The Effect of Sevoflurane and Isoflurane Anesthesia on Interictal Spike Activity Among Patients with Refractory Epilepsy

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The electrophysiologic effects of sevoflurane are not well characterized in humans. Among patients with refractory epilepsy, this study compared 1) electroencephalographic (EEG) interictal spike activity during wakefulness and sevoflurane anesthesia, and 2) electrocorticographically (ECoG) recorded interictal spike activity during sevoflurane and isoflurane anesthesia. We studied 12 patients undergoing insertion of subdural electrodes. Before commencing anesthesia, awake (baseline) EEG recordings were obtained. After inhaled induction, EEG interictal spike activity was evaluated during stable, normocapnic, and hypocapnic ($Paco_2$ = 28–30 mm Hg), sevoflurane anesthesia administered at 1.5 times the minimum alveolar anesthetic concentration (1.5 MAC). Immediately after surgery, ECoG recordings were obtained from subdural electrodes during 1) 1.5 MAC isoflurane, 2) 0.3 MAC isoflurane, and 3) 1.5 MAC sevoflurane anesthesia. EEG spike frequency increased in all patients during sevoflurane anesthesia compared with awake recordings ($P = 0.002$). Compared with 0.3 MAC isoflurane anesthesia, ECoG interictal spike frequency was higher in all patients during 1.5 MAC sevoflurane anesthesia ($P = 0.004$) and in 8 of 10 patients during 1.5 MAC isoflurane anesthesia ($P = 0.016$). Under sufficiently rigorous conditions, both sevoflurane and isoflurane can provoke interictal spike activity at near burst-suppression doses. This property is more prominent with sevoflurane than isoflurane.
Implications: The results of this study suggest that the capacity to modulate neuroexcitability is a dose-dependent feature of volatile anesthetics that is manifested most prominently at near burst-suppression doses (i.e., 1.5 times the minimum alveolar anesthetic concentration) and is minimal or absent at low doses.

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The electrophysiologic effects of sevoflurane have not been fully characterized in humans. Among healthy volunteers, electroencephalographic (EEG) studies during sevoflurane anesthesia have reported no evidence of neuroexcitation (1,2). Yet, several case reports have noted seizure-like movements as well as EEG-recorded seizures during induction of sevoflurane anesthesia (3,4). A study in cats (5) also reported spontaneous EEG spike activity and somatic stimulation-induced seizures during sevoflurane anesthesia.

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Many anesthetics have neuroexcitatory properties under certain circumstances. The volatile anesthetic drug enflurane has been studied extensively. Enflurane anesthesia can provoke EEG spikes as well as electrical seizure activity among both epileptic and nonepileptic patients (6,7). This effect is most prominent when enflurane is administered under hypocapnic conditions at 1.5 to 2 times the minimal alveolar anesthetic concentration (MAC) and can be provoked with somatic or auditory stimuli (8). Depth electrode studies suggest that the mesial temporal lobe structures (i.e., the hippocampus and amygdala) are particularly sensitive to these effects (9,10). In contrast, reports of seizure-like movements or electrical seizure activity during isoflurane anesthesia are available but extremely rare (11,12). In general, isoflurane is considered to be devoid of neuroexcitatory properties.

This study, performed in patients with refractory epilepsy, evaluated 1) the effect of induction of sevoflurane anesthesia on EEG-recorded interictal

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spike activity, and 2) the comparative effects of isoflurane and sevoflurane anesthesia on electrocorticographically (ECoG) recorded interictal spike activity. The study design incorporated the conditions under which the neuroexcitatory properties of enflurane have been reported to be most prominent (i.e., patients with refractory epilepsy, 1.5 MAC anesthesia, concomitant hyperventilation, and somatic and auditory stimulation).

Methods

After institutional review board approval and written consent, 12 adult patients with refractory epilepsy scheduled for insertion of subdural electrodes were studied. Patients with a history of substance abuse or gastroesophageal reflux were excluded.

The study consisted of two parts: 1) EEG study—after inhaled induction with sevoflurane anesthesia, EEG-recorded interictal spike activity was compared with awake recordings, and 2) ECoG study—after the insertion of subdural electrodes, ECoG-recorded interictal spike activity during sevoflurane anesthesia was compared with that observed during isoflurane anesthesia.

Monitoring for all patients consisted of an electrocardiogram, intraarterial cannula for blood pressure measurements and blood gas sampling, capnography, pulse oximetry, and an esophageal temperature probe. If necessary, phenylephrine was administered to maintain a mean arterial blood pressure (MAP) >50 mm Hg. A warming blanket (Warm Air®; Cincinnati Subzero, Cincinnati, OH) was used to maintain normothermia throughout the study.

EEG Study

A baseline (awake) EEG was recorded for 15 min. A continuous EEG recording was then obtained during inhaled induction and maintenance sevoflurane anesthesia. Eight-channel digital EEG recordings were obtained with a Neurotrac II Monitor (Moberg Medical, Amber, PA) with a sensitivity of 5 μV/mm and bandpass filters of 0.5 to 50 Hz. In one patient, a 16-channel EEG was recorded using a Grass Model 8 electroencephalograph (Grass Instrument Co., Quincy, MA) with a sensitivity of 5 μV/mm and bandpass filters of 0.3 to 70 Hz.

In each patient, inhaled induction was performed using 5–7 vol% sevoflurane in 100% oxygen (Capnomac Ultima™; Datex, Helsinki, Finland). Each patient was intubated using succinylcholine 1.5 mg/kg IV and anesthesia was maintained with sevoflurane at an age-adjusted end-tidal concentration (13) of 1.5 MAC in an air/oxygen mixture (fraction of inspired oxygen [F_{IO_2}] = 0.35). Under stable sevoflurane anesthesia, EEG recordings were obtained for 15-min intervals during normocapnia (P_{aCO_2} = 40 mm Hg) and during hypocapnia (P_{aCO_2} = 28–30 mm Hg). At the conclusion of the hypocapnic recording, auditory and somatic stimuli were applied. The auditory stimulus was produced by banging metal plates together and the somatic stimulus consisted of two 50 Hz (~60 milliampere) supramaximal tetanic stimuli applied percutaneously to the ulnar nerve for approximately 3 s each (5,14). EEG spike frequency and differences between cerebral hemispheres were compared at baseline and during stable sevoflurane anesthesia under normocapnic and hypocapnic conditions.

After completion of the EEG recording, sevoflurane administration was terminated. Isoflurane (0.5–1.5 vol%) in nitrous oxide and oxygen (F_{IO_2} = 0.33) supplemented with IV fentanyl (maximal dose = 5 μg/kg) was administered during the surgical procedure (insertion of subdural electrodes). Vecuronium was administered IV at the discretion of the attending anesthesiologist.

ECoG Study

After the operative procedure, the second part (ECoG) of the study was performed. Nitrous oxide was eliminated over a period of 15 to 20 min and muscle relaxation was reversed if there was evidence of neuromuscular blockade. After the elimination of nitrous oxide, air was added to the inspired gas mixture to maintain F_{IO_2} = 0.35.

ECoG recordings were obtained under hypocapnic conditions (P_{aCO_2} = 28–32 mm Hg) for 15-min intervals during 1) 1.5 MAC isoflurane anesthesia, 2) 0.3 MAC isoflurane anesthesia, and 3) 1.5 MAC sevoflurane anesthesia. At the end of each 15-min recording, period auditory and somatic stimuli were applied, as described above. Evidence of burst suppression was managed by reducing the administration of anesthetic drug in 0.2 MAC equivalents until ECoG activity returned. When feasible, before emergence, ECoG recordings were obtained for 2 to 3 min at 0.3 MAC sevoflurane anesthesia.

Eight-channel digital ECoG recordings were obtained from the freshly implanted subdural electrodes using a Neurotrac II Monitor with a sensitivity of 40 μV/mm and bandpass filters of 0.5 to 50 Hz. In 1 patient, 16 ECoG channels were recorded using a Grass Model 8 electroencephalograph with a sensitivity of 30 μV/mm and bandpass filters of 0.3 to 70 Hz.

The subdural electrodes were made of 316 stainless steel embedded in implant-grade silicon sheets. Electrode positions were confirmed fluoroscopically during the surgical procedure. An endeavor was made to record from the mesial temporal cortex in all patients and bilateral mesial temporal recordings were obtained when possible. In addition, recordings were made from electrodes located at the seizure focus, if

this was suspected, at a location other than the mesial temporal area.

The ECoG recordings were compared with respect to spike frequency and location during 1.5 MAC isoflurane anesthesia, 0.3 MAC isoflurane anesthesia, and 1.5 MAC sevoflurane anesthesia. After the study, anesthesia was terminated and patients were delivered to the postanesthesia care unit after emergence and extubation.

Data Analysis

In the EEG study, MAP was compared between baseline and stable sevoflurane anesthesia using analysis of variance for repeated measures and the Student-Newman-Keuls test. $Paco_2$ and sevoflurane MAC during normocapnia and hypocapnia were compared with paired *t*-tests. Spike frequencies recorded awake and during sevoflurane anesthesia were compared using Fisher's exact test.

In the ECoG study, MAP, $Paco_2$, and sevoflurane or isoflurane MAC were compared using Student's *t*-tests. ECoG recordings were coded nonsequentially and interpreted in a blinded fashion by a neurologist from the epilepsy service (RM). EEG recordings also were reviewed in random order but the distinct differences among awake and anesthetized EEG recordings precluded a truly blinded interpretation. EEG and ECoG interictal spike activity was graded on a four-point scale: 0 = no spikes identified; 1 = low spike frequency (<1 per 10 s); 2 = medium spike frequency (1–10 spikes per 10 s); 3 = high spike frequency (>10 spikes per 10 s). The ECoG interictal spike frequencies at each level of anesthesia (1.5 MAC isoflurane, 0.3 MAC isoflurane, and 1.5 MAC sevoflurane) were compared using the Sign test with a Bonferroni correction for multiple comparisons. For this, a P value of 0.017 was used for statistical significance. Values = mean ± SD.

Results

Twelve patients were studied, eight men and four women, with a mean age of 27 ± 8 yr (range 18–37 yr). Based on preoperative EEG studies, eleven patients had temporal lobe epilepsy and one patient had a seizure focus situated in the left orbital-frontal cortex. Two patients had their antiepileptic medication tapered before surgery. Four patients had one or more habitual seizures recorded in the 2 days preoperatively.

The mean duration of surgery was 198 ± 36 min. All patients received fentanyl during surgery. A mean dose of 242 ± 70 μg fentanyl was administered with the last dose at least 30 min before the conclusion of surgery. During the ECoG study, one patient required phenylephrine (total dose = 250 μg) during isoflurane anesthesia to maintain a MAP >50 mm Hg. No phenylephrine was required during anesthesia with sevoflurane. Normothermia was maintained throughout the study.

Satisfactory EEG and ECoG recordings were obtained from 11 and 10 patients, respectively. The EEG data for one patient and the ECoG data from two patients were technically unsuitable for interpretation. These patients were not included in the respective analyses.

EEG Study

After induction, EEG recordings were obtained under normocapnic ($Paco_2$ = 40 ± 1 mm Hg) and hypocapnic ($Paco_2$ = 29 ± 1 mm Hg) conditions ($P < 0.001$) during stable sevoflurane anesthesia (1.5 ± 0.1 MAC and 1.5 ± 0.2 MAC, respectively). MAP decreased during induction from 82 ± 8 mm Hg (awake) to 68 ± 8 mm Hg ($P < 0.005$) and remained stable during hypocapnia (66 ± 8 mm Hg).

All patients had a low spike frequency (grade 0 or 1) during awake EEG recording. A progressive decrease in background EEG frequency was observed after the induction of anesthesia. An increase in interictal spike frequency was observed in all patients during sevoflurane anesthesia at 1.5 MAC ($P = 0.002$, Fisher's exact test) (Table 1). Three patients displayed mild burst suppression with increasing depth of anesthesia. No change in spike activity was observed in response to hypocapnia or with auditory or somatic stimulation. Representative EEG recordings obtained from a single patient while awake and during normocapnic and hypocapnic sevoflurane anesthesia are shown in Figure 1.

ECoG Study

End-tidal concentrations of isoflurane and sevoflurane were 1.6 ± 0.1 MAC and 1.6 ± 0.2 MAC, respectively. There was no difference in MAP (65 ± 8 mm Hg vs 65 ± 10 mm Hg) or $Paco_2$ (28 ± 2 mm Hg vs 28 ± 1 mm Hg) during 1.5 MAC isoflurane and sevoflurane anesthesia.

Both isoflurane and sevoflurane produced slowing of background ECoG activity and an increase in amplitude with increasing depth of anesthesia. Early evidence of ECoG burst suppression was observed in two patients at similar MAC with each drug.

Compared with 0.3 MAC isoflurane anesthesia, interictal spike activity was greater in 8 of 10 patients during 1.5 MAC isoflurane anesthesia ($P = 0.016$) and in all patients during 1.5 MAC sevoflurane ($P = 0.004$) anesthesia (Figure 2). Interictal spike activity was more frequent during 1.5 MAC sevoflurane anesthesia compared with 1.5 MAC isoflurane anesthesia ($P = 0.016$). There was no increase in spike frequency with

Table 1. EEG Interictal Spike Frequency During Awake and 1.5 MAC Sevoflurane Anesthesia

	No. of patients (n = 11)	
Spike frequency	Awake	Sevoflurane (1.5 MAC)
Grade 0 (none)	10	0
Grade 1 (<1 per 10 s)	1	4
	*	
Grade 2 (1–10 per 10 s)	0	4
Grade 3 (>10 per 10 s)	0	3

No difference in interictal spike frequency grade was observed between normocapnic and hypocapnic sevoflurane anesthesia. Data for normocapnia are presented.

EEG = electroencephalographic, MAC = minimum alveolar concentration.

* Statistical difference among groups at $P < 0.05$ (Fisher's exact test).

auditory or somatic stimulation during 1.5 MAC anesthesia using either anesthetic.

After completion of ECoG recordings at 1.5 MAC, sevoflurane concentration declined rapidly creating difficulty establishing stable levels of anesthesia at 0.3 MAC before emergence. This often precluded obtaining technically satisfactory ECoG recordings at low doses of sevoflurane. Satisfactory ECoG recordings, of brief duration, were obtained in five patients. During 0.3 MAC sevoflurane anesthesia, interictal spike frequency was similar to that observed during 0.3 MAC isoflurane anesthesia (grade 0 or grade 1). Because the number of patients was small, statistical analysis was not performed on this group.

Representative ECoG recordings during sevoflurane and isoflurane anesthesia are shown in Figure 3. Interictal spikes were observed in all patients during sevoflurane anesthesia. In 6 of 10 patients, a single ECoG spike focus was observed. In the other four patients, multiple foci were noted; however, in three of these four patients, the predominant spike focus was consistent with the location of the seizure origin (based on perioperative studies). In the other patient, postoperative ECoG studies also failed to identify a discrete seizure focus.

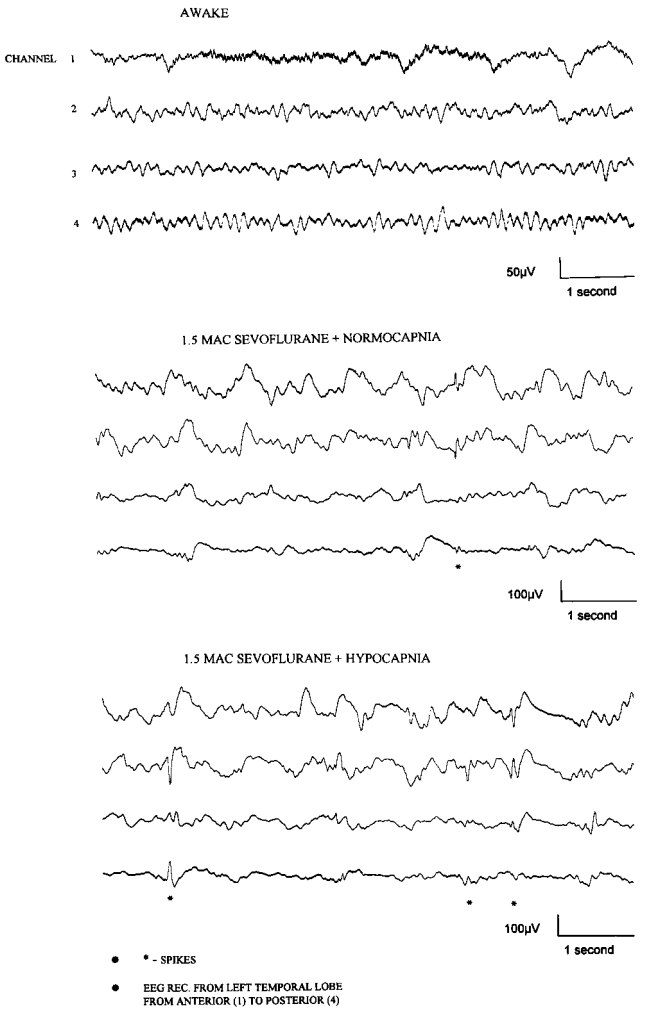

Figure 1. Representative temporal electroencephalographic (EEG) recordings obtained awake (top panel), during normocapnic (middle panel), and hypocapnic (bottom panel) sevoflurane anesthesia at 1.5 minimum alveolar anesthetic concentration.

Discussion

The neurophysiologic properties of isoflurane and sevoflurane have been reported to be similar (15,16). However, Scheller et al. (16) noted a brief epileptiform EEG discharge and clinical seizure in one of five dogs subjected to sevoflurane anesthesia and concluded that the EEG properties of sevoflurane reside between isoflurane and enflurane, with more similarity to isoflurane. Osawa et al. (5) reported that sevoflurane administration produced spontaneous, high-amplitude EEG spikes and somatic stimulation-induced seizures in 2 of 13 cats. In humans, a case report has implicated sevoflurane as the cause of clinical seizures, in the absence of EEG documentation, during induction of anesthesia (3). EEG seizure activity, without clinical manifestations, also has been reported during induction of sevoflurane anesthesia in two epileptic children (4).

In our study, among patients with refractory epilepsy, interictal spike activity increased after the induction of sevoflurane anesthesia and was greater during sevoflurane anesthesia than during isoflurane. These results support the premise that the neuroexcitatory properties of sevoflurane are somewhat more prominent than those associated with isoflurane.

We did not directly compare the neuroexcitatory properties of sevoflurane with enflurane. However, based on published experience (9,10,17), electrical seizure activity occurs spontaneously in about 50% of

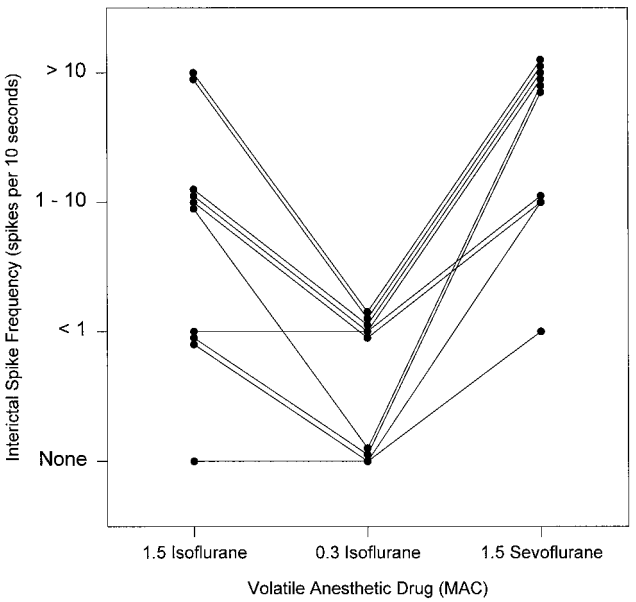

Figure 2. Electrocorticographic spike frequency during 1.5 minimum alveolar anesthetic concentration (MAC) isoflurane, 0.3 MAC isoflurane, and 1.5 MAC sevoflurane anesthesia. Each line represents the change in spike frequency for an individual patient.

epileptic and nonepileptic patients administered enflurane at a dose of 1.5 to 2.0 MAC and can be activated by hyperventilation as well as somatic and auditory stimuli. In contrast to these observations, hyperventilation did not provoke seizures or a substantial change in the frequency of EEG spike activity during sevoflurane anesthesia. Similarly, no substantial change in EEG or ECoG spike frequency was observed in response to auditory or somatic stimulation. Furthermore, enflurane also has been reported to indiscriminately activate the ECoG in epileptic patients (18,19). However, based on our results, sevoflurane activation occurs relatively selectively at the preexisting seizure focus suggesting that sevoflurane may be useful during epilepsy surgery—an observation that merits investigation. These results support the premise that the electrophysiologic properties of sevoflurane bear more similarity to those of isoflurane than enflurane.

The observation that 1.5 MAC isoflurane anesthesia provoked interictal spike activity in 8 of 10 patients compared with 0.3 MAC isoflurane is novel. Although this effect was somewhat more prominent during sevoflurane anesthesia, it demonstrates that isoflurane also can provoke interictal spike activity under appropriate conditions.

These observations suggest that the capacity to modulate neuroexcitability is a dose-dependent characteristic of most volatile anesthetics, and are consistent with reports of neuroexcitatory phenomena in association with many volatile anesthetics, albeit with differing incidence (6,7). The neuroexcitatory characteristics associated with volatile anesthetics seem to manifest at near burst-suppression doses (~1.5 MAC) (8,10,17) and are minimal or absent at low doses. Volatile anesthetics have been reported to possess potent anticonvulsant properties (6,7) and their use, particularly isoflurane, has been advocated for the management of refractory status epilepticus (20). Consistent with the recommendation of Kofke et al. (20), the results of this study suggest that when volatile anesthetics are used to manage refractory seizures, administration should begin at a low concentration and increase incrementally until the lowest effective concentration is identified. Our results would also suggest that under these conditions near burst-suppression doses should be avoided or administered in conjunction with EEG monitoring to facilitate the recognition of increased irritability.

The rigorous electrophysiologic conditions we used (refractory epileptic patients with electrically irritable brains after the insertion of subdural electrodes, 1.5 MAC anesthesia, hyperventilation, and seizure-activating activities) were chosen to optimize the neuroexcitatory potential of these two drugs. Because these conditions are rarely encountered during routine clinical anesthesia, the neuroexcitatory properties of both drugs are correspondingly much less prominent under normal clinical conditions.

This study compared the two drugs in the absence of confounding factors including other anesthetic drugs. Fentanyl was included in the anesthetic protocol during subdural electrode insertion to minimize restrictions on the clinical anesthetic administered for the surgical procedure. Although fentanyl has been reported to provoke ECoG seizure activity among patients with partial epilepsy (21), the dose used was very large (mean bolus dose = 25.7 μg/kg) relative to the small doses that were administered incrementally during the clinical component of this study (total fentanyl dose <5 μg/kg). Furthermore, fentanyl administration was terminated well in advance of performing the ECoG studies (>30 minutes). Under these conditions, fentanyl administration was not expected to influence subsequent ECoG recordings.

We designed this study as a case control comparison. Subdural electrodes are inserted through burr holes under fluoroscopic control and placement is individualized. The study design enabled comparison of both drugs under identical conditions in each patient, i.e., electrode placement relative to the seizure focus and electrode-induced irritability. However, the potential disadvantages associated with the study design include the fact that administration of the two drugs was not performed in random sequence. Anesthesia for subdural electrode insertion was standardized using isoflurane, supplemented with nitrous oxide and fentanyl, consistent with our routine clinical practice. To minimize the duration of anesthesia, the ECoG effects associated with isoflurane were evaluated first in all patients followed by

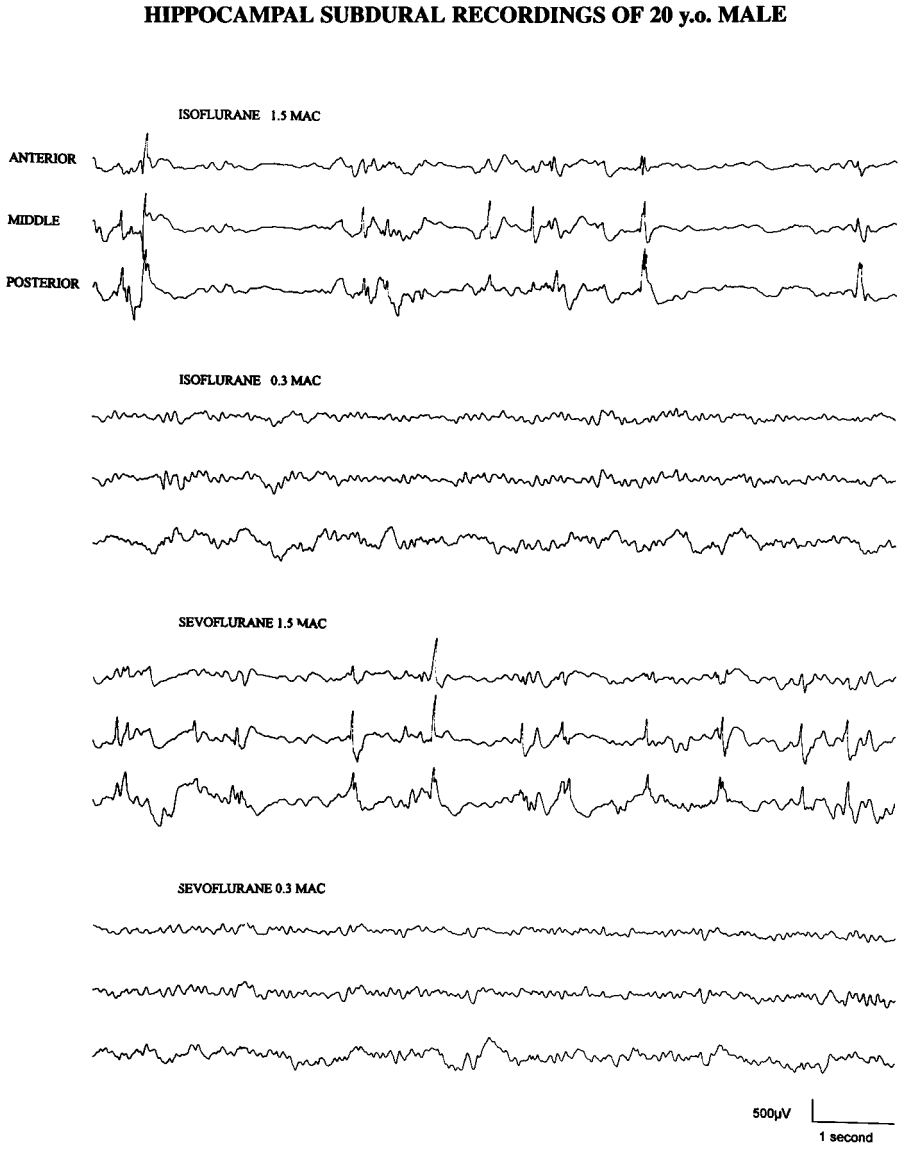

Figure 3. Representative electrocorticographic recordings during 1.5 minimum alveolar anesthetic concentration (MAC) isoflurane anesthesia (top panel), 0.3 MAC isoflurane anesthesia (second panel), 1.5 MAC sevoflurane anesthesia (third panel), and 0.3 MAC sevoflurane anesthesia (bottom panel).

sevoflurane. ECoG recordings were reviewed postoperatively in a randomized and blinded manner. Although we cannot exclude the possibility that residual isoflurane affected the ECoG recordings during sevoflurane anesthesia, such effects seem unlikely. Isoflurane was reduced to very low levels (0.3 MAC) before commencing sevoflurane anesthesia and continued to decline while stable 1.5 MAC sevoflurane anesthesia was achieved before ECoG recording. Furthermore, 0.3 MAC isoflurane anesthesia was associated with a low interictal spike frequency (grade 0–1) in all patients and hence is unlikely to have contributed to the increase in interictal spike activity observed during sevoflurane anesthesia.

In conclusion, we report that, under electrophysiologically irritable conditions, 1.5 MAC sevoflurane anesthesia increases interictal spike activity to a greater extent than 1.5 MAC isoflurane anesthesia. Compared with experience with enflurane, reported by other investigators, sevoflurane anesthesia activates interictal spike activity more selectively, and seems to be resistant to hyperventilation or other EEG activating activities in humans. We have noted also that isoflurane, an anesthetic traditionally considered essentially devoid of neuroexcitatory properties, can provoke interictal spike activity, under appropriate conditions. This observation supports the premise that the capacity to provoke neuroexcitation is a dose-dependent characteristic of most volatile anesthetics, which is manifest at near burst-suppression doses and is minimal at low doses.

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