CEREBRAL EFFECTS OF SEVOFLURANE IN THE DOG: COMPARISON WITH ISOFLURANE AND ENFLURANE

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SUMMARY

The cerebral effects of sevoflurane were compared in dogs with those of enflurane and isoflurane. Initially, the minimum alveolar concentrations (MAC) of sevoflurane and enflurane were determined and the electroencephalographic (EEG) responses to increasing doses of sevoflurane (1.5, 2.0 and 2.5 MAC) or enflurane (1.5 and 2.0 MAC) in unparalysed animals were examined. Administration of sevoflurane was not associated with seizure activity at any concentration either during normocapnia (Paco2 5.3 kPa) or hypocapnia (Paco2 2.7 kPa), even in the presence of intense auditory stimuli. All dogs anaesthetized with enflurane demonstrated sustained EEG and motor evidence of seizure activity induced by auditory stimuli at concentrations of enflurane > 1 MAC, particularly during hypocapnia. In a separate group of dogs, the effects of increasing concentrations of sevoflurane and isoflurane (0.5, 1.5 and 2.15 MAC) were compared directly on arterial pressure, cardiac output and heart rate, cerebral blood flow and the cerebral metabolic rate for oxygen (CMRO2) using the venous outflow technique. Sevoflurane, in common with isoflurane, had minimal effects on cerebral blood flow at the concentrations studied, but significantly reduced the CMRO2 at end-tidal concentrations sufficient to produce a burst suppression pattern on the EEG (approximately 2.15 MAC). Both sevoflurane and isoflurane significantly decreased arterial pressure in a dose-dependent manner, but neither drug significantly altered cardiac output.

KEY WORDS


Sevoflurane is a volatile anaesthetic with a relatively low blood:gas partition coefficient of 0.60, compared with 1.41 and 2.40 for isoflurane and halothane, respectively [1]. Sevoflurane also has a pleasant, non-pungent odour which permits a smooth and rapid inhalation induction. These characteristics suggest that it might be useful for neurosurgical patients, in whom rapid induction and recovery are often desired. However, because sevoflurane is an ether anaesthetic, there is some concern that it may induce seizure activity, as does enflurane, particularly in the presence of hypocapnia which is used frequently during neurosurgical procedures. Seizure activity is known to increase the metabolic rate of the brain (CMRO2), with attendant increases in cerebral blood flow (CBF) and intracranial pressure [2].

In a previous study we compared the effects in rabbits of increasing doses of sevoflurane and isoflurane on cortical cerebral blood flow, using the hydrogen clearance technique [3]. We demonstrated that the drugs did not alter cortical CBF. However, both drugs were administered in the presence of morphine and nitrous oxide and mean arterial pressure was maintained with angiotensin. The conditions were clearly different from those obtaining in clinical practice, and the haemodynamic effects of the drugs were not studied.

We therefore undertook the present study to compare the effects of sevoflurane, enflurane and isoflurane on the EEG, CBF, CMRO2 and cardiovascular system in a dog model which allowed us to administer the drugs in a clinically relevant fashion.

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MATERIALS AND METHODS

All studies were undertaken following institutional Animal Care Committee review and approval.

Part one

Mongrel dogs of both sexes were anaesthetized by mask with either sevoflurane (n = 5) or enflurane (n = 3), the trachea was intubated and the animal positioned prone. The biparietal fronto-occipital EEG, femoral arterial pressure, ECG, end-tidal concentration of carbon dioxide (\(FE'_{\text{CO}_2}\)), end-tidal concentration of the volatile drug \(FE'_{\text{drug}}\) (Puritan Bennett infra-red volatile agent analyser) and oesophageal temperature (servo-controlled to 37.5 °C) were recorded continuously. The base of the animal’s tail was shaved and MAC determined using the up-and-down method with a tail clamp as the stimulus [4]. \(FE'_{\text{drug}}\) was increased or decreased by 10%, depending on the response of the animal. Twenty minutes was allowed for equilibration after each new \(FE'_{\text{drug}}\) concentration was achieved. After MAC had been determined for a particular animal, the \(FE'_{\text{drug}}\) was increased to 1.5 MAC and the animal allowed to equilibrate for 15 min. Auditory stimuli (repetitive, loud clanging of resonant metal containers) were then applied and the animal observed for the presence of either motor or EEG evidence of seizure activity. Hypocapnia (\(Pa_{\text{CO}_2} 2.7 \text{kPa}\)) was then induced and the sequence repeated. In the animals anaesthetized initially with sevoflurane, three \(FE'_{\text{drug}}\) concentrations were studied in this manner: 1.5, 2.0 and 2.5 MAC. The animals receiving enflurane initially were studied only at 1.5 and 2.0 MAC. Following the observations of the animals at the greatest \(FE'_{\text{drug}}\), the volatile anaesthetic was discontinued. At the first sign of “light anaesthesia” such as coughing or movement, the other volatile anaesthetic was introduced and increased to 1.5 MAC. After 30 min of equilibration with the new agent, the entire sequence of increasing concentrations, hypocapnia and auditory stimuli was undertaken again and the presence or absence of seizure activity recorded. The animals were killed humanely while still anaesthetized.

Part two

Mongrel dogs of both sexes were anaesthetized by mask with either sevoflurane (n = 6) or enflurane (n = 6) on an alternating basis, the trachea was intubated and the animal paralysed with pancuronium. The lungs were ventilated with the volatile anaesthetic in oxygen. The animals were positioned prone and femoral arterial (for direct pressure monitoring and arterial blood-gas analysis) and venous cannulae (for cerebral venous outflow return) inserted. A pulmonary catheter was introduced via the right external jugular vein. Other monitors included temperature (servo-controlled to 37.5 °C), the EEG as described above, ECG, \(FE'_{\text{CO}_2}\) and \(FE'_{\text{drug}}\).

CBF was measured using the venous outflow technique. Briefly, following scalp incision, portions of the anterior skull were removed to expose diploic and ethmoidal veins which were occluded with bone wax or cauterized in order to exclude extracranial sources of blood. The sagittal sinus was exposed and a small plastic catheter inserted following systemic heparinization (3 mg kg\(^{-1}\) followed by 1 mg kg\(^{-1}\) h\(^{-1}\)). Sagittal sinus blood flow was measured using timed aliquots collected in triplicate. Global CBF was calculated from the sagittal sinus flow rate corrected for the weight of each dog’s brain and the previously determined volume of brain known to be drained by the sagittal sinus [5].

\(CMRO_2\) was calculated as the product of the arterial–sagittal sinus oxygen content difference and CBF. The arterial and venous blood oxygen contents were calculated from the oxyhaemoglobin saturation (IL 282 co-oximeter) and \(Pa_{\text{O}_2}\) (IL 813 blood gas analyser).

Following completion of the surgical preparation, all wounds were infiltrated with 0.25% bupivacaine and \(FE'_{\text{drug}}\) reduced to 0.5 MAC (0.64% isoflurane or 1.05% sevoflurane). The animals were left undisturbed for 30 min before any measurements were made. The following variables were then recorded: mean arterial pressure (MAP), heart rate (HR), oesophageal temperature, cardiac output (CO), pulmonary artery systolic and diastolic pressures (PAS, PAD), pulmonary capillary wedge pressure (PCWP), CBF, \(CMRO_2\), EEG, arterial blood-gases, and \(FE'_{\text{drug}}\). \(FE'_{\text{drug}}\) was then increased to 1.5 MAC and all variables recorded similarly after a 15-min equilibration period. Next, \(FE'_{\text{drug}}\) was increased until burst suppression was noted on the EEG. Again, after a 15-min equilibration period, all variables were recorded. Finally, \(FE'_{\text{drug}}\) was decreased to 0.5 MAC for 15 min and all variables recorded. The animals were killed humanely and the brains removed for weighing.
Statistical analysis

Cardiovascular variables, CBF and CMRO₂, were compared within groups at the various \( P_{\text{E}}^{\text{end}} \) by using a repeated measures analysis of variance followed by Dunnett's test where appropriate. \( P < 0.05 \) was considered statistically significant. Data are presented as mean (sd).

RESULTS

In all animals receiving sevoflurane in parts one and two, induction of anaesthesia was rapid and smooth. In part one animals, MAC of sevoflurane was 2.1 (sd 0.23) % and MAC of enflurane was 2.7 (0.36) %. Exposure to enflurane at both 1.5 and 2.0 MAC was associated with seizure activity (EEG and motor) during hypocapnia. This seizure activity could always be elicited by auditory stimuli and was nearly always sustained. In contrast, only one animal receiving sevoflurane demonstrated any evidence of seizure activity. This animal had first received enflurane and demonstrated only a brief EEG discharge associated with upper limb twitching, lasting less than 5 s during administration of 2.0 MAC sevoflurane during normocapnia, which was not elicited by auditory stimuli. Further attempts to elicit seizure activity in this animal, including the institution of hypocapnia and application of auditory stimuli, were unsuccessful.

EEG burst suppression was achieved with similar MAC multiples of sevoflurane and isoflurane: 2.14 MAC and 2.17 MAC, respectively. Both sevoflurane and isoflurane caused significant dose-dependent decreases in MAP, but CO was
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not affected significantly (table I). Increasing concentrations of sevoflurane or isoflurane did not significantly alter CBF (table I). However, CMRO₂ decreased significantly during burst suppression compared with 0.5 MAC in both groups (fig. 1). There were no differences in cerebral or haemodynamic variables between the first and second exposures to 0.5 MAC. Two animals in the isoflurane group and one animal in the sevoflurane group required phenylephrine to maintain MAP > 60 mm Hg during the administration of the highest concentration of volatile anaesthetic.

DISCUSSION

The MAC values of enflurane and sevoflurane in this study are in agreement with those found in previous studies [6, 7]. The present study also demonstrates that, in contrast with enflurane, sevoflurane in concentrations up to 2.5 MAC caused neither EEG nor gross motor evidence of seizure activity in dogs that were rendered hypocapnic, exposed to intense auditory stimuli, or both. This property is important for any agent which might be used for patients in whom sustained seizure activity could lead either to an imbalance in the oxygen supply: demand ratio or to an increase in intracranial pressure. However, it must be emphasized that these results were obtained from dogs with normal brains and extrapolation to animals or patients with intracranial disease may be unwarranted. Similar results have been found in swine anaesthetized with desflurane, another new volatile ether anaesthetic [8], although desflurane is more highly fluorinated than enflurane—a property that might make it more epileptogenic [9]. However, the correlation of the degree of fluorination with epileptic potential is disputed [10]. Both desflurane (six fluoride atoms) and sevoflurane (seven fluoride atoms) are more highly fluorinated than enflurane (five fluoride atoms), and yet neither drug appears to cause seizure activity at clinically relevant doses during hypocapnia, in contrast with enflurane.

Sevoflurane and isoflurane had minimal effects on CBF, in agreement with an earlier study in rabbits [3]. However, in that study, isoflurane and sevoflurane were added to an existing nitrous oxide—morphine anaesthetic. We have shown previously that nitrous oxide increased CBF in rabbits anaesthetized with halothane or isoflurane and that the increases in CBF correlated positively with the initial end-tidal concentration of volatile anaesthetic [11]. By avoiding the use of nitrous oxide or other background anaesthetic agents in the present study, we may conclude confidently that sevoflurane and isoflurane affect CBF similarly in the dog at equipotent concentrations.

The changes in CMRO₂ observed during administration of sevoflurane in the present study are also in agreement with those in our previous study in the rabbit [3]. However, a study in pigs demonstrated that sevoflurane 1 MAC decreased cerebral cortical oxygen consumption by 50% compared with the awake state [12]. In the present study, we noted a 30% decrease in CMRO₂ in response to an increase in end-tidal concentration of sevoflurane from 0.5 MAC to 2.14 MAC. Neglecting a possible species difference, the pigs in the earlier study had an unusually high awake mean CMRO₂ (7.66 ml/100 g min⁻¹) compared with the value with sevoflurane 0.5 MAC (2.7 ml/100 g min⁻¹), suggesting that sevoflurane 0.5 MAC was associated with significant metabolic depression compared with the awake state.

Cucchiara, Theye and Michenfelder [13] studied the effects of isoflurane on CBF in dogs using the venous outflow model. They found that CBF increased in response to an increase in end-tidal concentration of isoflurane from 0.1% to either 1.4% or 2.4%, but found no difference in CBF between the two greater concentrations. The results of the present study agree with their observations, although we studied slightly greater concentrations of isoflurane. In the present study, CBF did not change significantly in response to an increase in end-tidal concentration of isoflurane from 1.9% to 2.8%.

Inhalation induction of anaesthesia appeared more pleasant with sevoflurane than with either isoflurane or enflurane. In all cases, dogs readily inhaled sevoflurane and became unconscious quickly. In contrast, dogs breathing isoflurane or enflurane tended to struggle and breath-hold. Others have made this observation in dogs, swine and humans [7, 12, 14].

We conclude that the properties of isoflurane that make it suitable for use in neurosurgery, such as a negligible effect on CBF and a cerebral metabolic depressant effect, appear to be shared by sevoflurane. In contrast with enflurane, sevoflurane did not appear to cause either EEG or gross motor evidence of seizure activity in hypocapnic dogs, even in the presence of auditory
stimuli. In addition, inhalation induction of anaesthesia with sevoflurane appeared smoother than with either enflurane or isoflurane.

REFERENCES


