is agreement that a monitor with a P_K of 0.5 is worthless because it predicts anesthetic depth no better than by chance.[8] P_K has been found to be an appropriate measure for evaluation and comparing the performance of anesthetic-depth monitors. We observed no statistical significant difference in P_K between BIS and PSI, and hence regard none of the monitors as superior to the other. P_K itself is a nonparametric measure and therefore independent of scaling. However, comparison between P_K values obtained by different studies is limited, because it is valid only in the case of both similar study design and the same distribution of anesthetic depths.[8]

White *et al.*[21] reported PSI and BIS to be equally effective in predicting unconsciousness (receiver operating characteristics of 0.98 ± 0.05 and 0.97 ± 0.05, respectively). However, Chen *et al.*[23] found a better performance of PSI to detect consciousness (receiver operating characteristic 0.95 ± 0.04 for PSI *vs.* 0.79 ± 0.04 for BIS). Schneider *et al.*[24] estimated BIS and PSI as comparable but nonetheless insufficient to detect awareness (P_K = 0.68 ± 0.03 and 0.69 ± 0.03, respectively). The PSI has been shown to predict sedation levels during anesthesia[25] (r^2 for predicting Observer's Assessment of Alertness/Sedation Score = 0.71) and intensive care therapy[26] (P_K to predict Ramsey score = 0.92 ± 0.04). Initially, the PSI monitor was less interfered with by electrocautery[21,23]; however, both BIS and PSI have an improved ability to reject artifacts due to electrocautery. It is therefore unknown whether this difference remains with the most recent versions (BIS Vista and Hospira SEDline) of both depth-of-anesthesia monitors.

The effect site concentration of a given anesthetic is a widely used surrogate parameter for the validation of depth of anesthesia.[2,14,16,27,28] Based on this assumption, we have been able to show that both the BIS monitor and the PSI monitor are reliable and valid depth-of-anesthesia monitors. However, the electroencephalographic changes mainly reflect the hypnotic component of general anesthesia.[29] In contrast, quantification of the antinociceptive part of anesthesia remains a challenge, even though promising attempts have been made to do so.[30] Another limitation of our study deals with the fact that all depth-of-anesthesia monitors were designed for patients with a "normal" electroencephalogram. Hence, our results cannot be easily transferred to patients with definitely or potentially altered electroencephalographic activity, such as children, patients using central nervous system–affecting drugs, and patients with any severe brain-affecting disease or trauma.

In conclusion, neither BIS nor PSI was superior to the other monitor in predicting depth of sevoflurane anesthesia. Both measured to electroencephalographic effects of sevoflurane and hence correlated closely with each other, although they agreed poorly on a sample-to-sample basis, indicating a high variability. In general, the BIS reacted faster to changes in sevoflurane concentrations, whereas the PSI made a better use of the predefined index range from 100 to 0. However, despite major differences in their algorithms, we found only minor differences in their dose–response relations. This is the first study investigating the pharmacodynamic of sevoflurane with respect to PSI; further studies are required to compare the BIS and PSI monitors with respect to relevant clinical outcomes.

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