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aepEX monitor for the measurement of hypnotic depth in patients undergoing balanced xenon anaesthesia

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Editor's key points

- This study describes the behaviour of the auditory-evoked potential (AEP)-based AEP index (aepEX) for the measurement of hypnotic depth in patients undergoing general anaesthesia with xenon or sevoflurane.
- Intraoperative measurement of aepEX indices yielded a comparable behaviour with the bispectral index co-monitoring in patients undergoing anaesthesia with either xenon or sevoflurane.

Background. Previously, we showed a significant difference in the measurements of hypnotic depth by the bispectral index (BIS) and auditory-evoked potentials (AEPs) using the A-line autoregressive index during xenon anaesthesia. In the present study, we evaluate the alternative AEP-based auditory-evoked potential index (aepEX) for the measurement of hypnotic depth in patients undergoing general anaesthesia with xenon.

Methods. Forty-two patients undergoing elective abdominal surgery were enrolled in this controlled, double-blinded, randomized, clinical study. Patients were randomized to receive either xenon (n=21) or sevoflurane anaesthesia (n=21). During anaesthesia, BIS values were recorded simultaneously with the aepEX monitoring. The anaesthetist performing the anaesthesia was blinded to the hypnotic depth monitors. After surgery, the incidence of recalls and awareness was evaluated.

Results. Patients' characteristics such as gender, age, and weight did not differ between the groups. The aepEX and BIS values behaved similarly during anaesthesia. The comparison of aepEX values during xenon and sevoflurane anaesthesia revealed significantly lower aepEX values in the xenon group after 25 min [xenon: 32.9 (4.8) *vs* sevoflurane: 39.3 (9.0); P=0.008] and after 35 min [xenon: 31.4 (6.6) *vs* sevoflurane: 37.0 (6.8); P=0.012]. During anaesthesia, aepEX values correlated with the clinical evaluation of depth of anaesthesia (e.g. >20% changes of the baseline arterial pressure or heart rate, spontaneous breathing and/or intolerance of mechanical ventilation, coughing, abdominal pressing, sweating, eye tearing).

Conclusions. We found the aepEX monitor to provide index in the range of adequate depth of xenon anaesthesia, when combined with remifentanil infusion in intubated patients undergoing elective abdominal surgery.

Keywords: anaesthesia, general; anaesthetic gases; monitoring, depth of anaesthesia

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During the past decade, interest in the monitoring of hypnotic depth during general anaesthesia has been increased. The measurement of the EEG-derived bispectral index BIS™ is a widely used assessment of the actual state of cerebral activity.[1 2] Alternatively, the measurement of auditory-evoked potentials (AEPs) offers fast detection of neuronal information processing in response to acoustic stimuli. AEP measurements correlate with hypnotic depth measured by EEG and thus have been proposed as a reliable method for the assessment of anaesthetic depth during general anaesthesia.[3–7]

In a recent study, however, we found the AEP measurements to indicate a decrease in hypnotic depth after 35 min exposure to xenon anaesthesia, although simultaneously acquired BIS values indicated adequate anaesthetic depth, and although AEP values for patients undergoing sevoflurane anaesthesia remained stable.[8] In the previous study, hypnotic depth was determined using the A-line autoregressive index (cAAI), which assesses the response to acoustic signals in the cerebral auditory cortex using an individual algorithm (AEP Monitor/2™, software version 2, Danmeter A/S).[9] Recently, a new AEP monitor has been introduced into clinical routine [auditory-evoked potential index (aepEX) monitor, Medical Device Management Ltd, Essex, UK] that measures hypnotic depth during general anaesthesia by the means of direct EEG-derived values.[10 11] The aepEX values are closely related to the AEP

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waveforms and calculated within 144 ms after an intermittent auditory stimulation via earphones.[12–14]

The validity of aepEX monitoring during general anaesthesia with xenon during induction, maintenance, and emergence of anaesthesia has so far not been systematically investigated. The aim of the present study was therefore to evaluate anaesthetic depth monitoring using aepEX during general anaesthesia with xenon.

Given the derivation of aepEX values from EEG signals, we hypothesized that aepEX provides an adequate monitoring of anaesthetic depth during balanced xenon anaesthesia, which should be comparable with BIS monitoring and with aepEX measurement obtained during general anaesthesia with sevoflurane.

Methods

Patients and study design

After approval by the local institutional review board and the German federal drug administration (BfArM) and after obtaining written informed consent, 42 patients undergoing elective abdominal surgery were enrolled. This mono-centre study was designed as a multifactorial, randomized, double-blinded, controlled clinical trial and is in part presented here. The study was registered at the European Medicines Agency (EudraCT number: 2008-004132-20) and at ClinicalTrials.gov (NCT number: 00793663).

Patients were eligible, if they were classified as ASA I–III physical status category and were undergoing gynaecologic or urologic abdominal surgery. Baseline characteristics (age, sex, height, weight, and calculated BMI) were assessed and documented.

Exclusion criteria were severe cardiac, respiratory, liver, or kidney function failure, severe neurological dysfunctions, auditory problems, suspicion of malignant hyperthermia, and pregnancy. Patients enrolled in the trial were randomly assigned to one of the two study arms and blinded from receiving either sevoflurane or xenon.

Intervention

All patients received standardized anaesthesia and premedication according to our clinical standard. After admission to the operation theatre, the BIS (BIS VISTA™ monitor, software 2.00, Aspect Medical Systems//BIS Model A 2000®, Software Version 2.21, Aspect Medical Systems, Boston, MA, USA) and aepEX monitoring (aepEX monitor, Medical Device Management Ltd) were initiated in accordance with the manufacturer's guidelines. The BIS probe was placed on the forehead of each patient. For aepEX, two disposable electrodes were positioned on the centreline of the forehead (ground electrode) and, nearby, to the same side (active electrode). The reference electrode was placed over the mastoid on the same side of the head as the active electrode. By transmitting a regular click sound via earphones at a nominal frequency of 7 Hz, binaurally auditory potentials are evoked. The detected AEPs are consecutively extracted from the raw EEG signal by the internal processor. The EEG signal reflects the brainstem auditory-evoked potential and the middle latency auditory-evoked potential (MLAEP), which are the response of the brain to the auditory stimulation. The aepEX values are closely related to the AEP waveforms and are calculated as the sum of square roots of the absolute difference between every two successive 0.56 ms segments of the AEP waveforms. Finally, the determined characteristics of the present waveforms are expressed as a calculated index varying between 0 (no brain activity) and 100 (wide awake). The recommended reference range for general anaesthesia is from 30 to 45.[12] BIS and AEP data were continuously recorded during the monitoring process, which was maintained from the time of arrival in the operation theatre until full recovery after end of anaesthesia. The performing attending anaesthetist was blinded to the BIS and aepEX values. After termination of anaesthesia, all recovery-related data were collected with the dependent BIS and aepEX values on the predefined time points: eye opening, reaction on demand, extubation, and full orientation. Subsequently, the observer's assessment of alertness/sedation scale (OAA/S) was assessed.[15] Awakening was defined as an adequate response to verbal demand.

Throughout the surgery, haemodynamic parameters [HF, non-invasive arterial pressure (Datex Ohmeda AS/3 monitor, GE Healthcare, Helsinki, Finland)] were recorded every 5 min.

Xenon general anaesthesia was performed and maintained using a closed-circuit respirator (Felix Dual®, Taema, France).

Anaesthesia

In all patients, anaesthesia was performed according to our institutional routine [induction of anaesthesia: propofol (2.0 mg kg^{-1}), 0.5 μg kg^{-1} min^{-1} remifentanil infusion over a period of 60 s, followed by a reduction to 0.15 μg kg^{-1} min^{-1}, and rocuronium (0.6 mg kg^{-1})]. After tracheal intubation, general anaesthesia was maintained by remifentanil (0.15 μg kg^{-1} min^{-1}) and either sevoflurane (1–1.4 vol% MAC) or xenon (53–56 vol% MAC) after adequate denitrogenization for 2–3 min. Intraoperative treatment was standardized according to our clinical routine and thus remifentanil infusion was titrated to clinical needs. Adjustment of anaesthetic depth depended on significant physiological changes (e.g. changes >20% of the baseline arterial pressure or heart rate, increase in inspiratory pressure or expiratory CO_2, intermittent spontaneous breathing and/or intolerance of mechanical ventilation, coughing, abdominal pressing, sweating, and eye tearing) and was left to the discretion of the attending physician. Basic fluid substitution was performed according to our institutional standards. The administration of additional fluids, vasopressors, or inotropic drugs was left to the decision of the attending physicians.

Postoperative analgesia was started by the infusion of piritramide 0.05 mg kg^{-1} and metamizole 15 mg kg^{-1} about 30 min before the last suture. At the end of all surgical procedures, anaesthesia was terminated via high-flow 100% oxygen application, and remifentanil infusion was stopped