Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG

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Background. Sevoflurane is a methyl ether anaesthetic commonly used for induction and maintenance of general anaesthesia in children. Sevoflurane is a non-irritant and acts quickly so induction is usually calm. However, inhalation induction with high concentrations of sevoflurane can cause convulsion-like movements and seizure-like changes in the electroencephalogram (EEG). Little is known about the EEG during maintenance of anaesthesia with sevoflurane, so we planned a prospective trial of sevoflurane maintenance after i.v. induction with benzodiazepine and barbiturate, which is another common induction technique in children.

Methods. EEG recordings were made before premedication with midazolam (0.1 mg kg⁻¹ i.v.), during induction of anaesthesia with thiopental (5 mg kg⁻¹), and during maintenance with sevoflurane (2% end-tidal concentration in air/oxygen without nitrous oxide) in 30 generally healthy, 3- to 8-year-old children having adenoids removed. Noise-free EEG data of good quality were successfully recorded from all 30 children.

Results. Two independent neurophysiologists did not detect epileptiform discharges in any of the recordings.

Conclusion. Premedication with midazolam, i.v. induction with thiopental and maintenance of anaesthesia with 2% sevoflurane in air does not cause epileptiform EEG patterns in children.

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Sevoflurane is a rapid, potent, halogenated volatile anaesthetic with low solubility in blood. It is a non-irritant, of low pungency and children accept it easily. Therefore, sevoflurane is often used to induce and maintain anaesthesia in children.¹

Although sevoflurane is generally well tolerated, adverse effects have been reported. For example, coughing, laryngospasm, agitation and excitement may occur during sevoflurane anaesthesia.¹ In some reports of inhalation induction with high concentrations, seizure-like electrical activity or movement has been reported with an incidence of 20–88%.²–⁵ However, agitation during sevoflurane anaesthesia is not usually associated with seizures⁶ and sevoflurane is not contraindicated in patients with epilepsy.⁷

Although induction of anaesthesia with sevoflurane has been investigated extensively, less is known about the electroencephalogram (EEG) during maintenance of anaesthesia with sevoflurane. In our hospital we induce anaesthesia with i.v. midazolam and thiopental, and then maintain anaesthesia with sevoflurane. Because both midazolam and thiopental may reduce the likelihood of seizures, we studied this anaesthesia regimen, looking for epileptiform changes in the EEG during anaesthesia induction and maintenance. We recorded EEG before premedication and continuously during anaesthesia induction and maintenance until electrocautery was used for the first time.

Methods

We studied 30 children (aged 3–8 years) with ASA I physical status who were to undergo adenoectomy in our day-case surgery unit. Patients were excluded if they had epilepsy, a history of febrile convulsions, asthma, or kidney...
or liver dysfunction. Data were collected between October 2000 and February 2001. The study was approved by the Ethics Committee of Kuopio University Hospital and was conducted in accordance with the latest revision of the Declaration of Helsinki. All parents and children old enough were informed and gave written consent.

All children received the same anaesthesia. EMLA cream (Astra, Södertelje, Sweden) was used for skin analgesia. After baseline measurements, midazolam (0.1 mg kg⁻¹ i.v.) was given. Five minutes later, anaesthesia was induced with thiopental (5 mg kg⁻¹ i.v.) and tracheal intubation was facilitated by cis-atracurium (0.1 mg kg⁻¹ i.v.). Patients were ventilated with oxygen in air to maintain an end-tidal carbon dioxide partial pressure of 4.8–5.5 kPa. Sevoflurane was started 3 min after the induction and adjusted to keep the end-tidal concentration at 2%. Fentanyl (1 μg kg⁻¹ i.v.) was given before surgery started. On completion of surgery, neuromuscular block was antagonized with neostigmine and glycopyrrolate. All children were given 5% glucose in 0.3% saline for intraoperative fluid maintenance. Intraoperative, non-invasive arterial pressure, electrocardiography, peripheral oxygen saturation, inspiratory and end-tidal oxygen, carbon dioxide and sevoflurane concentrations were monitored continuously by Cardiocap/5 (Datex-Ohmeda, Helsinki, Finland).

The EEG was recorded with a five-channel EEG measuring machine, EMMA (developed at the Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland). The EMMA EEG machine has been validated and there are no differences compared with a standard EEG machine that could affect the results. Ag/AgCl electrodes were placed on the scalp according to the international 10–20 system. The EEG signal was recorded from the electrodes F4 and Fz which were referenced to C4 (2 cm behind C4). Additional M1 and O2 electrodes referenced to C4 were used for the first 11 patients. Electrode–skin impedances were <5 kΩ. The signal was amplified, digitized at a rate of 279 Hz and stored on a PC for off-line analysis. Baseline EEG was recorded before premedication. EEG was then recorded continuously until electrocautery was used for the first time. Two children received midazolam (0.1 mg kg⁻¹ i.v.) and one child thiopental (1 mg kg⁻¹ i.v.) before baseline recordings to facilitate connection of electrodes. These three children were included in the EEG analysis as agreed in the trial protocol.

The EEG signal was inspected by two independent neurophysiologists (S W-P, J P) for detecting possible epileptiform discharges. They knew the purpose of the study, but the records were viewed with no patient details given. The EEG signal was classified as fast beta activity (>13 Hz), alpha activity (8–13 Hz), theta activity (5–8 Hz) and delta activity (<4 Hz). Figure 1 shows the timing of the events during the EEG record.

After 30 min of EEG recording, a mouth gag was inserted and the adenoids were removed using a curette technique. Haemostasis was controlled with temporary nasopharyngeal packs and by suction electrocautery when needed. After surgery, children were transferred to the post-anaesthesia care unit for continuous monitoring of vital signs and measurement of pain. Postoperative pain was treated with ketoprofen (2 mg kg⁻¹ i.v.), and fentanyl (1 μg kg⁻¹ i.v.) was used for rescue analgesia. All children were discharged after 3–4 h.

### Statistical analysis

A sample size of 30 patients is commonly used in this kind of study, and was considered sufficient also for the present trial to detect a clinically important incidence of EEG abnormality. A sample size of 30 children has a 0.8 power to detect an incidence >27% at a significance level of 0.05.

Friedman’s test was used for statistical comparison of repeated measures of arterial pressure and heart rate, followed by Wilcoxon’s signed-rank test with Bonferroni correction if indicated. Significance was set at P<0.05.

Data are presented as mean (SD) and range as appropriate.

### Results

The patients’ characteristics are summarized in Table 1. All the parents/children asked gave consent and participated in the trial. Apart from two children who received midazolam and one child who received thiopental before the baseline measurements were taken, there were no other significant protocol violations. All 30 children were included in the EEG analysis.
Noise-free EEG data of good quality was successfully recorded for every child. Baseline EEG was normal and the background activity was according to age. A few seconds after midazolam injection, beta activity was seen in the EEG of each patient. Thiopental injection caused a prompt appearance of high amplitude delta waves. This delta activity gradually decreased over 3 min and had almost disappeared before sevoflurane was started.

After starting sevoflurane inhalation the EEG showed mainly mixed delta activity with various amounts of beta waves superimposed. Occasionally, this pattern resembled delta with spikes, but epileptiform spikes were not detected. No other epileptiform EEG pattern, such as suppression with spikes, rhythmic polyspikes or periodic epileptiform discharges, was seen. During anaesthesia with sevoflurane, the EEG showed mixed delta/theta/beta activity (Fig. 2).

Discussion

In clinical trials, volatile anaesthetics are commonly given as single agents to avoid interaction with other drugs. However, this is not often clinical routine so we designed the present study to determine whether sevoflurane may be used safely for anaesthesia maintenance following i.v. induction. It seems that the regimen used (i.e. premedication with midazolam, induction with thiopental and anaesthesia maintenance with sevoflurane in oxygen/air) does not cause any epileptiform activity. Our results suggest that sevoflurane administration is compatible with midazolam, thiopental, fentanyl and cis-atracurium as commonly used in paediatric anaesthesia.

Midazolam is frequently used in paediatric anaesthesia. In addition to anxiolysis and sedation, midazolam also has a significant anticonvulsant effect that makes it appropriate for co-induction with sevoflurane. Both midazolam and thiopental increase the threshold for convulsions and reduce the incidence of EEG abnormality. An increase in beta activity seen after midazolam injection was expected because benzodiazepines are known to enhance beta activity.

Sevoflurane can cause epileptiform EEG signals when used for inhalation induction with hyperventilation. Vakkuri and co-workers used high sevoflurane concentrations (8% in nitrous oxide in oxygen) for anaesthesia induction and found several forms of abnormal EEG. Suppression with spikes, rhythmic polyspikes and periodic epileptiform discharges were found in most children; the incidence of these abnormalities was 88%. In contrast, Constant and co-workers did not find any seizures in children during inhalation induction with three different regimens. After midazolam premedication children were given either a rapid induction with 7% sevoflurane in oxygen; induction with incremental concentrations of sevoflurane of 2, 4, 6 and 7% in oxygen; or induction with halothane. They found a difference between sevoflurane and halothane. With sevoflurane, sharp slow waves with very fast rhythms were commonly seen, whereas slow waves and fast rhythms were observed with halothane.

Recently, an increase in the heart rate has been shown to develop during inhalation induction with various volatile anaesthetics, and higher heart rates are particularly common during concurrent epileptiform discharges. In the present study the heart rate did not increase with sevoflurane inhalation. However, a significant increase in the heart rate and mean arterial pressure was seen during intubation, application of a mouth gag and surgical incision. This indicates that the anaesthesia used in the present study was insufficient to completely abolish the haemodynamic responses to nociceptive stimuli.

In previous studies, epileptiform potentials were seen during induction of anaesthesia with high sevoflurane concentrations. In the present study the end-tidal sevoflurane concentration was set at 2% and no EEG problems occurred. It is not clear whether the lack of epileptiform potentials is because thiopental and midazolam were given or because a lower dose of sevoflurane was used.

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<th>Table 1 Patient characteristics. Data are number of cases, mean (SD) and [range]</th>
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<td>Sex (M/F)</td>
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Fig 2 An EEG recording of a 6-yr-old girl. Time window is 5 s; derivation F4–Fz. (a) Baseline EEG with eyes open, (b) beta activity after midazolam, (c) high amplitude delta waves after thiopental induction, (d) mixed delta/theta/beta activity during sevoflurane maintenance.
We stopped recording when electrocautery was used for the first time and no EEG was recorded during emergence from anaesthesia. Because a high incidence of agitation during emergence from sevoflurane anaesthesia has been reported in previous trials, it would be interesting in future to record EEG during recovery from anaesthesia.

We conclude that anaesthesia maintenance with 2% sevoflurane in oxygen/air in children after i.v. induction with midazolam and thiopental does not elicit seizure-like changes in the EEG.

References