FAILURE OF TWO COMMERCIAL INDEXES AND SPECTRAL PARAMETERS TO REFLECT THE PHARMACODYNAMIC EFFECT OF DESFLURANE ON EEG

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Abstract. Objective. We compared two PK/PD models, one with and one without a plateau effect. Bispectral (BIS, Aspect Medical Systems, Natick, MA, version XP) and Narcotrend™ (NCT, MonitorTechnik, Bad Bramstedt, Germany, Version 4.0) indices were used as an electroencephalographic measure of desflurane drug effect.

Methods. With IRB approval and informed consent we investigated 20 adult patients scheduled for radical prostatectomy. At least 45 minutes after induction of general anaesthesia, end-tidal concentrations of desflurane was varied between 3 and 10 vol%. To evaluate the relationship between concentrations and EEG indices, two different pharmacodynamic models were applied: A conventional model based on a single sigmoidal curve, and a novel model based on two sigmoidal curves for BIS and NCT values with and without burst suppression. The parameters of the models were estimated by NONMEM V (GloboMax, Hanover, USA) by minimizing log likelihood. Statistical significance between the two models was calculated by the likelihood ratio test.

Results. The maximum end-tidal desflurane concentration during the two concentrations ramps was 10.0 ± 1.4 vol%. The mean BIS and NCT values decreased significantly but slightly with increasing end-tidal desflurane concentrations between 4 and 8 vol%. Therefore a two sigmoidal curves PK/PD model including a plateau describes the effects of desflurane on BIS and Narcotrend better than a single sigmoidal curve model. The difference between the log likelihood values of the new PK/PD model with two connected sigmoidal curves and the classical $E_{\text{max}}$ model with one sigmoidal curve is 634 ($P < 0.001$) for the BIS monitor and 4089 ($P < 0.001$) for the NCT. Conclusions. BIS and Narcotrend are not useful to differentiate pharmacodynamic changes in the EEG between 4 and 9 vol% desflurane.

Key Words. bispectral index, Narcotrend, desflurane, pharmacodynamic plateau, pharmacodynamic model.

Introduction

One of the primary goals of general anaesthesia is to eliminate consciousness and achieve amnesia for the duration of surgery. Since anaesthetics influence the electrical activity of the cortex, the electroencephalogram (EEG) seems to be the obvious choice for optimal monitoring of the depression of cerebral activity during general anaesthesia. Progress in computer and monitor technology allowed the development of indices for monitoring of the depth of anaesthesia. Now, a number of different monitor systems is commercially available.
The BIS-Monitor A-2000 (BIS-XP, Aspect Medical Systems Inc., Natick, MA) is known worldwide and has been validated as an automatic EEG interpretation system for general anaesthesia in innumerable studies. After transformation of the raw EEG signal with an analogue/digital converter the BIS value is calculated (BIS = Bispectral Index Scale). The BIS value is a dimensionless number between 0 (cortical silence) and 99 (awake) and is calculated using various subparameters, a part of which are the results of the name-giving bispectral analysis [1, 2].

The Narcotrend is an automatic EEG recording system which was developed by an interdisciplinary study group at Hannover Medical School, Germany (Version 4.0, MonitorTechnik, Bad Bramstedt, Germany). After an automatic artefact analysis the raw EEG signal is processed by the Narcotrend using a multivariate analysis algorithm and is then assigned to defined EEG stages. The Narcotrend algorithm is in part based on a classification of the sleep EEG and differentiates six EEG stages from A (awake) to F (burst suppression to cortical silence) with 15 substages. In addition, a Narcotrend index is displayed with a range from 99 (awake) to 0 [3–6].

In a preceding investigation we compared the applicability of the Bispectral index and the Narcotrend index for quantification of the pharmacodynamic effects of isoflurane [7] and sevoflurane [8] with a newly developed model with two connected sigmoidal curves, with the first sigmoidal curve describing the electroencephalogram response before the onset of burst suppression, and the second sigmoidal curve describing the electroencephalographic response with burst suppression.

In the present investigation first we visually investigated the dose–response relationship of BIS and Narcotrend values versus end-tidal desflurane concentrations. An individual \( k_{eo} \) value was chosen which collapsed the hysteresis loop adequately without any underlying model leading to a pronounced plateau effect for desflurane. Then we compared the applicability of the new model with two connected sigmoidal curves to the classical \( E_{max} \) model with one sigmoidal curve during desflurane anaesthesia. We hypothesized that the new model with two connected sigmoidal curves yielded into a better population fit than the classical \( E_{max} \) model with one sigmoidal curve. In addition, we tried to analyse the origin of the observed plateau by the investigation of spectral parameters and the burst suppression ratio.

### METHODS

**Patients and anaesthesia**

With local ethics committee (Ärztekammer des Saarlandes, Saarbrücken, Saarland, Germany) approval and written informed consent, we investigated 20 adult patients scheduled for radical prostatectomy. All patients were premedicated with midazolam 7.5 mg orally on the morning before surgery. After the skin of the forehead had been degreased with 70% isopropanol, the BIS (BIS-XP sensor, Aspect Medical Systems, Natick, MA) 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, 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 \( \leq 6 \, k\Omega \) for the Narcotrend and \( \leq 7.5 \, k\Omega \) for the BIS as required by the manufacturers.

While oxygen 10 l/minute was given over a face mask for preoxygenation, induction of anaesthesia was started with a remifentanil infusion at 0.4 \( \mu g \) kg\(^{-1} \) minute\(^{-1} \). Five minutes later the patients received 2.0 \( mg \) kg\(^{-1} \) propofol. After loss of consciousness and face mask ventilation, patients received 0.5 mg kg\(^{-1} \) of 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 desflurane in 1.5 l minute\(^{-1} \) fresh gas flow (0.5 l minute\(^{-1} \) O\(_2\) and 1 l minute\(^{-1} \) air) was given for hypnosis. End-tidal concentrations were measured using infrared absorption technology (PM 8050, Dräger, Lübeck, Germany). The precision of the end-tidal measurements was 0.1 vol%.

After induction of anaesthesia had been completed, patients received 12 ml bupivacaine 0.5% epidurally for intraoperative analgesia. Complete neuromuscular blockade during the investigation was ensured by repetitive injections of 0.25 mg kg\(^{-1} \) atracurium and ensured by neuromuscular monitoring, i.e. train-of-four and double burst stimulation monitoring. In order to rule out residual effects from propofol or remifentanil and to ensure a condition of constant surgical stimulation, study measurements were performed during dissection of the prostate, a minimum of 45 minutes after induction of anaesthesia. To obtain concentration response curves, end-tidal concentrations were subsequently increased and decreased two times: Starting at an end-tidal desflurane concentration of 3.0 vol%, the vaporizer was opened to the maximum of 14 vol% desflurane concentration until the end-tidal desflurane concentration reached 10 vol%. Thereafter, the vaporizer was closed (0 vol% desflurane concentration) until the end-tidal desflurane concentration had decreased to 3.0 vol% or a BIS value of 60 had been reached. After the final suture was placed, desflurane was discontinued and patients were allowed to awaken from anaesthesia. The measurements recorded during the