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Patient state index vs bispectral index as measures of the electroencephalographic effects of propofol

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Key points
- The effect of propofol on two EEG-indices (PSI and BIS) was analysed.
- Seventeen patients were investigated without surgical stimulus.
- PSI and BIS predicted depth of propofol anaesthesia with a comparable probability.
- At clinically relevant propofol concentrations, PSI was lower than BIS by ~10–15 points.

Background. The patient state index (PSI) and the bispectral index (BIS) quantify anaesthetic depth based on the EEG using different algorithms. We compared both indices with regard to the prediction of the depth of propofol anaesthesia.

Methods. In 17 patients, propofol was infused until burst suppression occurred and stopped thereafter until BIS recovered to values above 60. This was repeated; afterwards, patients were intubated, for subsequent surgery. Without surgical stimulus, PSI and BIS were measured simultaneously and compared with the estimated effect-site concentrations of propofol. These were derived from simultaneous pharmacokinetic and -dynamic modelling in an individual two-stage and a population-based NONMEM approach.

Results. A close sigmoid relationship was observed between the propofol effect-site concentration and both PSI [coefficient of determination $R^2 = 0.91$ (SD 0.05)] and BIS [$R^2 = 0.92 (0.03)$], which was significantly steeper for PSI [$\gamma = 2.2 (0.6)$] than for BIS [$\gamma = 1.8 (0.4)$], and reached significantly lower values for PSI [$E_{\text{max}} = 5.3 (6.7)$] at maximal propofol concentrations. A significantly smaller $k_{\text{e0}}$ was obtained for PSI [0.09 (0.03) min$^{-1}$] compared with BIS [0.10 (0.02) min$^{-1}$]. PSI and BIS correlated significantly with each other ($R^2 = 0.866$) and predicted propofol effect-site concentration with a comparable probability [PSI $= 0.87 (0.05)$ and 0.86 (0.05), respectively]. NONMEM revealed $E_0 = 89.3$ and 92.3, $E_{\text{max}} = 1.9$ and 8.6, $C_{\text{e50}} = 1.38$ and 1.92 μg ml$^{-1}$, $\gamma = 1.6$ and 1.48, and $k_{\text{e0}} = 0.103$ and 0.131 min$^{-1}$ as typical values for PSI and BIS, respectively.

Conclusions. The PSI and the BIS monitors performed equally well in predicting depth of propofol anaesthesia. However, PSI was lower than BIS by ~10–15 points at high propofol concentrations.

Keywords: depth of anaesthesia; EEG; pharmacodynamics; pharmacokinetics, propofol; propofol

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and obtained comparable results. Only slight differences between the monitors were noticed: whereas the BIS reacted faster to changes in sevoflurane concentrations, the PSI made a better use of the index range.4

In addition to these previous results obtained by using a volatile anaesthetic, we performed a study applying an i.v. drug: the aim of the current study was to analyse the pharmacodynamic effects of propofol on PSI and BIS and to compare the performance of both monitors to predict the depth of propofol anaesthesia.

Methods

After approval of the University of Bonn Ethics Committee (reference number 203/03) and written informed consent, we evaluated 17 patients undergoing otorhinolaryngologic surgery. Age was restricted to 18–65 yr, and ASA physical status to I or II. Pregnancy and any disease or (current) treatment affecting the central nervous system were exclusion criteria.

Patients were instructed to fast for 6 h and received midazolam 7.5 mg p.o. 45 min before induction of anaesthesia. Standard anaesthetic monitoring was applied upon arrival in the induction room, and mean arterial pressure (MAP) was measured non-invasively at intervals of 2.5 min. The forehead skin was cleaned with 70% isopropanol to improve skin conductance, and both EEG electrodes (Physiometrix PSArray2 Sensor, Hospira Inc., Lake Forest, IL, USA) and the Aspect A-2000 BIS monitor (version XP, Aspect Medical Systems, Newton, MA, USA) were used to record the EEG simultaneously and continuously.

A 14 G venous catheter was inserted into a large forearm vein and lactated Ringer’s solution was infused at a constant rate of 500 ml h⁻¹. Anaesthesia was induced solely by a continuous propofol 2% infusion at a rate of 2000 mg h⁻¹. The propofol infusion was stopped (Fig. 1) as soon as substantial burst suppression occurred (burst suppression rate >60% according to the BIS monitor) or arterial hypotension occurred (MAP <60 mm Hg). After discontinuation of the propofol application, depth of anaesthesia diminished slowly. When the BIS recovered to values >60, the propofol infusion was started again (Fig. 1) at an identical rate of 2000 mg h⁻¹ until a burst suppression rate >60% or an MAP <60 mm Hg was reached. Thereafter, propofol infusion was discontinued and started again as mentioned above to perform further cycles of increasing and decreasing propofol plasma concentration. After a maximum of three cycles—or sooner if necessary due to the OR management requirements—EEG measurements were stopped and patients received opioids and neuromuscular blocking agents for subsequent intubation and surgery. Until that time, patients breathed spontaneously during the entire study period. Fraction of inspired oxygen was reduced from 1.0 at preoxygenation to 0.5 during the study.

PSI (release 3.00.09, averaging time 25 s, PSI value updated every 1.25 s), BIS (version 4.0, smoothing time 15 s, BIS value updated every second), and haemodynamic data (S/5 monitor®, GE Healthcare, Helsinki, Finland) were stored simultaneously every 5 s using software supplied by the manufacturer (Aspect: Winlog software; Datex Ohmeda: S/5 Collect software V 4.0).

Arterial propofol plasma concentrations were calculated using an Excel spreadsheet described by Bruhn and Bouillon5 based on the pharmacokinetic data set published by Schnider and colleagues.6 The propofol effect-site concentration (Ce) was obtained by simultaneous pharmacokinetic–pharmacodynamic (pk/pd) modelling.7 First, Ce was estimated using the differential equation:

$$\frac{dC_e}{dt} = (C_{pl} - C_e) \times k_{e0}$$

where Ce is the plasma concentration of propofol, and k_{e0} denotes the first-order rate constant determining the efflux from the effect site. In practice, k_{e0} is approximated until the hysteresis loop between Ce and the EEG variable (BIS, PSI) has been collapsed. Secondly, a classic fractional sigmoid relation between Ce and the EEG effect E (BIS, PSI) was assumed.8

$$E = E_0 + (E_{max} - E_0) \left(\frac{C_e}{C_{e50} + C_e}\right)^{\gamma}$$

where E₀ denotes the EEG effect in the absence of propofol (=baseline or awake state), and E_{max} is the EEG value corresponding to the maximum propofol effect. C_{e50} describes the propofol effect-site concentration that causes 50% of the maximum EEG effect, and γ quantifies the slope of the sigmoid relationship between Ce and E.

Pk/pd parameters were determined offline using two different approaches: in a Fisherian statistics approach (also
known as classic two-stage approach), pk/pd parameters were first obtained for each individual patient (individual fit) applying the solver tool of the Excel 2000 software (Microsoft, Redmond, WA, USA): this tool was used to perform a sigmoid regression of the EEG effect based on \( C_e \). To quantify the goodness of the sigmoid fit, the coefficient of determination \( r^2 \) was calculated as

\[
r^2 = 1 - \frac{\sum (E_{\text{measured}} - E_{\text{calculated}})^2}{\sum (E_{\text{measured}} - E_{\text{measured}})^2}
\]

where \( E_{\text{measured}} \) is the averaged measured EEG effect. \( k_{e0} \) and the pd parameters \( E_0, E_{\text{max}}, C_{50}, \) and \( \gamma \) were simultaneously optimized by minimizing the ordinary least squares, which resulted from the difference between observed and estimated EEG effect. This yielded a collapse of the above-mentioned hysteresis loop. Subsequently, pk/pd parameters were averaged among all 17 patients.

In a second Bayesian statistics approach, it was assumed that a ‘typical value’ for the pk/pd parameters exist within a given patient population (population fit). Furthermore, it was hypothesized that additional random effects affect those pk/pd parameters, which are inter- and intra-individual variabilities. Whereas inter-individual variability reflects true biologic variability, intra-individual variability can be regarded as measurement noise or residual error. The NONMEM (NONlinear Mixed Effects Modelling) software (version V, GloboMax, Hanover, MD, USA) was used to perform this approach. \( k_{e0} \) and the pharmacodynamic parameters were estimated directly (in contrast to the above-mentioned two-stage approach) without fitting the pharmokinetic model itself. To do so, the so-called first-order conditional estimation method was applied. Inter-individual variability was calculated for \( C_{50} \) and \( k_{e0} \), and the intra-individual variability \( \sigma \) (residual error) of the EEG effect (BIS, PSI) was estimated using an additive error model:

\[
E_{\text{observed}} = E_{\text{expected}} + \epsilon
\]

where \( E_{\text{observed}} \) and \( E_{\text{expected}} \) refer to the observed and predicted EEG effects, respectively, and \( \epsilon \) is a normally distributed random variable with mean zero and variance \( \sigma^2 \). The software optimized the pk/pd parameters to obtain a close agreement between observed and estimated EEG effect: in statistical terms, NONMEM maximizes the likelihood that the observed EEG effect would have been observed based on the propofol \( C_{\text{pi}} \) data if the pk/pd parameters were chosen and the intra- and inter-individual variabilities were estimated as suggested by NONMEM assuming a certain (here: sigmoid) EEG effect model.

For measurement and comparison of the performance of anaesthetic depth monitors, the prediction probability \( P_k \) by which the EEG variable (BIS, PSI) correctly predicted the propofol effect-site concentration was calculated according to Smith and colleagues applying his Excel software program PKMACRO. \( P_k \) itself is a non-parametric measure ranging between 0 and 1. An anaesthetic depth monitor that always predicts depth of anaesthesia correctly will obtain a \( P_k \) value of 1, whereas a monitor that performs no better than by (50:50) chance will be characterized by a \( P_k \) value of 0.5. Since propofol concentration increases as BIS and PSI decrease, the actual \( P_k \) value we measure is \( 1-P_k \). Finally, Pearson’s product-moment correlation coefficient \( r \) and its square \( r^2 \) (coefficient of determination) were calculated to provide information on the goodness of the linear fit between PSI and BIS.

**Statistical analysis**

The study was designed to detect a change in the mean \( P_k \) value of 0.075, that is, 75% of the expected standard deviation (so) of the \( P_k \) value of 0.1 (as derived from our previous study). At a desired power of 0.8 and an \( \alpha \) of 0.05, 17 patients are required to do so, plus one additional patient to correct for a possible drop-out.

Statistical analysis was performed using the SigmaStat software (Jandel Scientific, Erkrath, Germany) applying Student’s t-test for paired samples in the case of normal distributed data. Otherwise, the Wilcoxon signed-rank test was performed. To comply with multiple comparisons, Bonferroni’s correction was applied and statistical significance was assumed at \( P<0.01 \) accordingly. Data are presented as mean (so) for the Fisherian and as typical value for the Bayesian approach.

**Results**

The 17 patients (seven women and 10 men) were 36 (12) yr old (mean (so)), had a body weight of 74 (17) kg, a height of 172 (11) cm, and a BMI of 25.0 (4.4) kg m\(^{-2}\).

PSI and BIS data from all 17 patients were available for final data analysis: one-and-a-half cycles of in- and decreasing propofol concentrations were analysed in one patient, two cycles in nine patients, and three cycles in seven patients. The endpoint of a burst suppression ratio of 60% was reached in all patients except for one, in which the propofol infusion was stopped at a burst suppression rate of 36% since the endpoint of an MAP <60 mm Hg was attained.

**Individual pk/pd fitting**

The pk/pd parameters obtained in the individual patients are shown in Table 1. \( E_{\text{max}} \) was significantly lower (\( P=0.007 \), Wilcoxon signed-rank test) for PSI [0.3 (1.1)] when compared with BIS [5.3 (6.7)], and \( \gamma \) was significantly higher (\( P=0.01 \), paired t-test) for PSI [2.18 (0.57)] as for BIS [1.75 (0.41)]. In addition, a significantly smaller \( k_{e0} \) (\( P=0.005 \), paired t-test) was observed using the PSI monitor [\( k_{e0}=0.088 \) (0.029)] compared with the BIS monitor [\( k_{e0}=0.104 \) (0.024)]. A close sigmoid relationship between \( C_e \) and PSI \( (r^2=0.91 \) (0.05)) or BIS \( (r^2=0.92 \) (0.03)) was obtained in individual patients, and the prediction probability of PSI \( (P_k=0.87 \) (0.05)) and BIS \( (P_k=0.86 \) (0.05)) to predict the propofol effect-site concentration did not differ statistically from each other (\( P=0.74 \), paired t-test).
Population-based pk/pd fitting

The sigmoid relationship between the propofol effect-site concentration and the PSI and BIS was assumed. A sigmoid relationship between propofol effect-site concentration and EEG effect (BIS and PSI) was obtained by population-based fitting. An intra-individual variability (residual error) of $s = 7.7$ and $6.4$ was obtained for PSI and BIS, respectively (Table 1). The typical value of $E_{\text{max}}$ was smaller for PSI (1.9) as for BIS (8.6), whereas the other pk/pd parameters were comparable between the monitors. The recommended intraoperative range for PSI (50–25) and BIS (60–40) corresponded to propofol effect-site concentrations of 1.2–2.6 and 1.4–2.7 $\mu$g ml$^{-1}$, respectively (Fig. 4).

Table 1 Pharmacokinetic and -dynamic parameters in comparison between PSI and BIS. Parameters were obtained by individual and population-based fitting. A sigmoid relationship between propofol effect-site concentration and EEG effect (BIS and PSI) was assumed. Data are expressed as mean (SD) for the individual fits and as typical value (so) for the population fit. $^{*}P<0.01$ vs BIS. PSI, patient state index; BIS, bispectral index; $E_0$, EEG effect without anaesthesia; $E_{\text{max}}$, EEG effect corresponding to maximum drug effect; $C_{50}^E$, propofol effect-site concentration that caused 50% of the maximum EEG effect; $\gamma$, slope of the sigmoid relationship; $k_{\text{es}}$, effect-site efflux constant; $\rho^2$, coefficient of determination; $P_K$, prediction probability by which the EEG variable (BIS, PSI) correctly predicted the propofol effect-site concentration; $\alpha$, intra-individual EEG variability (=residual error).

<table>
<thead>
<tr>
<th>Fit</th>
<th>PSI</th>
<th>BIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual</td>
<td>Population</td>
</tr>
<tr>
<td>$E_0$</td>
<td>86.9 (12.3)</td>
<td>89.3</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.3 (1.1)</td>
<td>1.9</td>
</tr>
<tr>
<td>$C_{50}^E$ (µg ml$^{-1}$)</td>
<td>1.87 (0.78)</td>
<td>1.38 (0.86)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>2.18 (0.57)</td>
<td>1.60</td>
</tr>
<tr>
<td>$k_{\text{es}}$ (min$^{-1}$)</td>
<td>0.088 (0.029)</td>
<td>0.103 (0.210)</td>
</tr>
<tr>
<td>$\rho^2$</td>
<td>0.913 (0.054)</td>
<td>0.922 (0.033)</td>
</tr>
<tr>
<td>$P_K$</td>
<td>0.867 (0.053)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Fig 2 The relationship between the propofol effect-site concentration and PSI is shown for the ‘typical patient’ as obtained by population fit using NONMEM. The residual data of the individual patients are marked by blue circles.

Fig 3 The response of the BIS to changes in the propofol effect-site concentration is displayed for the ‘typical patient’ as revealed by population fit using the NONMEM software. The blue triangles indicate the residual data of the individual patients.

Fig 4 For the recommended ranges (shown as bars on the left and right ordinate) of the PSI (25–50) and the BIS (40–60), the corresponding propofol effect-site concentration site ranges (displayed as bars on the abscissa) are shown. The relation is based on the pharmacodynamic effect of propofol on BIS (blue line) and PSI (dotted green line) for the ‘typical patient’ as revealed by NONMEM.

Population-based pk/pd fitting

The sigmoid relationship between the propofol effect-site concentration and the PSI and BIS as obtained by population-based fitting is shown in Figures 2 and 3, respectively. An intra-individual variability (residual error) of $\alpha=7.7$ and 6.4 was obtained for PSI and BIS, respectively (Table 1). The typical value of $E_{\text{max}}$ was smaller for PSI (1.9) as for BIS (8.6), whereas the other pk/pd parameters were comparable between the monitors. The recommended intraoperative range for PSI (50–25) and BIS (60–40) corresponded to propofol effect-site concentrations of 1.2–2.6 and 1.4–2.7 $\mu$g ml$^{-1}$, respectively (Fig. 4).
Correlation between BIS and PSI

A close and significant correlation between BIS and PSI was found ($p^2 = 0.866, P<0.001$). For PSI values between 25 and 50—the recommended range for general anaesthesia—44% of corresponding BIS data were within the range of 40–60, whereas for the recommended BIS range between 40 and 60, 69% of corresponding PSIs were within the range of 25–50.

Discussion

Both the PSI and BIS monitors performed equally well ($P_K=0.87 (0.05)$ for PSI and 0.86 (0.05) for BIS, respectively) in predicting the estimated propofol effect-site concentrations. According to the definition of the prediction probability $P_K$, this means that if one changes the depth of propofol anaesthesia in our data set a hundred times, the PSI and BIS would correctly indicate this change in 87 and 86 cases, respectively. These reasonably high values were obtained using the i.v. anaesthetic propofol and are lower than the recommended range for BIS ($40–60, 69\%$ of corresponding PSIs were within the range of 25–50). However, this significant difference in $P_K$ means that if one changes the depth of propofol anaesthesia in our data set a hundred times, the PSI and BIS monitors perform similarly. Consequently, the manufacturer of the PSI recommends a range of 25–50 for general anaesthesia, which is lower than the recommended range for BIS ($40–60, 69\%$ of corresponding BIS data were within the range of 25–50). However, neither condition existed in our study population.

All patients received midazolam as premedication. Since benzodiazepines alter the EEG, this might have influenced the propofol concentration–effect curve. However, the concentration of midazolam necessary to cause EEG changes (>100 ng ml$^{-1}$) exceed the peak plasma concentration (35 ng ml$^{-1}$, as extrapolated from Greenblatt and colleagues) after oral administration of 7.5 mg by a factor of three.

Since this is the first study, to our knowledge, that analyses the pharmacodynamic effect of propofol on PSI by application of a sigmoid pk/pd model, there are no other PSI pk/pd studies to refer to. However, with regard to the BIS during propofol anaesthesia, the following observations are noteworthy when comparing the pk/pd parameters of our study with the results of other investigators (Table 2): $E_{max}$ was lower in our study, indicating that we achieved deeper levels of propofol anaesthesia. In addition, we observed a lower $C_{e50}$ (1.9 μg ml$^{-1}$) which appears low from a clinical standpoint but is explained by the fact that the study was performed in the absence of any kind of stimulus. Thus, relatively low concentrations of propofol were required to achieve a level of general anaesthesia. Finally, the effect-site efflux constant $k_{eo}$ was lower. The pk/pd parameters described in the literature (Table 2) vary to a considerable amount reflecting the given inter-individual variability, which is an inherent feature of complex biological systems such as the human being.

To take this variability in pk/pd parameters into account, we performed a Bayesian statistics approach in addition to the classic Fisherian statistics: we applied the NONMEM software which estimated a pk/pd model based on fixed effects (the so-called ‘typical values’ in NONMEM parlance) and random effects, which are differentiated into effects due to inter- and intra-individual variabilities. As demonstrated in Table 1, the typical values of the pk/pd parameters which characterize a representative patient within a given population differ only slightly from the mean values obtained using the two-stage approach. However, the inter-individual variability of $C_{e50}$ and $k_{eo}$ is considerably high, whereas the intra-individual variability $σ$ of the PSI (±7.7 index points) and BIS (±6.4 index points) is low. Thus, our results confirm the general rule, that pharmacodynamic variability is pronounced (usually exceeding pharmacokinetic variability), and that inter-individual differences are large, whereas intra-individual differences are much smaller.

We observed a close sigmoid relationship ($p^2=0.91$ for PSI and 0.92 for BIS) between propofol effect-site concentration
and EEG effect (i.e. BIS and PSI). In the absence of a gold-standard defining depth of anaesthesia, effect-site concentration is a widely accepted surrogate parameter. Consequently, both the BIS and the PSI monitors can be regarded as monitors of depth of anaesthesia.

We noticed a close and significant linear correlation between PSI and BIS ($r^2 = 0.87$) during propofol anaesthesia which exceeded our previous findings obtained using sevoflurane ($r^2 = 0.75$). Nevertheless, we only found a poor agreement between the recommended ranges for PSI (25–50) and BIS (40–60), so that index values—which were within the recommended range in one monitor—were outside the range in the other monitor, as was previously reported by Schneider and colleagues. Other authors reported a rather modest correlation between PSI and BIS with a coefficient of determination $r^2$ ranging between 0.44 and 0.72. However, their data were based on a previous version of either the electrodes or the monitors, or used a different hypnotic regimen.

PSI and BIS have already been compared in the past and disagreeing assessments were published: PSI and BIS performed equally well in predicting unconsciousness [receiver operating characteristics, ROC = 0.98 (0.05) for PSI and 0.97 (0.05) for BIS] and detecting awareness $^2$ [PSI = 0.69 (0.03) for PSI and 0.68 (0.03) for BIS]; however, the latter ability was deemed to be nonetheless insufficient. In contrast, PSI was found to be superior to BIS in detecting consciousness [ROC = 0.95 (0.04) for PSI and ROC = 0.79 (0.04) for BIS] according to Chen and colleagues, and Adesanya and colleagues reported that BIS was consistently better in predicting oversedation than the PSI (area under the curve = 0.92 for BIS and 0.78 for PSI).

The PSI was approved in 2002 and has been evaluated since then in 15 publications (retrieval at PubMed on October 15, 2009). In contrast, the BIS has already been approved in 1996, subjected to 1417 publications (retrieval at PubMed on October 15, 2009) and applied to more than 34 million patients (according to manufacturer’s information). Hence, BIS technology is thought to be the most validated form of depth of anaesthesia monitoring so far.

We conclude that both the PSI and the BIS monitors predict depth of propofol anaesthesia with a similar and sufficient high probability. The major difference between the two monitors (besides their algorithm) refers to the fact that PSI values were lower than the BIS values by $\sim 10–15$ index points resulting in a lower recommended range (25 to 50 for PSI, and 40 to 60 for BIS) for general anaesthesia.

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## Conflict of interest

None declared.
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