Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats

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Summary
Several reports have appeared on postanaesthetic convulsive disorders in humans after enflurane and isoflurane anaesthesia. However, it is controversial if enflurane induces epileptiform electroencephalogram (EEG), abnormal behaviour, or both, lasting for several days after anaesthesia in laboratory animals. We chronically implanted electrodes for EEG recording in the cortex, medial amygdala and dorsal hippocampus, and for reticular multi-unit activity (R-MUA) in the midbrain reticular formation in five cats. Two weeks later they were anaesthetized with 5.0 % sevoflurane, 3.5 % enflurane or 4.8 % isoflurane for 3–4 h. EEG recordings, R-MUA and behaviour were observed for 1–3 h, during both wakefulness and sleep, every day for 5–7 days after anaesthesia. None of the cats showed abnormal behaviour, or EEG or R-MUA abnormalities after any of the anaesthetics, not only during wakefulness but during slow-wave and paradoxical phases of sleep. These results suggest that if seizures occur after anaesthesia, volatile anaesthesia itself may not be the cause. (Br. J. Anaesth. 1996; 76: 721–725)

Key words

Sevoflurane is a new volatile anaesthetic in current popular use in Japan. Using cats with chronically implanted brain electrodes, we have reported that sevoflurane suppresses central nervous system (CNS) background electrical activities and leaves reactive capability relatively unaffected during light planes of anaesthesia but facilitates it in deep anaesthesia to produce an epileptoid state [1]. These neurophysiological properties of sevoflurane are similar to those of enflurane which also induces convulsions in deep anaesthesia [1].

Using cats with chronically implanted brain electrodes, Julien and Kavan reported epileptiform electroencephalogram (EEG) activities and abnormal behaviour after enflurane anaesthesia: the epileptic actions appeared on the second, peaked on the fourth and disappeared by the 16th day after anaesthesia [2]. However, such postanaesthetic neurological sequelae of enflurane were not reproduced in cats and humans by other investigators [3–5]. Nevertheless, the postanaesthetic epileptic effects are controversial in humans because many clinical cases of postanaesthetic seizure have been reported [6–16].

As sevoflurane has an epileptogenic property in deep anaesthesia [1], it is more than scientific interest to examine if sevoflurane has neurological or epileptoid effects in the postanaesthetic period. In this study, we recorded serial EEG before, during and after sevoflurane, enflurane and isoflurane anaesthesia in cats with chronically implanted brain electrodes, and examined the EEG and behavioural effects for 5–7 days after anaesthesia. It is well known that an abnormal EEG becomes manifest during light sleep in epileptic patients and amygdaloid kindled cats [17–22]. Therefore, EEG patterns were compared not only during wakefulness, but during slow-wave and paradoxical phases of sleep.

Materials and methods
Five cats of both sexes, weighing 2.3–4.1 kg, were used in this study, which was approved by our Institutional Animal Research Committee. The anaesthetic agents studied were sevoflurane (n = 5), enflurane (n = 5) and isoflurane (n = 3). At least 2 weeks after implantation of brain electrodes, each anaesthetic was administered to the cats with intervals greater than 4 weeks. EEG activities of wakefulness and sleep were studied before and after anaesthesia. The overall timetable of the experiment on each cat is shown in figure 1.

Placement of electrodes
The surgical procedures were performed during pentobarbitone anaesthesia (40 mg kg⁻¹ i.p.). Cats were placed on a stereotaxic apparatus and electrodes implanted over the frontal sinus, parietal cortex, occipital cortex and in the amygdala (A : 12, L : 11, D : −6), dorsal hippocampus (A : 2, L : 9, D : 9) and midbrain reticular formation (A : 2, L : ± 3, D : −2),

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According to the atlas of Snider and Niemer [23]. The cortical electrodes were made of stainless steel screws, 2 mm in diameter, and the subcortical bipolar electrodes were made of side-by-side stainless steel wires, 0.2 mm in diameter, insulated with epoxy resin except for the cut-end tips. The distance between the tips was 0.5–1.0 mm. Electrode position in the limbic structures was confirmed by probing the EEG activities: the electrodes were advanced by 1-mm steps until seizure activity appeared on the EEG [1]. This seizure was induced by an injury discharge, typical of the limbic structures [1]. All leads were soldered to a miniature vacuum tube socket, which was fixed to the skull with dental cement. During recording of CNS electrical activities, the socket was connected to the recording devices with a bundle of flexible cables of 5 m in length to allow for free movement of the cats.

**Recording of CNS Electrical Activities**

Preanaesthetic control and postanaesthetic recordings of EEG and reticular multunit activity (R-MUA) were made during three behavioural states of wakefulness, and slow-wave and paradoxical phases of sleep. These recordings lasted 1–3 h. The EEG and R-MUA were recorded for 1–3 h, every day, for 5–7 days after anaesthesia. We considered that observation for the first 5 days after anaesthesia would be sufficient to identify any possible neurological abnormality [2]. During the recording, behavioural changes were confirmed by visual observation through a one-way window of the EEG recording box, and EEG changes were correlated with either wakefulness, slow-wave or paradoxical phases of sleep. These CNS electrical activity recordings were performed between 10:00 and 17:00.

Cortical and subcortical EEG were recorded on an eight-channel polygraph (Recti-Horiz-8K, San-ei, Tokyo) at a recording paper speed of 10 mm s⁻¹. The frontal sinus electrode was used as a reference for the cortical EEG. The subcortical EEG were recorded with the bipolar depth electrodes. The time constant was set at 0.1 s and the high-cut filter at 100 Hz.

The R-MUA was measured according to the method described previously [27]. The depth bipolar electrode implanted in the midbrain reticular formation differentially recorded discharge of a population of neurones included in an area with a radius of approximately 1 mm around the tip of the electrode. The wide-band signal obtained was amplified (1205C, San-ei, Tokyo) and then sent to a high-frequency band-pass filter, the peak frequency response of which was centred at 1300 Hz, with 3-dB attenuation at 600 and 2500 Hz. This high-frequency activity was rectified and smoothed with an electronic circuit (envelope detector), with a smoothing time constant of 50 ms, and was expressed as an oscillation of direct current (DC) voltage: the higher the DC level, the greater the firing of a population of neurones. This signal was recorded on a paper recorder (Rectigraph-8K, San-ei, Tokyo) at a speed of 5 mm min⁻¹. The noise level of the recording system was estimated as the distance between the DC level obtained by inserting a 10-kΩ resistor and that obtained by inserting a short across the input in place of the animal. The R-MUA level was measured as the distance from the lower limit of the multi-unit tracing to the 10-kΩ resistor line. The signal-to-noise ratio exceeded 10 in all cases.

**Results**

Before anaesthesia, all cats showed alternating patterns of typical EEG activities of wakefulness, and slow-wave and paradoxical phases of sleep. Inhalation of the anaesthetics induced EEG activities characteristic of each agent [1, 26]. During enflurane anaesthesia we were able to induce EEG seizures by auditory stimulation by clapping hands [25], but not during sevoflurane or isoflurane anaesthesia.

EEG activities before and after anaesthesia with each anaesthetic did not differ. Characteristic patterns of EEG alternated, coinciding with each of the three phases: wakefulness, slow-wave sleep and paradoxical sleep (fig. 2). These patterns were the same before and for the 5–7 days after anaesthesia. During wakefulness, there were theta waves and high-frequency small amplitude activities in the dorsal hippocampus, desynchronized activities in the cortex and relatively small amplitude activities in...
During slow-wave sleep, large amplitude slow waves appeared in all leads and spindle bursts in the cortex. Most characteristics was large amplitude sharp waves in the amygdala but not in the other brain areas. During the paradoxical phase of sleep, small amplitude activities in the dorsal hippocampus disappeared leaving the 4–7 Hz theta waves more prominent, and the EEG of the cortex and amygdala were represented by desynchronized activities.

Large amplitude delta wave bursts sometimes appeared repetitively in the cortex during wakefulness, both before and after anaesthesia, when the cats were either grooming, drinking water or eating (fig. 3). These activities were, however, best understood as movement artefacts. Large amplitude spikes appeared in any lead of the cortex, amygdala and dorsal hippocampus when the cats moved the head in grooming, drinking or eating. These large amplitude spike-like activities did not synchronize with those of the other brain areas.

The R-MUA changed in a characteristic manner according to the three phases stated above: the averaged R-MUA was largest during the paradoxical phase of sleep, smaller during wakefulness, and smallest during slow-wave sleep. Figure 2 shows typical tracings of R-MUA after anaesthesia, which did not differ. The intermittent bursts of cortical EEG during wakefulness were usually associated with gross body movements.

The behaviour of the cats was normal and no movements implicating abnormal CNS activities.
were noted throughout the postanaesthetic period. They remained tame and in good temper as before anaesthesia.

Discussion
This study has confirmed the absence of an abnormal EEG and abnormal behaviour after sevoflurane, enflurane and isoflurane anaesthesia, not only during wakefulness but during slow-wave and paradoxical sleep throughout the postanaesthetic period. The anaesthetic concentrations of sevoflurane and enflurane were in the convulsive range [1, 25]. These findings indicate that these anaesthetics do not induce an epileptoid state after anaesthesia. This is the first study that provides evidence that sevoflurane does not cause persistent postanaesthetic EEG or behavioural abnormalities.

Julien and Kavan first reported the central nervous system effects of enflurane in cats with chronically implanted brain electrodes [2]. They observed residual behavioural and electroencephalographic abnormalities on the second day after anaesthesia and these abnormalities persisted for 14–16 days. Their cats appeared to be frightened, resisted handling and, at the same time, large amplitude spike activities were observed in the cerebral cortex and thalamic nuclei. Such abnormal EEG peaked at day 4, the intensity and frequency of the spike activity decreased by day 8, and the EEG returned to normal by day 16 [2]. Their study was contradicted by a series of other studies. Bassell and co-workers [5] conducted 2 MAC h of enflurane anaesthesia in cats with chronically implanted brain electrodes and observed no abnormal EEG or behaviour for 4 weeks after anaesthesia. Heavner and Amory [4] reported that seizure-inducing thresholds for lignocaine and pentylenetetrazol were not reduced after anaesthesia with 4 % enflurane for 2 h over the 4 successive days in cats with chronically implanted brain electrodes. They also reported the absence of behavioural or EEG changes suggestive of long-lasting effects of enflurane exposure [4]. In humans, Burchiel and co-workers were not able to observe de novo epileptoid EEG after 9.6 MAC h of enflurane anaesthesia in 12 volunteers for 30 days [3]. However, these earlier studies [3–5], and those of Julien and Kavan on enflurane [2] and isoflurane [28], did not observe EEG during sleep. It is well known that drowsiness and sleep increase the probability of finding epileptiform discharges in the EEG of epileptic patients [17–21], and the EEG of natural or soporific-induced sleep is examined routinely, especially in temporal lobe seizures and nocturnal seizures [20]. In this study we demonstrated the absence of abnormal EEG not only during wakefulness but also during slow-wave and paradoxical phases of sleep after sevoflurane, enflurane and isoflurane anaesthesia.

In the present study, the EEG appeared normal throughout the postanaesthetic period, and large amplitude spike activity was always associated with either slow-wave sleep in the limbic structures or body movements such as grooming, drinking or eating. The large amplitude delta wave bursts, similar to the so-called hypersynchronous delta rhythm, pathognomonic for epilepsy [20], were observed when the cats were grooming, drinking or eating. Such activity is usually provoked by hyperventilation in epileptic patients [20]. This activity resembled the abnormal EEG activities reported by Julien and Kavan [2]. In their experiments no myoclonic movement linked with the abnormal EEG was noted, and movement artefacts might possibly have been misinterpreted as abnormal EEG. In the present study this type of activity appeared even before anaesthesia during head movement, and may be explained by head movement, that is movement artefacts. The cats remained tame, in good temper, with a good appetite and showed no resistance to handling or a frightened appearance such as Julien and Kavan had described [2].

Our experimental conditions were a little different from those of Julien and Kavan [2]. They conducted enflurane anaesthesia during spontaneous ventilation via a face mask with a 2 : 1 mixture of air and oxygen, while we conducted anaesthesia via a tracheal tube and artificial ventilation with oxygen. They administered 4.5–5.5 % enflurane for approximately 30 min, while we gave 3.5 % enflurane for 3–4 h. We chose this concentration of enflurane because induction of seizures is known to be easiest with 3.5 % enflurane [25]. If the cause of the persistent abnormality of EEG and behaviour in their experiment was the metabolite(s) of enflurane as they suggested, such a metabolite(s) would accumulate more during a longer period of anaesthesia and would tend to induce abnormalities. Therefore, our experimental condition should have been more likely to induce persistent abnormalities in the EEG or behaviour.

Enflurane, during deep anaesthesia, is known to induce an epileptoid state in humans [29, 30] and cats [26], characterized by suppression of background reticular cell firing and augmentation of the reactive capability of the brain [26]. Although there have been several clinical reports of seizures after enflurane anaesthesia [6–15], in this study we may speculate that enflurane itself might not have been the causative agent.

Sevoflurane was confirmed to have similar neurophysiological properties to enflurane in cats [1]. It induces seizures during deep anaesthesia by somatic stimulation, although less frequently than enflurane [1]. In humans, however, a sevoflurane-induced epileptoid state has not yet been reported, and there has been no report of seizure after sevoflurane anaesthesia [3].

The convulsive property of isoflurane is less potent than that of enflurane in cats [26]. It does not induce seizures even during deep anaesthesia marked by isoelectric EEG with spikes in cats [26] or by isoelectric EEG in humans [31]. Clinically there is only one case report of seizure just after isoflurane anaesthesia, which was characterized by myoclonus [16].

In conclusion, we did not observe abnormal behaviour or epileptic EEG after sevoflurane, enflurane and isoflurane anaesthesia, not only during wakefulness, but also during slow-wave and paradoxical phases of sleep. These results suggest that
even convulsant anaesthetics do not produce an epileptoid state after anaesthesia, and if seizures occur after anaesthesia, the anaesthetic itself may not be the cause of the seizure.

References


