

Review article

Sevoflurane and epileptiform EEG changes

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Summary

Sevoflurane has become the volatile agent of choice for inhalation induction of anesthesia. Hemodynamic stability and lack of respiratory irritation have justified its rapid extension to pediatric inhalation induction. The epileptogenic potential of sevoflurane has been suspected since the first case reports of abnormal movements in children without a history of epilepsy. The objectives of this short review are to: (i) analyze clinical and electroencephalographic (EEG) features supporting epileptogenic activity of sevoflurane, (ii) identify factors which may modulate that activity, and (iii) suggest guidelines of clinical practice to limit expression of this epileptiform phenomenon, which has thus far unknown morbidity. The use of sevoflurane may be associated with cortical epileptiform EEG signs, usually without clinical manifestation. No lasting neurological or EEG sequelae have been described thus far, and the potential morbidity of this epileptogenic effect is unknown. The use of sevoflurane in children, with its remarkable cardiovascular profile, should include a number of precautions. Among them, the limitation of the depth of anesthesia is essential. The wide use of cerebral function monitoring (the most simple being the EEG), may permit optimization of sevoflurane dose and avoidance of burst suppression and major epileptiform signs in fragile subjects, notably the very young and the very old.

Keywords: sevoflurane; children; electroencephalogram; burst suppression; epileptiform; seizure

Introduction

Sevoflurane has become the volatile agent of choice for inhalation induction in anesthesia. Hemodynamic stability and lack of respiratory irritation have justified its rapid extension to pediatric inhalation induction, and its pharmaco-

dynamic profile has been further defined. The epileptogenic potential of sevoflurane has been suspected since the first case reports of abnormal movements in children without a history of epilepsy(1,2).

In 1992, Haga *et al.* reported abnormal movements labeled 'convulsive' in 6% of 180 children receiving 6% sevoflurane for induction (3). The first abnormal electroencephalographic (EEG) findings under sevoflurane anesthesia were described in children with known seizure disorders (4). By the late 1990s, the

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first controlled studies of EEG changes under sevoflurane were carried out.

The objectives of this review are to: (i) analyze clinical and EEG features supporting epileptogenic activity of sevoflurane, (ii) identify factors which may modulate that activity, and (iii) suggest guidelines of clinical practice to limit expression of this epileptiform phenomenon, which has thus far unknown morbidity.

Clinical features: abnormal movements

Gathering data from various studies is complicated by semantic issues, notably in regard to accurate description of abnormal movement during sevoflurane anesthesia. Movement reported as 'tonic-clonic' can be separated into two types.

1. Agitation in early induction shortly after loss of eyelash reflex, characterized by discoordinate movements of arms and legs, followed frequently by hypertonia and some respiratory obstruction, both of which resolve with deepening of anesthesia.
2. Localized or generalized tonic-clonic movements occurring under deep anesthesia at the end of induction and persisting at that level of anesthesia.

Although this second profile intuitively suggests an epileptogenic activity of sevoflurane, this is more difficult to prove during early induction. This agitation associated with increase in heart rate and transient elevation of blood pressure may be due to brief cortical-subcortical dissociation as seen with other anesthetic agents. Nonetheless, a subcortical convulsive activity causing agitation and hemodynamic changes without cortical epileptiform events cannot be ruled out. In any case, continuous EEG monitoring during sevoflurane induction is a simple way to observe directly the cortical effects of this halogenated agent.

EEG features

Normal EEG in adults and children

The EEG, as the continuous noise of the brain, is a complex sinusoid with a fairly wide frequency spectrum. The frequency range lies between 0.3 and 70 Hz. In the normal waking adult, the slow

range (0.3–7 Hz) and the very fast range (above 30 Hz) are sparsely represented; medium (8–13 Hz) and fast (14–30 Hz) ranges predominate. These frequencies are broken down into the following bands or ranges.

Delta below 3.5 Hz (usually 0.1–3.5 Hz); theta 4–7.5 Hz; alpha 8–13 Hz; beta above 13 Hz (usually 14–40 Hz but unlimited in the upper range) or more recently, beta 14–30 Hz and gamma above 30 Hz.

The amplitude of the scalp EEG lies between 10 and 100 μV (in adults, more commonly between 10 and 50 μV).

The EEG tracing changes with age reflect cerebral maturation processes, particularly the neuronal myelination process. Thus, a number of EEG variables change appreciably from birth to adolescence; a newborn tracing shows abundant slow oscillations; the dominant frequency of the tracing gradually increases with age, while the amplitude of the oscillations decreases. This maturation, which is especially pronounced in the first year of life, leads to an adult-type tracing in adolescence.

Effect of anesthesia on the EEG

As previously stated, the EEG of the awake subject is characterized by irregular rapid activity of low amplitude with a dominant frequency of 13 Hz (alpha waves 8–13 Hz). Loss of consciousness induced by hypnotic agents is accompanied by EEG changes, which are close to those seen in normal sleep (except for burst suppression). With anesthesia sedation, beta-type rapid oscillations increase in amplitude (13–20 Hz); deeper anesthesia is associated with global slowing of theta, then delta type (0–4 Hz) which becomes regular, before disappearing into an isoelectric tracing of very deep anesthesia (burst suppression).

The EEG effects of general anesthesia in children over 1 year old seem comparable with those observed in adults (slow down and increase in amplitude) (Figure 1).

EEG changes specific to sevoflurane anesthesia

Sevoflurane induction and deepening of anesthesia follow a similar pattern to that described above, with the following exception. With 'rapid'

Estimation of depth of anesthesia: EEG monitoring

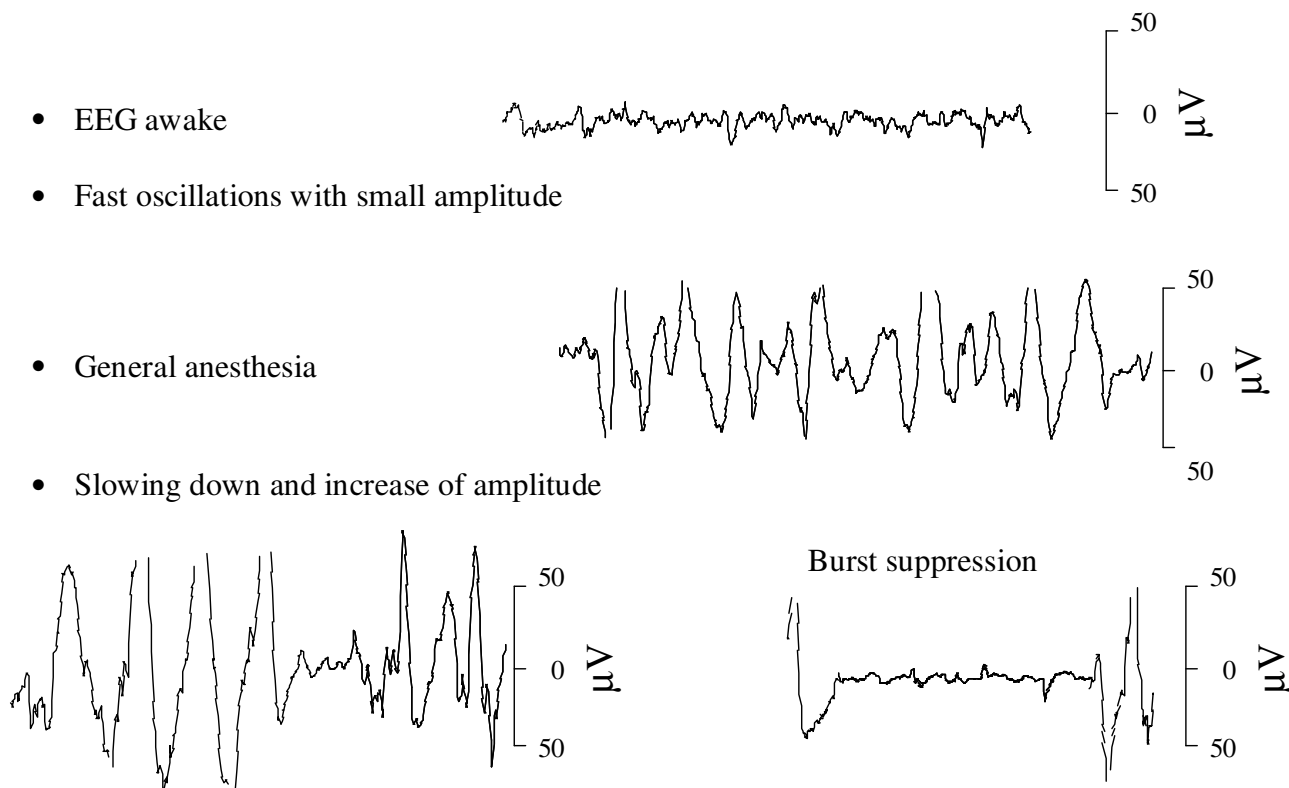


Figure 1
Classical electroencephalographic (EEG) changes during anesthesia.

induction with 7–8% sevoflurane in $\text{O}_2\text{-N}_2\text{O}$ (50 : 50), the EEG shows a brief increase of beta activity occurring around the loss of eyelash reflex (30–60 s after beginning induction), which is rapidly followed by sudden slowing down to <2 Hz delta activity maximal at the end of the second minute of induction, and then acceleration to delta predominance (2–4 Hz) until the pupils are constricted and central. The bispectral index (BIS) monitor also shows a higher index number at concentric pupils than during the middle of induction, where slowing down is maximal (5). Some subjects show episodes of burst suppression with deeper anesthesia (higher endtidal sevoflurane and longer duration of anesthesia). Basically EEG component oscillations at 2 MAC sevoflurane are faster than at 1.5 MAC (6), and the EEG constitutive oscillations seem to be faster under sevoflurane than under propofol at equipotent doses (Figure 2).

Epileptiform activity under sevoflurane

Describing epileptiform activity is complex and differs among authors. An example of this activity is presented in relation to deepening anesthesia during sevoflurane induction (Figure 3).

Spikes are the earliest element to appear and usually during delta oscillations (spike-wave). They may be simple or complex (spike with greater than two positive or negative deflexions, multiple spike-waves, or multiple spikes) or in periodic discharge (rhythmic polyspikes) leading to periods of epileptiform discharges or frank EEG seizure. These elements may appear against a background of slow (delta) activity or burst suppression. Generally major seizure manifestations (periodic discharge or frank seizure activity) are observed under deep anesthesia around occurrence of burst suppression, sometimes accompanied by tonic-clonic movements, but most often without clinical signs. Abnormal fluctuation in

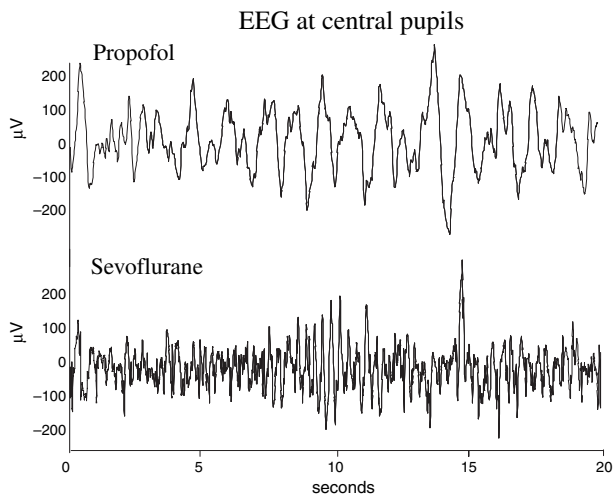


Figure 2
Electroencephalographic (EEG) traces recorded at central pupils during propofol anesthesia and sevoflurane anesthesia in children.

BIS caused by EEG epileptoid changes may be observed (7) (Figure 3).

The incidence of seizure activity during sevoflurane induction in children and adults varies between studies (Table 1). For example, under steady-state conditions in adults, Jaaskelainen *et al.* and Sato *et al.* found seizure-like activity in all patients at >1.5 MAC sevoflurane in 100% O₂ (6,8), while Iijima *et al.* found none under similar conditions (9). During sevoflurane induction (8% in O₂-N₂O, 50 : 50) in children, Vakkuri *et al.* described minimal (minor) seizure-like activity in 80% (10), while our team found none during similar conditions of induction (11). Apparently the observation of minor epileptiform changes may be tied to the neurophysiologist observer, the major epileptoid signs such as periodic discharge, epileptiform discharge, or frank seizure activity seem to be more obvious.

Some patient and induction factors probably modulate the appearance of EEG abnormalities.

Factors which modulate epileptogenic potential of sevoflurane

Patient factors

Epilepsy. Seizure-like EEG changes appear earliest in children already taking anticonvulsive medication (4). In adults Iijima *et al.* confirmed that

epileptic subjects were particularly sensitive to the epileptogenic effect (purely electrical) of sevoflurane at 1, 1.5, and 2 MAC; these effects were more marked than with isoflurane (9,12,13). The studies performed in neurosurgical patients with refractory localized epileptic foci had divergent results. Endo *et al.* showed that sevoflurane (0.5 and 1.5 MAC) diminished the numbers of spikes from baseline and therefore was not helpful in mapping such seizure foci (12). Iijima *et al.* and Watts *et al.* found an increase in spikes above 1.5 MAC (9,14). In all cases the authors noted the proximity of epileptiform discharges to periods of burst suppression.

Febrile convulsions. This condition is probably the most common epileptic seizure disorder; about 3–4% of all children below 5 years of age have presented at least one febrile seizure. The genetic predisposition to febrile convulsions may be strong. In the interictal stage, the EEG records are usually normalized. The vast majority of febrile convulsions have an excellent prognosis. Anticonvulsive medications are not necessary in this context. However, the degree to which prior history of febrile convulsions contributes to epileptogenic effects of sevoflurane has not been determined, although intuitively this would seem likely.

Intracranial pathology. One case of seizure has been reported in a 19-year old with a cerebral cortical lesion but no prior convulsion, who experienced a generalized tonic-clonic seizure during emergence from sevoflurane anesthesia (15).

Anesthetic factors

Premedication. In oral doses commonly used for premedication, benzodiazepines decrease alpha activity and increase beta activity with the EEG effect reflecting blood levels. Benzodiazepine premedication with its known anticonvulsive effect may explain the absence of epileptiform EEG changes during subsequent sevoflurane anesthesia (11,16). However, no randomized study has demonstrated such a protective effect and it was not seen by Scandinavian investigators (10,17,18).

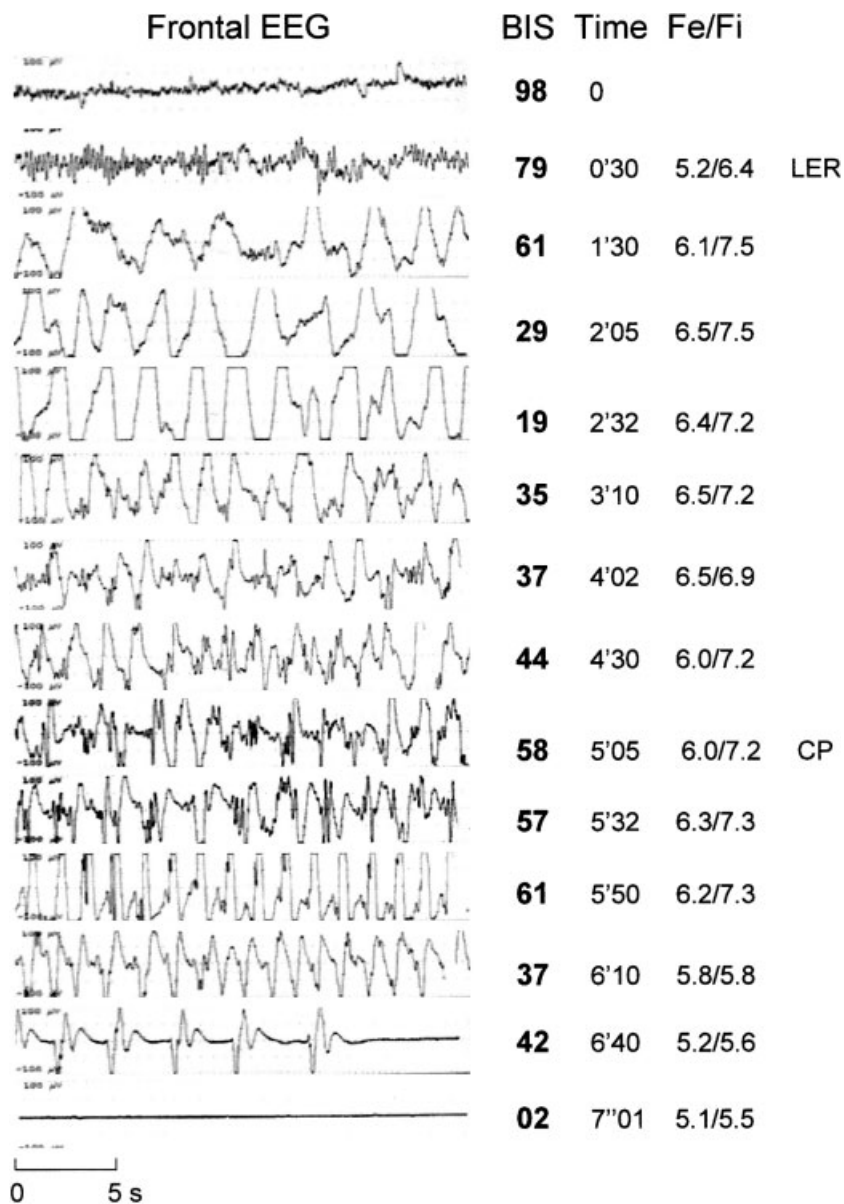


Figure 3

Frontal electroencephalographic (EEG) traces recorded in a 5-year child during sevoflurane induction (8% in O_2-N_2O , 50 : 50). Epileptiform signs occur around the fourth minute of induction with some spike waves, simple or multiple, followed by periodic discharge (rhythmic polyspikes) leading to periods of epileptiform discharges just before occurrence of burst suppression. The corresponding bispectral index (BIS), time and Fe/Fi ratio of sevoflurane are noted. The loss of eye lash reflex (LER) and the centralization of the pupils (CP) are indicated.

Hyperventilation. Hyperventilation has long been used in neurophysiology laboratories to provoke generalized-synchronous paroxysmal discharges and absence seizure in susceptible patients. Hyperventilation classically causes EEG slowing with appearance of bilateral synchronous delta waves and a diminution of alpha and beta activity. These

phenomena are pronounced in the young child (age 3–12 years). They are present in 95% of children with epilepsy and 70% of healthy children. However they are present in only 40% of adults with epilepsy and 10% of healthy adults (19). Epileptiform activity elicited by hyperventilation are one diagnostic element for epilepsy. The

Table 1

Summary of the publications dedicated to the epileptogenic effect of the sevoflurane

Adachi <i>et al.</i> (2)	Case report, one child	Seizure-like movements (induction S _{4%})
Haga <i>et al.</i> (3)	Prospective study, 180 children	Seizure-like movements in 6% of children (induction S _{4-6%})
Komatsu <i>et al.</i> (4)	Case report, two epileptic children	Spikes at S _{2-7%} , BS and spikes at S _{5-7%} (induction S _{2-4%})
Terasako and Ishii (24)	Case report, one adult	Seizure-like movements (recovery S _{1-3%})
Woodforth <i>et al.</i> (25)	Case report, one child	Epileptiform EEG changes followed by BS (maintenance, S _{7%})
Bösenberg (1)	Case report, one child	Seizure-like movements (induction)
Artru <i>et al.</i> (22)	Randomized study, 14 epileptic adults	No epileptiform EEG change (maintenance S _{0.5-1.0-1.5 MAC} and Iso _{0.5-1.0-1.5 MAC})
Zacharias (26)	Case report, two children	Seizure-like movements (induction S _{7-8%})
Baines (27)	Answer to Zacharias	Seizure-like movements during S induction
Schultz and Schultz (28)	Answer to Zacharias	Epileptiform EEG changes under S _{>5%} induction
Kaisti <i>et al.</i> (29)	Case report, two adults	Epileptiform EEG changes with BS (maintenance S _{4%})
Watts <i>et al.</i> (14)	Prospective study, 11 epileptic adults	Epileptiform EEG changes under S _{1.5MAC} > Iso _{1.5MAC} . Spikes near BS
Constant <i>et al.</i> (11)	Randomized study, 45 children	No epileptiform EEG change in the two groups (induction S _{7%} , vs halo _{3%})
Yli-Hankala <i>et al.</i> (18)	Randomized study, 30 adults	Spikes and BS under controlled ventilation >spontaneous ventilation (induction S _{8%})
Iijima <i>et al.</i> (9)	Crossover study, S vs Iso	In epileptic patients: epileptiform EEG changes under S _{1, 1.5, 2 MAC} > Iso _{1, 1.5, 2 MAC}
Vakkuri <i>et al.</i> (17)	Twelve epileptic and 12 nonepileptic adults Randomized study, 30 adults	In nonepileptic patients: no epileptiform EEG changes in the two groups Major epileptiform EEG changes more frequent under immediate hyperventilation than under delayed hyperventilation (induction S _{8%})
Hilty and Drummond (15)	Case report, one adult	Seizure-like movements (recovery). Cerebral imaging showed cerebral cortex lesion
Schultz <i>et al.</i> (30)	Case report, two children	Epileptiform EEG changes under S _{7-8%}
Schultz <i>et al.</i> (31)	Case report, one adult	Spikes under S _{5-6%}
Vakkuri <i>et al.</i> (10)	Randomized study, 31 children	Major epileptiform EEG changes more frequent under controlled ventilation than under spontaneous ventilation (induction S _{8%})
Conreux <i>et al.</i> (32)	Prospective study, 20 children	2/20 children: seizure like movements + epileptiform EEG changes + BS (induction S _{8%})
Shultz <i>et al.</i> (33)	Prospective study, seven adults	6/7adults: spikes (induction S _{5-6%})
Hisada <i>et al.</i> (13)	Crossover study, six epileptic adults	Epileptiform EEG changes S _{1.5 MAC} > Iso _{1.5 MAC} (maintenance)
Sato <i>et al.</i> (8)	Prospective study, seven adults	Epileptiform EEG changes and BS in all patients (maintenance S _{2.5-3.3%})
Endo <i>et al.</i> (12)	Prospective study, 10 epileptic adults	Decrease of epileptiform EEG changes compared with baseline (maintenance S _{0.5-1.5MAC})
Nieminen <i>et al.</i> (16)	Prospective study, 30 children	No epileptiform EEG changes (maintenance S _{2%})
Koyama <i>et al.</i> (23)	Case report, one epileptic adult	Fentanyl (0.1 mg) decreased the number of spikes (maintenance S _{1.5%})
Jaaskelainen <i>et al.</i> (6)	Prospective study, 16 adults	Major epileptiform EEG changes and BS in all patients under S _{1.5-2 MAC}
	S vs propofol	No epileptiform EEG changes, but BS in all patients under propofol _{1-1.5-2EC₅₀}
Akeson and Didriksson (34)	Case report, two children	Seizure-like movements at induction, family history of epilepsy in one of two children
Chinzei <i>et al.</i> (7)	Case report, one epileptic adult	Epileptiform EEG changes associated with fluctuations of BIS (maintenance S _{1%})

EEG epileptiform activity: spike, spike-wave, polyspikes or polyspike-waves. Major EEG epileptiform activity: periodic discharge, epileptiform discharge, or seizure activity. S, sevoflurane; Iso, isoflurane; BS, burst suppression.

optimal conditions for adequate EEG activation were found to be: a respiratory rate of 30 min⁻¹, a threefold elevation of total expiratory minute

volume and a duration of 4 min; with this activation the degree of EEG slowing was found to be nearly inversely proportional to the age (in the age

range of 6–17 years) (20). As to the relationship between the appearance of EEG slowing and changes in respiratory factors, the PCO₂ decrease and the cerebral blood flow decrease, which may be caused by the PCO₂ decrease, are the most fundamental factors that produce EEG slowing during hyperventilation. The difference in the response to hyperventilation between children and adults may be caused by age-related central nervous system sensitivity to CO₂ and/or cerebral vascular CO₂ responsiveness.

During sevoflurane induction, hypocapnia induced by assisted ventilation appears to be associated with greater EEG changes (10,17,18).

Nitrous oxide. Fast oscillatory activity of the EEG is produced by nitrous oxide in concentrations that produce unconsciousness in unpremedicated humans. This activity has a peak frequency of 34 Hz, and its amplitude and quantity increase with concentration of nitrous oxide.

Nitrous oxide decreases seizure activity in known epileptic subjects (21) and may diminish epileptogenic effects of sevoflurane (9). Based on Scandinavian studies this effect appears to be minor (10,17,18).

Other drugs. Narcotics used in large dose cause a dose-dependent slowing of the EEG. However in current clinical practice, narcotics used in low doses have few effects on EEG. Narcotics such as fentanyl and sufentanil may protect against epileptogenic effects of sevoflurane (12,22,23).

Thiopental causes a biphasic effect on EEG with an initial increase in fast activity, with slowing, burst suppression and electrocortical silence occurring with higher doses. As expected a barbiturate induction would diminish these effects during maintenance anesthesia with sevoflurane (16,22).

Conclusions and recommendations

The mechanism of the epileptogenic effect of sevoflurane is thus far unknown. The hypothesis that it resembles that of enflurane (biphasic and dose-dependent activation of NMDA neuronal receptors) is supported by similarity in molecular structure, but remains to be proved.

No neurological sequelae such as seizure have been thus far attributed to the use of sevoflurane. However, until now no study looking at the persistence or emergence of epileptiform EEG activity on follow-up has been published and further research in this area is required. However, in view of the tens of millions of sevoflurane anesthetics given worldwide, concern about epileptogenic potential of sevoflurane is expected to be minimal. This perspective is further justified by the excellent cardiovascular stability preserved during sevoflurane inhalation induction.

In general certain practice recommendations may be made in view of the epileptogenic activity of sevoflurane and to protect against it. Such recommendations should be adapted to each patient's history and physical condition.

- Benzodiazepine premedication might be useful, such as midazolam in children.
- N₂O might have a minimal protective effect.
- Use of narcotics might be useful but protective qualities have not yet been documented.

These three points may be interesting, because they allow the required concentration of sevoflurane to be decreased.

- Hypocapnea should be avoided, especially in the youngest patient.
- Using a maximum of 1.5 MAC sevoflurane for maintenance anesthesia (in spite of excellent cardiovascular tolerance of higher concentrations) will limit epileptogenic activity of sevoflurane, which increases at higher concentrations. The incidence and the periodicity of epileptiform EEG changes correlate with the increasing expired fraction of sevoflurane.

An analysis of the literature clearly shows that major epileptiform signs under sevoflurane precede and accompany the appearance of burst suppression. These periods of near-electrical silence indicate a dramatic decrease in cerebral activity and are not limited to sevoflurane, but always indicate very (too) deep anesthesia. With the development of better monitors of cortical activity (EEG, BIS, entropy of EEG, spectral analyses of EEG, etc.) the administration of hypnotic agents could possibly be refined. The therapeutic interval of well tolerated cardiovascular hypnotic agents such as sevoflurane could be defined between the risk of recall on the one hand,

and the risk of cerebral overdose (burst suppression?) on the other.

The use of sevoflurane may be associated with cortical epileptiform EEG signs, usually without clinical manifestation. No enduring neurological or EEG sequelae have been described thus far, and the potential morbidity of this epileptogenic effect is unknown. The use of sevoflurane in children, with its remarkable cardiovascular profile, should include a number of precautions. Among them, the limitation of the depth of anesthesia is essential. The wide use of cerebral function monitoring (the most simple being the EEG), may permit optimization of sevoflurane dose, and avoidance of burst suppression and major epileptiform signs in fragile subject, notably the very young and the very old.

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