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Evaluation of bispectral index and auditory evoked potentials for hypnotic depth monitoring during balanced xenon anaesthesia compared with sevoflurane

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Key points

- The bispectral index was confirmed to be a suitable tool to survey the depth of hypnosis in addition to clinical parameters during balanced xenon anaesthesia.
- The composite A-line autoregressive index exceeded the recommended value range after about an hour.
- Further evaluation will be needed to evaluate whether auditory signal processing recovers during extended exposure to xenon.

Background. None of the currently available hypnosis monitoring systems have evaluated balanced xenon anaesthesia. We investigated the performance of the bispectral index (BIS) and the composite A-line autoregressive index (cAAI) while comparing balanced xenon with sevoflurane anaesthesia.

Methods. Sixty patients undergoing elective abdominal surgery participated in this registered double-blinded, controlled trial and—after written informed consent—were randomly assigned to one of the study groups (xenon, $n=30$; sevoflurane, $n=30$). After induction, general anaesthesia was maintained with xenon 60% or sevoflurane 2.0% in 30% O_2. Remifentanil was titrated to clinical needs. BIS and cAAI values were recorded electronically and blinded to the performing physician. Emergence from anaesthesia was evaluated and during 12 h follow-up, patients were questioned twice for signs of recalls.

Results. During induction and maintenance of anaesthesia, BIS values in the xenon group were comparable with sevoflurane anaesthesia and within the recommended range. Although the cAAI remained stable in the sevoflurane group, values increased during balanced xenon anaesthesia and exceeded the recommended upper limit after 65 min. Emergence from xenon anaesthesia was significantly faster than from sevoflurane (eye opening at 3.8 *vs* 10.3 min, $P<0.001$), and BIS values were concordant with the washout of both anaesthetics. No incident of recall was reported.

Conclusions. During surgery, xenon/remifentanil anaesthesia can be monitored using BIS and cAAI. However, cAAI values changed after about 1 h of anaesthesia. Further studies will be needed to address the question whether auditory signal processing is altered during extended xenon exposure.

Keywords: anaesthesia, depth; anaesthetics gases; anaesthetics volatile, sevoflurane; brain, evoked potentials; monitoring, bispectral index

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The assessment of the hypnotic component of anaesthesia by an objective monitoring system may be a reasonable addendum to existing anaesthesia monitoring, although debate on its use is still ongoing.[1–3] Several distinct methods for hypnotic depth assessment are commercially available. The most popular monitoring index is certainly the bispectral index (BIS). It is generated through computation of continuously recorded EEG information.[4] Alternatively, the composite A-line autoregressive index (cAAI) assesses the retardation of acoustic signals to evoked potentials in the cerebral auditory cortex.[5] To date, the BIS has been evaluated for the depth of hypnosis monitoring during general anaesthesia with numerous anaesthetic agents,[1–3] whereas information about the cAAI's role in monitoring the depth of hypnosis is still growing.[6]

The noble gas xenon is an extraordinary anaesthetic with many advantageous characteristics,[7] for example, its haemodynamic stability[8–10] and its possible neuroprotective effects.[11] However, neither the BIS nor the cAAI has been validated for monitoring hypnosis during balanced xenon anaesthesia. The role of BIS monitoring during single-agent xenon anaesthesia is discussed controversially,[12 13] as *N*-methyl-D-aspartate (NMDA) antagonists are known to interfere with the EEG.[14]

The aim of this study was to investigate the efficiency and performance of the BIS and cAAI to measure the hypnotic component of anaesthesia during balanced xenon anaesthesia. The hypothesis was that the BIS and cAAI values correlate (i) with the clinical assessment and (ii) with the value range recommended for balanced anaesthesia with other volatile anaesthetics (i.e. sevoflurane). The primary outcome parameters were the BIS and cAAI values during maintenance and recovery from balanced general anaesthesia. The secondary outcome parameters were the velocity of awakening estimated by the OAA/S[15] and the occurrence of awareness in the form of recalls assessed with the Brice questionnaire.[16]

Methods

Study design

The study was designed and performed as a mono-centre, multifactorial, randomized, double-blinded, controlled clinical trial. The design was approved by both the local clinical ethical review committee and the German federal drug administration (BfArM). The trial consisted of several distinct study parameters, of which the assessment of hypnotic depth with BIS VISTA™ monitor (Aspect Medical Systems, Natick, MA, USA) and AEP Monitor/2™ (Danmeter A/S, Odense, Denmark) (at present, Danmeter A/S is no longer a functioning business and cannot be contacted) was studied here. The trial was registered at the EMEA (EudraCT number: 2008-004132-20) and at ClinicalTrials.gov (NCT number: 00793663) (http://clinicaltrials.gov).

Subjects

After completing written informed consent, 60 patients aged 18–75 yr, ASA status I–II undergoing elective abdominal (i.e. gynaecological, urological or abdomino-surgical) surgery with a planned duration $\geq$60 min, were enrolled in the trial. Among exclusion criteria were severe cardiac, respiratory, liver, or kidney function disorders, history of hypersensitivity, suspicion of malignant hyperthermia, and pregnancy. Patients enrolled in the trial were randomly assigned to one of the two study groups using a randomization software (RandList version 1.2, DatInf GmbH, Tübingen, Germany) and blinded to receiving either sevoflurane or xenon.

Trial procedure

Hypnotic depth was monitored in all patients using the BIS (BIS VISTA™ monitor, software 2.00, Aspect Medical Systems) and the cAAI (AEP Monitor/2™, software version 2, Danmeter A/S) during induction, maintenance, and recovery of anaesthesia. Drugs were titrated as needed for clinical requirements. The attending anaesthetist was blinded to both BIS and cAAI monitoring. For BIS monitoring, the forehead skin was meticulously cleaned, and disposable sensors (Aspect Medical Systems) were placed on the forehead in a line extending to the temple. For AEP monitoring, disposable electrodes (Danmeter A/S) were positioned on the temple and mastoid of the patient, and auditory potentials were evoked binaurally via earphones transmitting a regular click sound pattern using automatic volume level control. Tests for impedance and signal quality were performed with both monitoring systems before the beginning of the recording. BIS and cAAI values were recorded electronically every 5 s. They were analysed minute by minute during induction, intubation, surgical incision, and emergence and every 5 min during maintenance of anaesthesia. The recommended ranges for surgical anaesthesia are 40–60 for the BIS and 15–25 for the cAAI. Good signal quality during recording of BIS and cAAI values (minimum four of five possible quality bars, respectively, signal quality index or signal quality bar $>$80%) and no or little electromyographic activity (electromyography EMG bars $<$20%) were maintained to assure the quality of measurement. Haemodynamic parameters, that is, heart rate, three-channel ECG, pulse oximetry, systolic and diastolic arterial pressure, oesophageal temperature (Datex Ohmeda AS/3 monitor, GE Healthcare, Helsinki, Finland), end-tidal O_2, CO_2, end-tidal concentrations of anaesthetics, and infusion rate of remifentanil were logged and evaluated at the same intervals. Muscle relaxation was monitored using the train-of-four electrical stimulation to the nervus ulnaris, and the stimulatory response was measured at the musculus adductor pollicis and logged at 5 min intervals.

Medical quality xenon was provided by Air Liquide Santé International (Paris, France); sevoflurane inhalation anaesthetic was provided by Abbott (Wiesbaden, Germany). Both anaesthetics were administered using a closed circuit respirator (Felix Dual®, Taema, France) and concordant software. Xenon use was only permitted with closed circuit conditions, whereas sevoflurane was administered under low-flow conditions.

After a premedication (oral midazolam 7.5 mg, 45 min before) and a 3 min pre-oxygenation period immediately preceding induction, general anaesthesia was induced by boli of propofol (2.0 mg kg^{-1} initially, repeating dose if necessary 0.5–1.0 mg kg^{-1}) and 0.5 μg kg^{-1} min^{-1} remifentanil infusion over a period of 60 s, followed by an immediate reduction to 0.15 μg kg^{-1} min^{-1}. After administration of 0.6 mg kg^{-1} rocuronium, tracheal intubation was performed. Xenon or sevoflurane wash-in was started with a target end-tidal concentration of 60 (5) vol.% xenon or 2 (0.2) vol.% sevoflurane, both in a minimum of 30% oxygen. General anaesthesia was maintained through xenon or sevoflurane inhalation and supported by remifentanil infusion titrated to clinical needs, assessed by physiological criteria according to the standard operational procedures of our clinic (e.g. changes in haemodynamic parameters more than 20% of the baseline arterial pressure or heart rate level during general anaesthesia, intermittent spontaneous breathing and/or intolerance of mechanical ventilation, coughing, abdominal pressing, movements, sweating, eye tearing). Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.8–6.0 kPa; normothermia (35.5–37.0°C) was achieved using warming blankets. Standard treatment of blood loss, fluid replacement, and