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 pharmacodynamic 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
first controlled studies of EEG changes under sevo-
flurane 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 guide-
lines 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 sevoflu-
rane 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 anesthe-
sia.

2. Localized or generalized tonic-clonic movements
occurring under deep anesthesia at the end
of induction and persisting at that level of anes-
thesia.

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 hemody-
namic 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. Theses
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 my-
elinization 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 in-
duced 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 associ-
ated 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 ob-
served in adults (slow down and increase in ampi-
itude) (Figure 1).

EEG changes specific to sevoflurane
anesthesia

Sevoflurane induction and deepening of anesthe-
sia follow a similar pattern to that described
above, with the following exception. With ‘rapid’
Estimation of depth of anesthesia: EEG monitoring

- EEG awake
  
  ![EEG awake](https://via.placeholder.com/150)

- Fast oscillations with small amplitude
  
  ![Fast oscillations with small amplitude](https://via.placeholder.com/150)

- General anesthesia
  
  ![General anesthesia](https://via.placeholder.com/150)

- Slowing down and increase of amplitude
  
  ![Slowing down and increase of amplitude](https://via.placeholder.com/150)

**Figure 1**
Classical electroencephalographic (EEG) changes during anesthesia.

induction with 7–8% sevoflurane in O₂-N₂O (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
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).
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

Figure 3
Frontal electroencephalographic (EEG) traces recorded in a 5-year child during sevoflurane induction (8% in O₂–N₂O, 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.
Table 1
Summary of the publications dedicated to the epileptogenic effect of the sevoflurane

<table>
<thead>
<tr>
<th>Publication</th>
<th>Design</th>
<th>Children/Adults</th>
<th>EEG Changes in Adults</th>
<th>EEG Changes in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adachi et al. (2)</td>
<td>Case report, one child</td>
<td>Seizure-like movements (induction S&lt;4 MAC)</td>
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<tr>
<td>Haga et al. (3)</td>
<td>Prospective study, 180 children</td>
<td>Seizure-like movements in 6% of children (induction S&lt;4-4.5 MAC)</td>
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<tr>
<td>Komatsu et al. (4)</td>
<td>Case report, two epileptic children</td>
<td>Spikes at S&lt;2 MAC, BS and spikes at S&lt;5 MAC (induction S&lt;2-4 MAC)</td>
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<tr>
<td>Terasako and Ishii (24)</td>
<td>Case report, one adult</td>
<td>Seizure-like movements (recovery S&lt;3 MAC)</td>
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<tr>
<td>Woodforth et al. (25)</td>
<td>Case report, one child</td>
<td>Epileptiform EEG changes followed by BS (maintenance, S&lt;7 MAC)</td>
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<tr>
<td>Bösenberg (1)</td>
<td>Case report, one child</td>
<td>Seizure-like movements (induction)</td>
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<tr>
<td>Artru et al. (22)</td>
<td>Randomized study, 14 epileptic adults</td>
<td>No epileptiform EEG change (maintenance S&lt;5.1-1.5 MAC and Iso&lt;5.1-1.5 MAC)</td>
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<tr>
<td>Zacharias (26)</td>
<td>Case report, two children</td>
<td>Seizure-like movements (induction S&lt;7 MAC)</td>
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<tr>
<td>Baines (27)</td>
<td>Answer to Zacharias</td>
<td>Seizure-like movements during S induction</td>
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<tr>
<td>Schultz and Schultz (28)</td>
<td>Answer to Zacharias</td>
<td>Epileptiform EEG changes under S&lt;8% induction</td>
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<tr>
<td>Kaisti et al. (29)</td>
<td>Case report, two adults</td>
<td>Epileptiform EEG changes with BS (maintenance S&lt;4 MAC)</td>
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<tr>
<td>Watts et al. (14)</td>
<td>Prospective study, 11 epileptic adults</td>
<td>Epileptiform EEG changes under S&lt;1.5 MAC &gt;Iso&lt;1.5 MAC. Spikes near BS</td>
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<tr>
<td>Constant et al. (11)</td>
<td>Randomized study, 45 children</td>
<td>No epileptiform EEG change in the two groups (induction S&lt;7 MAC vs halothane &lt;3 MAC)</td>
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<tr>
<td>Yli-Hankala et al. (18)</td>
<td>Randomized study, 30 adults</td>
<td>Spikes and BS under controlled ventilation &gt;spontaneous ventilation (induction S&lt;8 MAC)</td>
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<tr>
<td>Iijima et al. (9)</td>
<td>Crossover study, S vs Iso</td>
<td>In epileptic patients: epileptiform EEG changes under S&lt;1.5, 1.2 MAC &gt; Iso&lt;1.5, 2 MAC</td>
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<tr>
<td>Twelve epileptic and 12 nonepileptic adults</td>
<td>In nonepileptic patients: no epileptiform EEG changes</td>
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<tr>
<td>Vakkuri et al. (17)</td>
<td>Randomized study, 30 adults</td>
<td>Major epileptiform EEG changes more frequent under immediate hyperventilation than under delayed hyperventilation (induction S&lt;8 MAC)</td>
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<tr>
<td>Hilty and Drummond (15)</td>
<td>Case report, one adult</td>
<td>Seizure-like movements (recovery). Cerebral imaging showed cerebral cortex lesion</td>
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<tr>
<td>Schultz et al. (30)</td>
<td>Case report, two children</td>
<td>Epileptiform EEG changes under S&lt;7-8%</td>
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<tr>
<td>Schultz et al. (31)</td>
<td>Case report, one adult</td>
<td>Spikes under S&lt;6-8%</td>
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<tr>
<td>Vakkuri et al. (10)</td>
<td>Randomized study, 31 children</td>
<td>Major epileptiform EEG changes more frequent under controlled ventilation than under spontaneous ventilation (induction S&lt;8 MAC)</td>
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<tr>
<td>Conreux et al. (32)</td>
<td>Prospective study, 20 children</td>
<td>2/20 children: seizure like movements + epileptiform EEG changes + BS (induction S&lt;3 MAC)</td>
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<tr>
<td>Shultz et al. (33)</td>
<td>Prospective study, seven adults</td>
<td>6/7 adults: spikes (induction S&lt;5-6 MAC)</td>
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<tr>
<td>Hisada et al. (13)</td>
<td>Crossover study, six epileptic adults</td>
<td>Epileptiform EEG changes S&lt;1.5 MAC &gt; Iso&lt;1.5 MAC (maintenance)</td>
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<tr>
<td>Sato et al. (8)</td>
<td>Prospective study, seven adults</td>
<td>Epileptiform EEG changes and BS in all patients (maintenance S&lt;5.1-3.3 MAC)</td>
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<tr>
<td>Endo et al. (12)</td>
<td>Prospective study, 10 epileptic adults</td>
<td>Decrease of epileptiform EEG changes compared with baseline (maintenance S&lt;5.1-1.5 MAC)</td>
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<tr>
<td>Nieminen et al. (16)</td>
<td>Prospective study, 30 children</td>
<td>No epileptiform EEG changes (maintenance S&lt;2 MAC)</td>
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<tr>
<td>Koyama et al. (23)</td>
<td>Case report, one epileptic adult</td>
<td>Fentanyl (0.1 mg) decreased the number of spikes (maintenance S&lt;1.5 MAC)</td>
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<tr>
<td>Jaaskelainen et al. (6)</td>
<td>Prospective study, 16 adults</td>
<td>Major epileptiform EEG changes and BS in all patients under S&lt;1.5 MAC</td>
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<tr>
<td>S vs propofol</td>
<td></td>
<td>No epileptiform EEG changes, but BS in all patients under propofol&lt;1.5-2 MAC</td>
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<tr>
<td>Akeson and Didriksson (34)</td>
<td>Case report, two children</td>
<td>Seizure-like movements at induction, family history of epilepsy in one of two children</td>
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<tr>
<td>Chinzei et al. (7)</td>
<td>Case report, one epileptic adult</td>
<td>Epileptiform EEG changes associated with fluctuations of BS (maintenance S&lt;1.5 MAC)</td>
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</tbody>
</table>

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 in-
duced by assisted ventilation appears to be associ-
ated 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 hu-
mans. This activity has a peak frequency of 34 Hz,
and its amplitude and quantity increase with con-
centration of nitrous oxide.

Nitrous oxide decreases seizure activity in known
epileptic subjects (21) and may diminish epileptogen-
ic 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 occur-
rising 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 sevo-
flurane 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 persist-
ence 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 world-
wide, concern about epileptogenic potential of sevo-
flurane 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 recom-
mendations 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 car-
diovascular 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 suppres-
sion. 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 administra-
tion of hypnotic agents could possibly be refined.
The therapeutic interval of well tolerated cardiovas-
cular hypnotic agents such as sevoflurane could be
defined between the risk of recall on the one hand,
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.

References


Accepted 30 September 2004