Epileptogenic Effect of Sevoflurane

Determination of the Minimal Alveolar Concentration of Sevoflurane Associated with Major Epileptoid Signs in Children

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ABSTRACT

Background: Sevoflurane has become the gold standard for inhalation induction in children. However in children as in adults, epileptiform electroencephalographic signs have been described under high concentrations of sevoflurane. The aim of this study was to determine the minimal alveolar concentration (MAC) of sevoflurane associated with the occurrence of major epileptiform signs (MES) in 50% children under steady-state conditions. The MAC of MES (MAC MES) was determined in 100% oxygen and with the addition of 50% nitrous oxide or after the injection of alfentanil (ALFENTA).

Methods: Seventy-nine children (3–11 yr), undergoing elective surgery and premedicated with hydroxyzine were included. After induction by inhalation and tracheal intubation, a 10-min period with a stable expired fraction of sevoflurane was obtained. The MES were defined as rhythmic polyspikes or epileptiform discharges. Electroencephalographic recordings were blindly analyzed by two independent experts. The MAC MES were determined by the Dixon method: the concentration of sevoflurane was determined by the result from the previous patient: increase of 0.2% if MES were absent or decrease of 0.2% if MES were present. Three consecutive series were performed: (1) in 100% oxygen (MAC MESO2); (2) in 50% oxygen and 50% nitrous oxide (MAC MESN2O); and (3) in 100% oxygen with a bolus of alfentanil (MAC MESALFENTA).

Results: The MAC MESO2 was 4.3 ± 0.1% (mean ± SD), the MAC MESN2O and the MAC MESALFENTA were higher, respectively: 4.6 ± 0.2% (P = 0.01) and 4.6 ± 0.2% (P = 0.02).

Conclusions: In children premedicated with hydroxyzine, the MAC MES of sevoflurane calculated in 100% O2 corresponded to 1.75 surgical MAC. In addition, our results have demonstrated a moderate effect of nitrous oxide and alfentanil in raising the threshold of MES.

What We Already Know about This Topic

- Sevoflurane, commonly used for induction and maintenance of anesthesia in children, has been reported to cause epileptiform electroencephalographic signs at high concentrations
- Quantification of concentrations causing these signs has not been performed

What This Article Tells Us That Is New

- In 79 children receiving sevoflurane anesthesia and using an up-down method similar to that of minimal alveolar concentration, the median concentration causing major epileptiform signs was 4.3% (nearly 1.75 minimal alveolar concentration)
- Addition of N2O or alfentanil modestly increased the sevoflurane concentration causing these signs to 4.6–4.7%
The electroencephalographic epileptoid signs described under sevoflurane are polymorphic. “Spikes” are the earliest elements to appear. When they occur during delta oscillations, they form a “spike-wave.” Spikes can be isolated, or grouped in a “polyspike,” forming a “polyspike-wave” if they are associated with a delta wave. These different electroencephalographic profiles may occur during burst suppression or become “periodic” and form periodic epileptiform discharges. This rhythmicity described by electrophysiologists in several neurological pathologies, may be an early electroencephalographic sign of electrical seizure. Consequently, these periodic epileptoid signs are classically considered as major epileptoid signs (MES). The physiopathology of these epileptoid signs is still not well understood. Nevertheless, their occurrence seems to be concentration dependent in adults with a high incidence at two minimum alveolar concentrations (MAC). It has been demonstrated that periodic epileptiform discharges precede electroencephalographic or clinical seizure, and that clinical seizure are much less frequent than MES.

Since few years, many publications suggesting the neuronal potential toxicity of anesthetics, have led the community of pediatric anesthesiologists to question the safety of practice. In this context, it makes sense to seek the necessary and sufficient dose of drugs to achieve our anesthetic goals. Our approach was in this perspective. Therefore, to decrease the potential risk of anesthetic toxicity, we might have to revisit the therapeutic range of anesthetic agents by taking into account their possible neurological consequences. Regarding the sevoflurane, a relevant information might be the threshold concentration at which sevoflurane is associated with electroencephalographic epileptoid signs.

Therefore, the aim of our study was to determine the minimal alveolar concentration of sevoflurane associated with the occurrence of major electroencephalographic epileptoid signs in 50% of children, during a steady-state anesthesia, in 100% oxygen (MAC MES). The secondary objectives were to study the influence on this MAC MES of 50% inhaled nitrous oxide (MAC MESN2O) and the influence of a bolus of alfentanil (ALFENTA) (MAC MESALFENTA).

Materials and Methods

Patients and Study Design

After approval of our institutional review board (Comité de Protection des Personnes, Saint-Antoine Hospital, Paris, France), and informed consent of the parents (and of the child if able to understand), we performed a prospective study from February to October 2008.

Inclusion criteria were: prepubertal children aged from 3 to 11 yr, American Society of Anesthesiologists physical status I, scheduled for surgery under general anesthesia, and agreement for mask induction. Noninclusion criteria included a history of neurological, hepatic or metabolic disease, and the prescription of any medication with a neurological impact (antiepileptic drugs, opioids, neuroleptics, benzodiazepines, etc.). Exclusion criteria were deviation from the anesthetic protocol, or technical problems preventing the recording of data.

The main outcome event was the occurrence of MES on the electroencephalogram.

Anesthetic Protocol

The children received a premedication with hydroxyzine 1 mg/kg per os 1 h before induction. Inhalational induction was standardized with 6% sevoflurane in a mixture of 50% oxygen and 50% nitrous oxide. Tracheal intubation was performed when the pupils were in myosis, in the central position. Ventilation was initiated with a Pmax of 15 cm H2O, and an appropriate frequency for the age of the patient. This pattern was then adapted to keep the EtCO2 at 35 ± 5 mmHg. Sevoflurane concentration was then lowered to a chosen value and kept constant during 10 min to achieve steady-state conditions for data recording. The expired fraction of sevoflurane (FeSevo) was determined for each patient according to Dixon up-and-down method (see section Electroencephalograms Analysis), and depended on the results obtained in the previous patient. After the end of the recording, anesthesia was left to the choice of the anesthesiologist, and surgery could begin.

This anesthetic protocol was applied for all children. We recorded three consecutive groups of patients. In group “O,” the steady-state conditions were obtained under 100% oxygen, allowing us to determine the MAC MES. In group “N2O,” the steady-state periods were obtained under a mixture of oxygen and nitrous oxide (50–50) allowing us to determine the MAC MESN2O. In group “ALFENTA,” all patients received a bolus of alfentanil (20 µg/kg) just before orotracheal intubation, and the steady-state periods were obtained under 100% oxygen. This last group allowed us to determine MAC MESALFENTA.

Data Recordings

A frontal electrode designed to monitor the bispectral index (BIS 3.0, Aspect Medical Systems, Norwood, MA) was placed on the forehead, according to the manufacturer’s instructions, before the beginning of induction. This electrode allowed us to continuously record the raw cortical electroencephalograms, using a laptop with WINLOG software (provided by Aspect Medical Systems). The sampling rate used for signal acquisition was 128 Hz and the signal was filtered with a band pass filter 0.5–47.5 Hz. The reading of the electroencephalographic recordings was performed using the software DLreview for windows (v 0.0407, Aspect Medical Systems 1995). Heart rate, noninvasive blood pressure, SpO2, EtCO2, FeO2, FeSevo, and FeN2O were monitored. These data were recorded every minute, by the investigator, who was not responsible for the anesthetic management.
After each recording, the electroencephalogram was analyzed by two independent experts (Dr. Moutard, pediatric neurologist, and Dr. Constant, pediatric anesthesiologist), blinded to the FeSevo used for the patient. These experts assessed the presence or not of MES, the validation of the presence of MES required the agreement of the two experts. These MES were defined as rhythmic polyspikes or periodic epileptiform discharges or electric seizures4,8 (fig. 1). According to the Dixon method, if MES were found on the electroencephalogram, the steady-state FeSevo was lowered by 0.2% for the next patient. On the contrary, if no MES were found, FeSevo during steady-state was increased by 0.2% for the next patient. A “pair” (or crossover responses) was defined as the consecutive inclusion of a patient who presented MES, followed by another patient who did not present MES. The value of a pair was the average of the FeSevo used for the two patients of this pair. In each group, we could determine the MAC MES by averaging the values of six consecutive pairs.15

FeSevo for the first patient of group O2 was chosen at 2.5%, which is the MAC determined by Lerman in children aged 6 months-11 yrs.16 For groups N2O and ALFENTA, FeSevo for the first patient was chosen at the MAC MESO2, the number of patients necessary to achieve this goal, based on previous results. In our study, given the expected threshold of MES of approximately 4%,2,5,18,19 the chosen FeSevo for the first patient (2.5% or 1 MAC),16 and the incremental pace of 0.2%, we anticipated approximately 30 patients for group 1. For groups 2 and 3, because the FeSevo of the first patient was taken from the results of the first group, we expected only approximately 20 patients per group.

Demographic data and vital parameters are presented as mean ± SD. The three different MAC values were calculated as the mean of six independent pairs of FeSevo.

Data were also analyzed using a logistic model to calculate the effective FeSevo associated with MES in 50% (ED50) of patients (XLSTAT 2011.4.04, Microsoft18, Redmond, WA).20

The methodology of logistic regression aims at modeling the probability of success (occurrence of MES) depending on the values of the explanatory variables (expired concentration of sevoflurane). The model used was the logit model, where the response variable was binary (yes/no MES) and the quantitative variables were the tested expired concentrations of sevoflurane. The quality of the fit was based on maximization of the likelihood function using an iterative algorithm (Newton-Raphson). The maximum number of iterations was fixed at 100 and the convergence threshold at 0.000001.

The logistic regression was evaluated by the Hosmer–Lemeshow test. The significance of the regression coefficients was assessed by the likelihood ratio test and the Wald statistic.

Comparisons between the different MACs used a one-way ANOVA followed by a Tukey test if needed for a post hoc analysis. A value of P < 0.05 was considered significant.

### Results

#### Clinical Data

Seventy-nine children were successively included in the study. Three were excluded: one for protocol violation (laryngospasm during induction requiring intravenous propofol), and two for technical problems leading to a lack of electroencephalographic recording. Demographic data are presented in table 1.

A brief episode of tonic-clonic movement occurred in one patient from the group ALFENTA. This 5-yr-old girl

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**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th>Group</th>
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<tbody>
<tr>
<td>O2</td>
<td>N2O</td>
<td>ALFENTA</td>
</tr>
<tr>
<td>(n = 32)</td>
<td>(n = 21)</td>
<td>(n = 23)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>6.0 ± 2.2</td>
<td>6.8 ± 2.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>21.5 ± 6.6</td>
<td>25.7 ± 8.0</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>18/14</td>
<td>11/10</td>
</tr>
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ALFENTA = alfentanil.
had no personal or familial history of epilepsy. The seizure occurred after 5 min of steady-state anesthesia. FeSevo was 4.9%, Et\textsubscript{CO\textsubscript{2}} was 38 mmHg. Heart rate was 95 beats/min, systolic blood pressure was 113 mmHg. FeSevo was immediately lowered to 3%, and abnormal movement stopped within 1 min. The electroencephalogram of this patient was normal before induction. At the moment of the seizure, it showed a typical electrical seizure quickly followed by burst suppression (fig. 2). The electroencephalogram returned to a normal delta wave pattern when FeSevo was lowered to 3%. This episode had no further per or postoperative consequence for the child.

All the other children with MES did not demonstrate motor activity. No hemodynamic or respiratory complication occurred during the recordings. Et\textsubscript{CO\textsubscript{2}} remained between 33 and 39 mmHg at all times for the 76 children. Surgery, emergence, and postoperative evolution were uncomplicated.

**Determination of the MAC MES**

Examples of positive (presence of MES) and negative (absence of MES) electroencephalographic traces are shown in figure 3.

Regarding to the MES assessment, the two experts were 100% concordant. About the electroencephalographic traces classified as positive, the experts found that in general, the periodic sequences included a dozen of spikes or polyspikes, and always at least five. In addition, all positive electroencephalograms demonstrated several periodic sequences.

The up–down progressions are shown in figure 4. In the group O\textsubscript{2} (fig. 4A), 32 children were included; the stabilization of the crossover responses was rapidly observed, allowing MAC MES\textsubscript{O\textsubscript{2}} calculation. The lowest FeSevo at which MES were observed was 4.3%. Eleven children showed MES on their electroencephalographic recordings during steady-state periods. MAC MES\textsubscript{O\textsubscript{2}} determined by Dixon method was 4.3 ± 0.1%.

In group N\textsubscript{2}O (fig. 4B), 21 children were included. The lowest FeSevo at which MES were observed was 4.5%. Ten children showed MES on their electroencephalographic recordings during steady-state periods. MAC MES\textsubscript{N\textsubscript{2}O} was 4.6 ± 0.2%. This value was significantly higher than MAC MES\textsubscript{O\textsubscript{2}} (P = 0.01).

In group ALFENTA (fig. 4C), 23 patients were included. The average time elapsed between alfentanil injection and tracheal intubation was 3.8 ± 1.6 min, and the time elapsed between alfentanil injection and the end of the steady-state period was 15.8 ± 1.7 min. The lowest FeSevo for which MES were observed was 4.5%. Twelve children showed MES on their electroencephalographic recordings. MAC MES\textsubscript{ALFENTA} was 4.6 ± 0.2%. This value was significantly higher than MAC MES\textsubscript{O\textsubscript{2}} (P = 0.020).

ED50 calculated by logistic regression are illustrated in figure 5. ED50 for group O\textsubscript{2}, N\textsubscript{2}O, and ALFENTA were respectively 4.42 (4.31–4.57)%, 4.67 (4.08–5.25)% and 4.68 (4.24–5.20)% (median CI 95%).

The statistically calculated probabilities of occurrence of MES in the group O\textsubscript{2} are detailed in table 2.

**Discussion**

In this study, we have demonstrated that MES occurred in 50% of the children receiving 1.7 MAC of sevoflurane in 100% oxygen. In addition, our results suggested a protective effect of nitrous oxide or alfentanil on these electrical epileptogenic properties.

Regarding our methodology, the tracheal intubation and use of pressure-controlled ventilation allowed us to keep all our patients normocapnic under steady-state conditions, and provided accurate measures of FeSevo at all time. The raw electroencephalogram was obtained from the frontal sensors of the bispectral index, thus providing investigation restricted to the frontal cortex. However, because periodic epileptiform discharges and burst suppression have been demonstrated to be synchronous over the whole cortex,\textsuperscript{7} this limitation may not affect the clinical relevance.

Rhythmicity is a classical characteristic of MES. To minimize the subjectivity and possible discrepancy in the
interporation of electroencephalograms, we chose these periodic criteria to define a dichotomous variable to classify the electroencephalogram as positive or negative, rather than a particular shape or intensity of electroencephalographic activity. The high level of agreement regarding the assessment of MES by the two independent experts, suggests that the criterion of rhythmicity allows reproducible judgment. Some electroencephalograms displayed epileptoid signs such as spikes, or polyspikes, but were not classified as “major” if these anomalies were not rhythmic. In fact, our criteria selected the most typical electroencephalographic epileptoid patterns, the ones most at risk to be followed by a typical electrical seizure.

This study is the first to investigate the incidence of MES in children during maintenance of anesthesia under steady-state conditions. Since the first report of abnormal

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**Fig. 3.** Examples of negative (absence of MES−) or positive (presence of MES+) electroencephalographic traces in children from group receiving 100% oxygen (A), from group receiving a mixture of 50% oxygen and 50% nitrous oxide (B), and from group receiving a bolus of alfentanil (C). Etsevo = end tidal concentration of sevoflurane; MES = major epileptoid signs; N₂O = group receiving a mixture of 50% oxygen and 50% nitrous oxide; O₂ = group receiving 100% oxygen.
movements during sevoflurane induction, many studies have demonstrated that electroencephalographic epileptoid signs may occur under sevoflurane in both epileptic and healthy children. However, the incidence varies according to the study design and the electroencephalographic criteria of abnormality. Indeed during induction, some investigators reported MES in more than 80% of children, whereas others found negligible incidences. Different designs of induction, and difficulties of standardized assessment of epileptoid signs may explain these discrepancies; for instance, some authors take into account minor epileptoid signs such as spikes and isolated polyspikes whereas others focus on periodic signs that are considered more disturbing by neuroelectrophysiologists.

Despite this heterogeneity, several factors, related to the modalities of induction, have been suspected to enhance the epileptogenic potential of sevoflurane. Among these factors, the speed of induction can be cited, but, in fact, the level
of FeSevo seems to be the most influential parameter. In an adult study, Jääskeläinen3 showed that the incidence of MES under sevoflurane steady-state anesthesia was dose dependent. Moreover, all eight subjects of this study displayed MES at 1.5 surgical MAC of sevoflurane, which is a concentration close to the one we found in our study. Many other studies report the occurrence of MES for sevoflurane concentrations higher than 1.5 MAC in epileptic adults,24,25 healthy adults,3–5,26–29 or healthy children.2,18,19,29 Our results are consistent with that notion of “epileptogenic threshold” of approximately 1.5 MAC of sevoflurane.53

Using the up–down progression we observed a clear stabilization of the crossover responses demonstrating that the occurrence of MES under sevoflurane could be a reproducible event. These features may suggest a specific mechanism independent of the individual profile.

The physiopathology of these epileptiform discharges remains unclear. Basically, all anesthetic agents may be pro- or anticonvulsivant, depending not only on the targeted receptors but also on the concentration of the agent. Sevoflurane mainly enhances GABA-mediated neurotransmission, thus it should rather play the role of an inhibitor. In fact, sevoflurane has a complex mix of both excitatory and inhibitory actions on several different receptors coupled to GABA neurotransmitters such as N-Methyl-D-aspartate or Acetylcholine and ionic channels.30 Most of the hypotheses regarding the proconvulsant effects of anesthetics, involve synaptic transmission and interaction of excitatory and inhibitory neurons in the neocortex.

There is now a growing body of experimental work suggesting that the seizures are not simply caused by “too much excitation,” but rather by excitation applied to a group of neurons that have natural propensity to react to the excitation by going into an oscillatory seizure state.31 Increased inhibition by the GABA can sensitize the cortex so that only a small excitation may induce an electrical seizure.32 The electroencephalographic epileptoid signs observed under sevoflurane look like those recorded under another halogenated agent, enflurane, even if the incidence seems lower with sevoflurane.33 The mechanisms of the epileptogenic effect of the sevoflurane might be close to those of the enflurane. The latter has been modeled and is thought to involve specific prolongation of GABA-mediated inhibitory postsynaptic potentials favoring the onset of an electrical seizure from a small residual excitatory activity.31 It has been suggested that changes of permeability of potassium and chloride channels might be involved in the lengthening of the duration of the postsynaptic potentials. Recent experimental and neuropathological studies have implicated excitatory signaling mediated by GABA in the genesis of neonatal seizures, temporal lobe epilepsy, and ischemic-hypoxic seizures. A feature common to these disorders is that neurons adopt transmembrane chloride gradients that phenotypically resemble those of immature neurons, which consequently renders GABA excitatory instead of inhibitory.34 In rodents, the epileptogenic and neurotoxic effects of sevoflurane on the immature brain have been described. Indeed, in neonatal rats, sevoflurane-induced seizures and apoptosis were blocked by the preadministration of an Na/K/Cl transporter inhibitor.53 This study highlights that, because of altered chloride gradients, an inhibitory agent such as sevoflurane can become excitatory on a subgroup of immature neurons. However, these experimental data can hardly be extrapolated to our findings, because the chloride gradient is likely not relevant in children with an average age of 6 yr.

Our results showed that the addition of nitrous oxide seems to limit the epileptogenic potential of sevoflurane. This finding is consistent with most of the former data available in the literature in animal studies36,37 as well as in the epileptic adult.38,39 In these studies the addition of 50% nitrous oxide decreases the epileptogenicity at 1.5 MAC of sevoflurane in epileptic subjects. At sedative doses (20–50%), nitrous oxide alone has been shown to increase cerebral blood flow in humans and when nitrous oxide is added to sevoflurane, it has been shown to diminish or abolish the reduction of cerebral blood flow and metabolism classically induced by sevoflurane.40 The protective effect of nitrous oxide might be explained by the fact that its effect on the cerebral metabolic rate of oxygen is in opposition to the effect of sevoflurane.40 Others recommend the use of nitrous oxide, as an N-methyl-D-aspartate receptor blocker impairing calcium entry into neurons.51

We have also demonstrated that an injection of a bolus of alfentanil, a mu opioid receptor agonist, limits the epileptogenic activity of sevoflurane. This result seems to contradict the data from the literature according to which alfentanil rather has a proconvulsant effect. However, all the studies demonstrating this epileptogenic effect used high doses of alfentanil and were performed in epileptic subjects, a population very different from ours.41–45 Moreover in epileptic patients, alfentanil failed to induce any epileptic activity in healthy areas of the brain.46 In a 36-yr-old man with intractable epileptic seizures, anesthetized with 1.5% sevoflurane, the injection of 0.1 mg/kg of fentanyl reduced the frequency of spike waves.47 Our results are consistent with this case report.

A limitation of our study is that all included patients were premedicated by oral hydroxyzine. This histamine H1 blocker is frequently used in Europe and provides a light sedative premedication. We chose this agent because it has no known pro- or anticonvulsant effect, and it does not modify baseline electroencephalogram. This allowed us to study more specifically the electroencephalogram effects of sevoflurane while maintaining the clinical benefit provided by an anxiolytic premedication.

An interesting further step would be to investigate a possible effect of midazolam on the occurrence of MES, given the anticonvulsive properties of the benzodiazepines. However, the fact that most of the studies showing epileptoid electroencephalogram signs associated with the use of...
Sevoflurane, have been conducted in patients premedicated with benzodiazepines,2–4,27,48,49 might suggest that the influence of midazolam should not be very significant.

The potential morbidity of MES is unknown. As the physiopathology of the MES under sevoflurane may be different from what happens during a typical epileptic seizure, we cannot extrapolate the consequences of epilepsy to the postanesthetic setting. Indeed, given the very high number of sevoflurane anesthesia performed since the release of this halogenated agent, we can assume that the long-term consequences of MES, if they exist, are not of major importance.

However as long as the question of the morbidity of MES has not been fully elucidated, it seems reasonable to avoid the circumstances favoring the emergence of these signs, particularly because there are concerns about the safety of anesthetic agents in the brain of young children.10,11,50

As suggested in adults by the study of Jääskeläinen,5 our results demonstrated that the occurrence of MES is highly dependent on the sevoflurane concentration. Moreover, we have determined a minimal alveolar concentration associated with MES in 50% of the children. Thus from these results, we can choose the level of the potential risk we accept and find a compromise between depth of sevoflurane anesthesia and occurrence of MES. We have previously suggested that, in accordance with the adult studies, sevoflurane concentrations may be limited to 1.5 MAC for maintenance in children; this study confirms these previous recommendations. Indeed, according to our results, 1.5 MAC seems to be associated with a very low probability of occurrence of MES.

In keeping with the same idea, the use of adjuvants like nitrous oxide or alfentanil may be valuable during induction and maintenance phases. They allow a reduction of the concentration of sevoflurane needed to achieve an adequate depth of anesthesia, by 20–40%.51,52 and moreover, our results suggest that nitrous oxide and alfentanil may have some intrinsic protective effect against sevoflurane epileptogenic properties.

With the emergence of new anesthetic agents, whose cardiovascular safety is excellent, the preoccupations of anesthetists turn to the medium- and long-term complications related to deleterious neurocognitive effects. To optimize the risk–benefit ratio, the “brain therapeutic range” of sevoflurane might be limited from a neurological point of view, by the risk of recall on the one hand, and the risk of dose-dependent MES on the other.

Our work has determined an “epileptic threshold” for sevoflurane anesthesia in children by calculating MAC MES in different steady-state conditions.

References

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