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A Comparison of Auditory Evoked Potentials and Spectral EEG in the Ability to Detect Marked Sevoflurane Concentration Alterations and Clinical Events

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Abstract

Background. Level of consciousness monitors can distinguish between consciousness and unconsciousness during anaesthesia induction and awakening. However, this distinction is rarely a clinical problem. What we do need is a peroperative indicator signalling when the anaesthetic depth comes close to awakening, or when it is too deep. We investigated the ability of the Alaris fast extracted AEP (AAI) and the GE Healthcare Spectral Entropy algorithms State- and Response Entropy (SE/RE) to respond to marked changes in sevoflurane concentration during stable surgery and to clinical incidents.

Methods. Both monitors were used simultaneously in 9 patients during sevoflurane-based anaesthesia, which at low concentrations was combined with remifentanil. Additionally, most patients had an epidural block. The response of each monitor to sevoflurane concentration alterations within 0.5–1.5 age-adjusted MAC was recorded, mainly during periods with no surgical stimulation, as was the response to stimulation during surgery and at anaesthesia induction and awakening. Off-line, the numbers of correctly detected events were calculated.

Results. In total, 114 events were found. The response rate of all events (95% c.i.) was 20–37% and 40–57% for the AAI- and the Entropy-monitors, respectively, $P<0.05$ (Wilcoxon Matched Pair test).

Conclusions. The Spectral EEG monitor performed significantly better, with a larger number of events detected, compared with the AAI-monitor. However, at the best half the number of events was detected. An anaesthetic ceiling effect might to some part explain this finding. Notwithstanding, continuous anaesthetic depth monitoring may add information to low sensitive semi-continuous standard autonomic monitoring.

Introduction

The evaluation of anaesthetic depth is a challenge, especially in situations when neuro-muscular blocking agents are used, or in situations when disease and medication alter the autonomic response. Of autonomic monitoring only heart rate is monitored continuously in routine care. Monitoring of arterial pressure is often intermittent, as is the surveillance of sweating and pupil reactions. Continuous, computerised EEG is a potential aid. Several level of consciousness-monitors based on EEG are commercially available, and the use of such techniques seems to be in progress. Such monitors have the indisputable capacity to distinguish between consciousness and unconsciousness. But, how accurately do they indicate that patients are near awakening or that patients are too deeply anaesthetised?

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We aimed to investigate the ability of the GE Healthcare Spectral Entropy algorithms State- and Response Entropy (SE/RE) (1–6) and the Alaris fast extracted AEP (AAI) (6–11) to respond to marked changes in sevoflurane concentration during periods with no surgical stimulation and to clinical events, such as anaesthesia induction and awakening, or instant surgical stimulation not "covered" by anaesthesia. A value of monitor sensitivity would then be calculated (the proportion of correct response to defined events of the total number of defined events).

Material and methods

Ten patients were enrolled for the study after approval of the Regional Ethics Committee. Men and women (non-pregnant), minimum 18 years of age, without neurological- or psychiatric disorders, or abuse, in ASA class I or II, scheduled for abdominal- or breast surgical procedures with an expected duration longer than 2 h were considered for participation.

Anaesthesia

The patients scheduled for major abdominal surgery were given a thoracic epidural catheter before general anaesthesia induction. Bupivacaine, 5 mg · mL^{-1}, 2–4 mL was then injected, and the block was evaluated before the induction of general anaesthesia. The epidural block was maintained peroperatively by a continuous infusion of bupivacaine, fentanyl and adrenaline (12). Propofol and remifentanil induced general anaesthesia in all patients. Atracurium was used for intubation. Thereafter, sevoflurane maintained anaesthesia. Liquid sevoflurane was administered by a syringe infusion pump (Perfusor fm, B.Braun, Melsungen, Germany) through the Anaesthetic Conserving Device (AnaConDa, Hudson RCI, Upplands Väsby, Sweden) rather than through a vaporiser, in order to make rapid adjustments of the end-tidal concentration (13,14). A target-controlled infusion (TCI) of remifentanil was started immediately before surgery (SIMS Graseby Ltd, Watford, UK; prototype system using Minto (15) pharmacokinetic parameters, personal communication, G. Kenny). Remifentanil was used during periods with low concentrations of sevoflurane for minimising discomfort from the endotracheal tube, for protection from instant, unanticipated heavy stimulation in the case of surgery outside the field of epidural anaesthesia, and if no epidural block was used, i.e. in breast surgery. The initial target concentration of remifentanil was chosen according to age (2.5–6.0 ng · mL^{-1}). The target was modified in the case of pain-breakthrough situations and set to zero at high sevoflurane concentrations (mainly >1 MAC, age adjusted). Phenylephrine i.v. was used in the case of hypotension (<80 mmHg, or <60% of the preoperative systolic arterial pressure).

Some "perturbations" were undertaken during periods with stable or no peroperative stimulation, mainly during cleaning and draping. The end-tidal sevoflurane concentration was altered between 0.5 and 1.5 age-adjusted MAC, or to the

point when an unfavourable haemodynamic effect was noticed (>40% change of the preoperative systolic arterial pressure, or when outside an interval of 80–160 mmHg).

Monitoring and data acquisition

An Alaris AAI monitor, version 4.2 (software version 1.61) (Danmeter, Odense, Denmark) registered AEP-index (7). The recommended index interval of 15–25 for surgical anaesthesia was aimed at. We used Alaris AEP Monitor electrodes (Medicotest A/S, Ølstykke, Denmark) and headphones from the monitor producer for auditory stimulation. The recorded data were sampled every second in a sampling program, AAI Graph, version 2.0 for off-line analysis. An Entropy Module in a Datex-Ohmeda S/5 monitor (GE Healthcare, Helsinki, Finland) registered Spectral Entropy EEG (2). The monitor presents two indices, state entropy (SE), computed over the frequency range of 0.8–32 Hz, and response entropy (RE), computed over the frequency range of 0.8–47 Hz. The recommended index interval of 40–55 for surgical anaesthesia was aimed at. We used the specially designed three-in-one-electrode for Entropy monitoring (Datex-Ohmeda division, Instrumentarium Corp., Helsinki, Finland). Datex-Ohmeda S/5 Collect program, version 4.0, sampled SE and RE data every 5th second into a laptop computer. We performed skin preparation and electrode applications according to instructions from the monitor producers.

Monitoring by a Datex-Ohmeda S/5 monitor included non-invasive blood pressure (every 5th minute), and continuously: heart rate, peripheral oxygen saturation, and oxygen- and CO_2 concentrations. All variables were sampled every 5th second in the same way as for Entropy data. A synchronisation procedure with the precision of <1 sec between the S/5- and the AAI monitors made correct off-line comparisons possible between the two anaesthetic depth indices.

Definitions

We defined two kinds of events to be detected by the monitors: 1) An instant change in sevoflurane concentration of ≥20% was considered as a true event if undertaken during a period of no surgical stimulation, or during surgical stimulation blocked by a well functioning epidural anaesthetic. 2) Clinical situations, such as anaesthesia induction, awakening, laryngoscopy, endotracheal intubation, and skin incision were definite clinical events. Surgery outside the field of epidural anaesthesia, or pain-break-through during breast surgery was annotated potential events. They were defined as true events, if there was a response (defined down) in both monitors concomitantly, or in one monitor and a concomitant autonomic response (≥20% change in heart rate or systolic blood pressure, or obvious sweating). We considered a change in an AEP- or Entropy index of ≥20% as a correct response to a true event (increased sevoflurane concentration (negative change), decreased sevoflurane concentration (positive change), or stimulation (positive change)). Monitor sensitivity was defined as the proportion of correct responses to true events of all true events.

Statistics

We assumed the two monitors to be equal in sensitivity, >80%. However, for confirmation of the null hypothesis an unpractical number of patients would be needed. On the other hand, each patient was assumed to generate a minimum of 6 true events for comparison. So, in 10 patients a minimum of 60 pairs of response or no response would be enough to detect a difference in sensitivity between the two monitors that would be of reasonable clinical interest, B25% difference between monitors. Wilcoxon Matched Pair Test was used for the statistical comparison (Statistica 6.0, StatSoft, Tulsa, OK, USA). The level of statistical significance was set to 5%. Specificity could not be calculated, since the number of true non-events could not be defined. Likewise, we were unable to identify false positive events because of lack of a golden standard.

Results

Data from 9 patients were analysed off-line. One data set (breast surgery) was excluded because of technical errors in data sampling. Seven patients had working epidural blocks for abdominal surgery, while two patients for breast resection did not. No adverse events were documented from anaesthesia or surgery. Patient characteristics for the 5 male and 4 female patients are presented together with the span in individual age-adjusted sevoflurane MAC administered, and the number of responses for each monitor (Table 1).

Table 1. Some patient characteristics, age adjusted sevoflurane MAC interval, the total number of true events per patient, and the number of true events detected by the Auditory Evoked Potential (AAI) and EEG Entropy (SE/RE) monitors, respectively, in 9 patients given sevoflurane in varied concentrations

Gender	Age (year)	Weight (kg)	Sevoflurane age adjusted MAC interval (%)	Total number of events	Number of events detected by AAI monitor	Number of events detected by SE/RE monitor
M	61	80	0,5–1,3	11	2	6
M	34	75	0,6–1,5	13	3	2
F	81	59	0,6–1,1	8	4	5
M	34	96	0,5–1,1	12	6	9
F	65	70	0,6–1,5	10	3	5
M	66	83	0,5–1,3	21	8	10
F	71	56	0,6–1,3	17	2	8
M	74	58	0,7–1,7	10	2	6
F	66	81	0,8–1,5	12	2	4
Median	66	75		12	3	6
Total				114	32	55

M = male, F = female.
The outcome of numbers of event detected by the two monitors differed significantly, P=0.013 (Wilcoxon Matched Pair test).

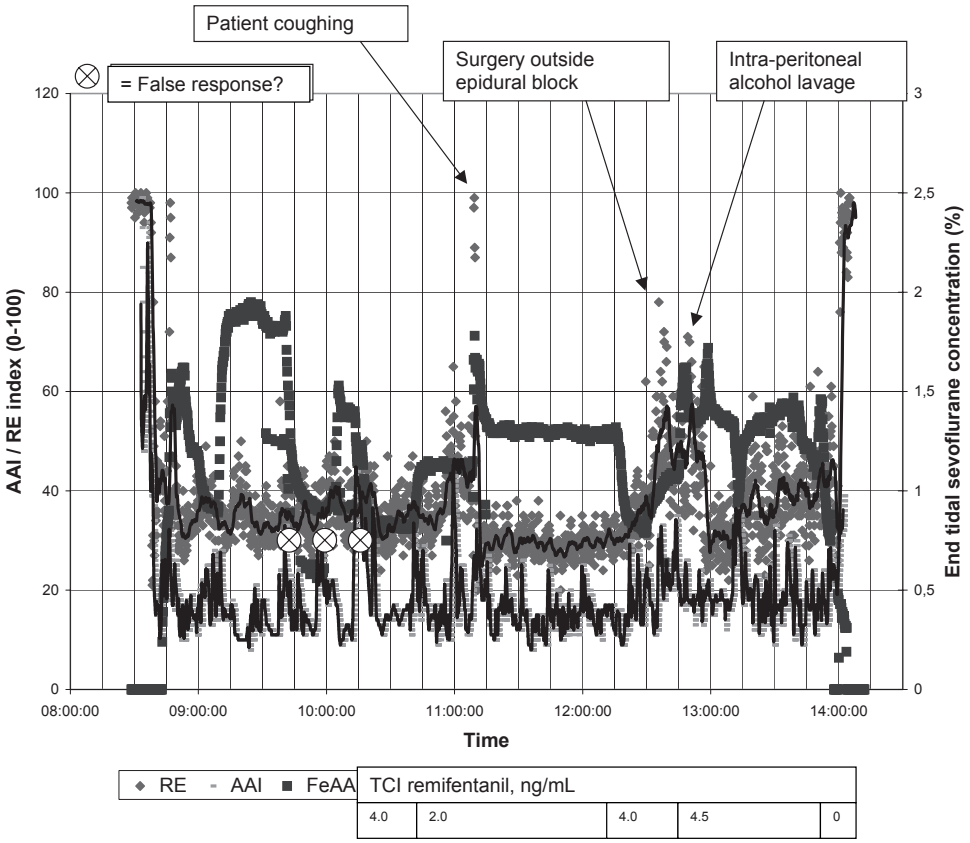

Figure 1. An illustrative (although for the entire study not fully representative) graph of the alterations in end-tidal sevoflurane concentration (FeAA) and the recorded Auditory Evoked Potential index (AAI) and Response Entropy index (RE) in a 66-year-old male patient, operated on for colon cancer. For clarity SE was omitted from the figure. Some clinical events are indicated. Preoperatively, he received a continuous epidural block with an initial spreading between Th_5 and L_1. General anaesthesia was induced at 08.34, and extubation was commenced at 14.03. A target controlled infusion of remifentanil, 2.0–4.5 ng/mL, was in this case infused during a major part of anaesthesia (10.15–13.50, indicated in Figure 1), because of irritable airway. Normally, remifentanil was infused only during periods of low sevoflurane concentration. A moving average is inserted in each scatter of data points for the two indices, mimicking the trend curve presented in each monitor. Marked alterations in end-tidal sevoflurane concentration were included in the study protocol, in this case with an interval of 0.5–1.3 MAC (age-adjusted). None of the monitors responded properly on sevoflurane concentration alterations in this patient. However, different stimuli, e.g. those originating from a hyper-reactive airway were detected. The AAI response was instantly strong at several occasions (∞) with a high index, but without a concomitant stimulus, and without autonomic response (potentially false responses). On average, both indices were unusually low in this patient. The recommended index intervals are 15–25 and 40–55 for the AAI- and RE-indices, respectively.

In total, we found 114 true events (Table 1). A majority, 73%, of the events was alterations in sevoflurane concentrations. Other events were anaesthesia induction and awakening, 16%, and various moments of stimulation, 11%. Examples of the latter were intra-peritoneal alcohol rinse after surgery for colon- or rectal cancer, sudden pain break-through when surgery in a few instances reached outside the

cover of the epidural block, or coughing (in a patient with an unanticipated highly reactive airway, Figure 1).

Both SE and RE were compared with AAI with the same results. The correlation coefficients between SE and RE in individual patients were in the interval of 0.97–0.99 (off-line ad hoc analysis). The AAI-monitor responded to 28.1% of all events (20–37%, 95% c.i.), and the Entropy-monitor responded to 48.2% (40–57%, 95% c.i.) (Table 1). This difference in sensitivity between the two monitors was statistically significant, $P<0.05$ (Wilcoxon Matched Pair test). The AAI-monitor responded to 68.4% of events from different kinds of stimulation, and to 22.0% of sevoflurane concentration alterations. The corresponding distribution of response from the Entropy-monitor was 42.1 and 58.5%. Ad hoc, this difference in sensitivity for different kinds of events was statistically tested and found significant, $P<0.01$ (Chi-2 test, calculated on absolute numbers).

Discussion

The sensitivity of both monitors was less than expected, although the Spectral Entropy-monitor did significantly better, 48.2% of events detected, compared with 28.1% with the AAI-monitor. The Spectral Entropy-monitor did better regarding events from altered sevoflurane concentration than stimulation events, while the opposite was true for the AAI-monitor. Alpiger and co-workers reported a similar observation with the AAI-monitor, which did not show a graded response with changing end-expiratory steady-state concentrations of sevoflurane (8).

A general impression of this study is that the two monitors clearly distinguished between consciousness and unconsciousness at induction and awakening, but that in between even marked alterations in sevoflurane concentration of sometimes more than the double might pass undetected. It could be argued that the definition of response, ≥20% change in index, was too wide, resulting in a falsely low sensitivity. A change in Spectral Entropy index from 40 to 47 (17.5%), almost half the recommended interval of 40–55, was not a response by our definition, while a change from 40 to 48 (20%) was. Two problems would arise from a more narrow definition of response. Firstly, by definition, specificity would decrease; i.e. the number of false positive responses would increase (not measured here). Secondly, since both indices expressed marked oscillations (Figure 1) it would be difficult to differentiate a response from the inborn oscillation. A number of false responses might have been hidden in the continuous oscillations. On the other hand, both monitors present a trend curve, a moving average, which to a certain extent make the real-time interpretation of data easier. However, also the trend curve had a certain degree of oscillation (Figure 1).

Response to clinical incidents might be more interesting to register than gross sevoflurane alterations. However, it would be unethical to purposely create incidents or situations with light anaesthesia. Therefore, we modified the anaesthetic agent concentration and looked at the EEG response, rather than looking at the

EEG response at incidents and light anaesthesia. Despite this fact, we regard this comparative study as being clinically adapted.

Since the data analysis was open, there was a certain risk of evaluation bias. We consider this risk to be low. The criteria for different definitions were strict, and they were strictly followed, leaving no room for drift in the calculations. No hypothesis was favoured.

A more severe objection to the study protocol is the possible influence of different remifentanil concentrations on the ability of the two monitors to react on alterations in sevoflurane concentration. It was reported that remifentanil either decreased, but not abolished, the ability of AAI to detect loss of response for noxious stimuli (9), or it did not influence the AAI at all (10,11). Spectral Entropy might be more sensitive to remifentanil (4,5,11). Though, in the current study most of sevoflurane concentration adjustments were undertaken before the start of peroperative TCI remifentanil, and remifentanil was not used at all at sevoflurane concentrations >1 MAC (age adjusted). However, even as low as 0.5 MAC sevoflurane might give adequate anaesthesia in conjunction with remifentanil, especially in the majority of patients having an effective epidural block (11,14). Then, the EEG reaction on "more than enough" might not change substantially. Thus, a ceiling effect might explain the relatively low sensitivity of the monitors.

According to the manufacturer, complementary information will be given from the two entropy parameters. It will indicate pain-break-through if RE-SE diverge >5. Off-line ad hoc analysis revealed, however, only two periods in one patient with a RE-SE difference of 5–10 during a little more than 2 minutes (not in Tables). This lack of divergence was reflected in the almost total concordance between the two entropy indices.

In conclusion, the Spectral EEG monitor performed significantly better, in terms of a higher sensitivity, compared with the AAI-monitor. However, less than 2/3 of marked alterations in end-tidal sevoflurane concentration were detected by the best monitor in this respect (SE/RE). A ceiling effect might explain this result (11). Further, approximately 2/3 of moments of clinical stimulation, including induction of anaesthesia and awakening, was detected by the best monitor in this respect (AAI), when considering an index change of B20% as the detection limit. Moreover, indices oscillated considerably. Real-time use of the monitors might, on the other hand, be of more value than now described, because of the existence of a trend curve, which will reduce the influence of index oscillations. Continuous level of consciousness monitoring might add information to intermittent, low sensitive and low specific standard autonomic monitoring, especially when the autonomic response is influenced by disease or potent drugs, or when a neuro-muscular blocking agent is in use (5,10,16). Further development of the technique is of need for increased sensitivity of the monitors.

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