Investigation of changes in the middle latency auditory evoked potential during anesthesia with sevoflurane in dogs

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Objective—To investigate the middle latency auditory evoked potential (MLAEP) in awake dogs and dogs anesthetized with 2 concentrations of sevoflurane.

Animals—10 adult Beagles.

Procedure—The MLAEP was recorded while dogs were awake and anesthetized with sevoflurane (end-tidal concentration, 2.7% or 3.5%). Three needle electrodes were inserted SC, and click stimuli were delivered binaurally. Signal acquisition, averaging, and analysis were performed by use of computer software developed in-house. Signals were recorded for 128 milliseconds, and the responses to 1,024 stimuli were averaged. Waveforms from 10 recordings in each dog were averaged, and latencies of peaks were measured. Data acquired for awake dogs and dogs anesthetized with high and low sevoflurane concentrations were compared statistically.

Results—Sevoflurane anesthesia attenuated the MLAEP so that only peaks P0, Na, and Pa could be identified. The MLAEP changes were maximal at the lower concentration of sevoflurane evaluated. The latencies of these peaks were significantly shorter in awake dogs, compared with values in anesthetized dogs. No difference in the peak latency was detected between the sevoflurane concentrations.

Conclusions and Clinical Relevance—In terms of CNS responsiveness, the effects of anesthesia with sevoflurane are similar to those of anesthesia with isoflurane. Data suggest that sevoflurane is not the inhalant agent of choice in a research setting where monitoring the depth of anesthesia is desirable. Attention has therefore turned to evaluation of evoked responses in the EEG. Assessment of auditory evoked potentials that are derived from the EEG provides a tool to investigate and compare the CNS effects of different anesthetic agents. The MLAEP is altered in response to administration of most anesthetic agents; the characteristic pattern of change in response to increasing drug concentrations is an increase in latency and decrease in amplitude of the waveform peaks. Administration of opioids or midazolam has minimal effects on the MLAEP. Middle latency auditory evoked potential monitoring has also been proposed as a measure to ascertain the adequacy of the hypnotic state during surgery, suggesting that it can be used to detect graded changes in the depth of anesthesia.

The MLAEP may have potential both as a tool to monitor depth of anesthesia in dogs and as a research technique to investigate and compare the CNS effects of different anesthetic agents. However, it is important that the effects of individual anesthetic agents on the MLAEP of dogs are first investigated. In a study in dogs, sedation with acepromazine caused an increase in latency of the peaks of the MLAEP compared with that in the awake state; this confirmed that the awake state should be used as a baseline comparison for changes in the MLAEP following drug administration. A limited number of studies has investigated changes in the MLAEP during anesthesia in dogs. Administration of thiopentone caused a profound modification of the associated with potentially severe psychological implications for those patients postoperatively. Conversely, anesthesia that is excessively deep is also undesirable because of the dose-related cardiovascular and respiratory adverse effects of many anesthetic agents.

In the search for a reliable means by which to monitor depth of anesthesia, the interpretation of electroencephalograms (EEGs) was an obvious avenue to investigate. However, despite extensive research in humans, no unique feature in the basal EEG has been identified that can reliably indicate depth of anesthesia when combinations of anesthetic drugs are used. Attention has therefore turned to evaluation of evoked responses in the EEG. Assessment of auditory evoked potentials that are derived from the EEG provides a tool to investigate and compare the CNS effects of different anesthetic agents. The MLAEP is altered in response to administration of most anesthetic agents; the characteristic pattern of change in response to increasing drug concentrations is an increase in latency and decrease in amplitude of the waveform peaks. Administration of opioids or midazolam has minimal effects on the MLAEP. Middle latency auditory evoked potential monitoring has also been proposed as a measure to ascertain the adequacy of the hypnotic state during surgery, suggesting that it can be used to detect graded changes in the depth of anesthesia.

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Materials and Methods

MLAEP waveform with loss of several peaks,11,12 whereas administration of a combination of midazolam and butorphanol appeared to increase the latency of the peaks but to a lesser extent than that associated with thiopentone.11 The effects of sevoflurane alone on the MLAEP of dogs have not been previously investigated. Ono et al13 investigated the relative effects of halothane, enflurane, and isoflurane on the basal EEG and MLAEP of dogs and determined that the amplitude of one of the positive waveforms (Pa) was larger at 1.0X the minimal alveolar concentration (MAC) of halothane than it was at 1.0X MAC of enflurane, suggesting that the inhibitory effects on evoked potentials were different among the 3 volatile anesthetics investigated. In humans, the MLAEP changes linearly with sevoflurane concentration.14,15 Greene et al16 investigated changes in the bispectral index (BIS) of dogs at multiples of sevoflurane MAC and found that BIS significantly decreased with increasing sevoflurane concentration.

The purpose of the study reported here was to investigate the MLAEP in awake dogs and dogs anesthetized with 2 concentrations of sevoflurane (approx 1.2X and 1.5X MAC). Our hypothesis was that the changes in the MLAEP would be graded in response to the concentration of sevoflurane administered. The MLAEP was first recorded in each dog while awake to obtain a baseline trace for the purposes of comparison.

Click stimuli of positive polarity (corresponding to condensation pulses) were generated as rectangular waves (duration, 0.2 milliseconds; hearing level, 80 dB [based on hearing thresholds in young human adults]). The intervals between consecutive clicks alternated between 136 and 146 milliseconds (depending on the positive or negative phase of the power line), resulting in a mean repetition rate of 7 Hz. This phase-synchronized triggering reduced the power line-derived noise. Further reduction of noise was achieved by application of a 50-Hz notch filter. The generation of click stimuli was triggered by the data acquisition software and the stimuli were delivered binaurally via in-the-ear earphones.3 The latter were firmly fitted into the external ear canal. All amplified response signals were inputted in an analogue-to-digital converter interfaced to a personal computer. Signal acquisition, averaging, and artifact rejection and analysis were controlled by dedicated software that had been developed in-house. Signals were recorded for 128 milliseconds (including a 25-millisecond stimulus delay) with a sampling rate of 2,000 Hz. The responses to 1,024 stimuli were averaged. Each recording was repeated 10 times; during recordings, the running mean was displayed in real time. Results were stored for subsequent analysis by use of the dedicated software developed in-house.

During the awake recording, each dog was suspended in a sling with its legs hanging down toward the ground. The head was also supported by the sling. At the end of this recording session, an interval of approximately 20 minutes was allowed to elapse before proceeding to the second part of the experiment, during which the MLAEP was recorded while the dog was anesthetized with sevoflurane.

For each dog, anesthesia was induced with sevoflurane (dialized vaporizer setting, 8%) vaporized in oxygen and air (1:1 ratio) delivered via a circle breathing system and face mask. When depth of anesthesia was judged to be adequate, a suitably sized endotracheal tube was placed and connected to the circle breathing system. The dog was allowed to breathe spontaneously unless the end-tidal C02 concentration increased to > 5.7 kPa, when respiration was supported via manual intermittent positive pressure ventilation. An 18-gauge catheter was placed in the right cephalic vein, and a continuous infusion of lactated Ringer’s solution (5 mL·kg−1·h−1) was administered. Samples of airway gases were collected continuously from the end of the endotracheal tube adjacent to the circle system. Carbon dioxide and sevoflurane concentration were measured by use of an infrared monitor. A lead II ECG tracing was recorded via disposable surface electrodes placed on the pads of the left and right forelimbs and left hind limb, and hemoglobin saturation was measured via a pulse oximeter probe that was placed on the tongue. Rectal temperature was measured intermittently by use of a thermometer. Monitoring of these physiological parameters ensured safe anesthesia and excluded physiological disturbances from being a cause of changes in EEG data. The dialized vaporizer setting was adjusted to achieve the target end-tidal sevoflurane concentration (2.7% or 3.5%); once achieved, the concentration was held constant for 15 minutes before the start of MLAEP recording. This process was repeated for the second recording at the other end-tidal sevoflurane concentration. At the end of the recording session (total anesthesia time was approx 1.5 to 2 hours), administration of sevoflurane was stopped and the dog was allowed to recover from anesthesia.

The waveforms from the 10 recordings in each of the 3 different states (awake and anesthetized at end-tidal sevoflurane concentrations of 2.7% and 3.5%) were averaged so that the MLAEP for each individual dog for each state was the mean value of 10 recordings (each recording comprised of 1,024 sweeps). The amplitudes and latencies of the peaks that could be consistently identified were measured off-line.

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Statistical analyses—Following confirmation that data were normally distributed (determined by use of the Kolmogorov-Smirnov test) and after testing for homogeneity of variance with a Levene test, data obtained for each dog while it was awake and anesthetized were compared by use of a repeated-measures ANOVA; the Dunnett post hoc test was applied when significant differences were found. Differences were considered to be significant at values of \( P \leq 0.05 \).

Results
The awake MLAEP recordings could not be completed in 1 dog because of excessive movement; therefore, further recordings in this dog during anesthesia were abandoned, and data from this dog were excluded from further analysis. Manual intermittent positive pressure ventilation was required in 3 dogs during anesthesia with sevoflurane at a concentration of 3.5%.

There were no complications during anesthesia in any dog, and all dogs recovered rapidly and without difficulty from anesthesia.

The MLAEP waveform recorded in the dogs while awake and during anesthesia consisted of a series of positive (P) and negative (N) peaks that were labeled according to terminology used in humans\(^{17}\) (Figure 1). On visual assessment of the traces, there were no differences between the waveform recorded on channels 1 and 2; therefore, the data recorded from channel 2 (15- to 100-Hz band pass filter) were selected for further analyses. In the awake recording, 3 positive peaks could be identified in all dogs: P0, Pa, and Pb. The corresponding negative peaks, Na and Nb, could also be identified. Sevoflurane anesthesia abolished Pb in 8 of 9 dogs, whereas P0 and Pa remained. The latencies of P0, Na, and Pa were significantly shorter in recordings obtained from awake dogs than the corresponding latencies in recordings obtained from dogs anesthetized with sevoflurane at concentrations of 2.7% or 3.5% \( (P < 0.001, P = 0.001, \text{ and } P = 0.001, \text{ respectively}; \text{Table 1}) \). No difference in the latency of these peaks was found between the 2 concentrations of sevoflurane.

Discussion
In the present study, the MLAEP waveform recorded in the awake dogs was comprised of a series of positive and negative peaks, similar to the waveform described previously in awake dogs and dogs sedated with acepromazine or medetomidine.\(^{10,11}\) Sevoflurane anesthesia caused changes in the MLAEP waveform with disappearance of the later peaks (Nb and Pb) and an increase in latency in the earlier peaks (P0, Na, and Pa).

The peak P0 was consistently detected in recordings from all dogs in the present investigation, in contrast to findings of a previous study\(^{10}\) carried out by our group that indicated that the presence of this peak was variable among dogs. The MLAEP recording protocol and breed of dog investigated (Beagle) were identical in the 2 studies; therefore, this difference in waveform is difficult to explain, although P0 has been noted to be variably present in MLAEP recordings obtained from dogs in other studies.\(^{11,12}\) The peak P0 is most likely to be part of the postauricular muscle response, which is a large sound-evoked muscle action potential. In humans, the postauricular muscle response can be triggered by rapid-onset acoustic stimuli and comprises a positive peak between 12.5 and 15 milliseconds and a negative peak between 15 and 18 milliseconds,\(^{14}\) which is in the same time frame as P0 identified in the present study. Myogenic responses to the auditory stimulus can be many times larger than the MLAEP, which potentially makes analysis impossible. Use of an alternative electrode configuration in which the reference electrode is not placed on the ear pinna may be advantageous for future studies.

Although the MLAEP recorded in the awake state in the present investigation was quantitatively similar to the waveform recorded in the previous study,\(^{10}\) the latency of Pa was slightly longer in the present study. This could be explained by the constant presence of P0 detected in recordings in the present study that caused interference with the Pa waveform and prolonged the measured latency.\(^{10}\)

In the dogs in the present study, anesthesia with sevoflurane caused a marked increase in the latency of Na and Pa, compared with findings in the awake state, and was associated with the disappearance of the Pb waveform. These depressive changes in the MLAEP waveform appeared to be already maximal at the lower sevoflurane concentration administered. An increase in latency and decrease in amplitude of the components

![Figure 1](image-url)
of the MLAEP waveform have been described following administration of sevoflurane and other inhalant anesthetic agents in humans.\textsuperscript{14,20} In humans, administration of sevoflurane at 1.0× MAC severely attenuated or almost completely suppressed the MLAEP components.\textsuperscript{21} The amplitude of the peaks P0, Pa, and Pb were not compared in the present study. When the MLAEP waveforms of individual dogs were analyzed, it was not possible to consistently identify a common reference point with which to compare the relative amplitude of the individual peaks, thereby making comparative measurements invalid. When the mean MLAEPs from all dogs in the awake and each anesthetized state were compared, it appeared that sevoflurane anesthesia caused a reduction in amplitude of Pa that is similar to the effect of sevoflurane and other inhalant anesthetic agents in humans. Interestingly, in dogs anesthetized with sevoflurane, the amplitude of P0 appeared to be larger than that amplitude in the awake state; however, this may be a result of interference between peaks P0, Na, and Pa, which are much closer together in latency in awake animals. From assessment of the mean MLAEP waveforms there did not appear to be any difference in the amplitude of any peaks between dogs anesthetized with the low and high concentration of sevoflurane, confirming that depression of the signal was maximal at the lower concentration tested.

The sevoflurane MAC in dogs has been reported to be 2.10% to 2.36%\textsuperscript{21,22}; therefore, end-tidal sevoflurane concentrations of 2.7% and 3.5% correspond to 1.14× MAC and 1.48× MAC, respectively. In humans, the components of the MLAEP waveform are almost completely suppressed by administration of sevoflurane at 1.0× MAC,\textsuperscript{15} a concentration similar to the concentration required to produce maximum MLAEP suppression in the dogs in the present study. This suggests that the effects of sevoflurane on the MLAEP waveform of dogs are both quantitatively and qualitatively similar to those in humans.

Johnson and Taylor\textsuperscript{23} compared the relative effects of halothane, isoflurane, and methoxyflurane on EEG and MLAEP responses in horses and identified quantitative differences when the agents were administered at MAC equivalent concentrations; in that study, isoflurane caused more CNS depression than halothane in horses. The relative and different effects of isoflurane and halothane were later confirmed in a similar study\textsuperscript{24} in rats. Johnson and Taylor\textsuperscript{23} hypothesized that halothane is more antinociceptive than isoflurane because the concentration of halothane at which the response to a standard nociceptive stimulus was prevented induced less CNS depression than the concentration of isoflurane that was required to similarly prevent the response. However, differences in CNS reactivity with equipotent concentrations of inhalant agents have not been a universal finding. In humans, MAC equivalent administrations of isoflurane, desflurane, and sevoflurane were associated with similar levels of EEG suppression.\textsuperscript{25,26} Although only 2 concentrations of sevoflurane (approx 1.0× and 1.5× MAC) were investigated in the present study, the results suggest that sevoflurane resembles isoflurane in terms of changes in CNS reactivity, as characterized by Johnson and Taylor.\textsuperscript{23}

The effects of sevoflurane on the MLAEP of dogs have not been previously described, although Greene et al\textsuperscript{27} investigated the relationship of canine BIS to administration of sevoflurane at multiples of MAC. In that study, the BIS significantly decreased with increasing concentration of sevoflurane (range, 0.8× to 2.0× MAC); this suggests that the CNS remained responsive over this dose range, which is in contrast to findings of the present study. The BIS is an index derived from human data that is dependent on a measure of the “coherence” among components of electroencephalography,\textsuperscript{28} although a detailed knowledge of how the index is derived from EEGs and other data is hidden to the user. However, for assessment of several anesthetic regimens and end points in humans, the BIS has been shown to yield the best combination of sensitivity and specificity of any commercially available device for monitoring the depth of anesthesia.\textsuperscript{29} In contrast to the BIS, the MLAEP becomes attenuated and almost undetectable relatively early after loss of consciousness, which imposes a limitation on its use as a potential monitor of depth of anesthesia. The attenuation of the MLAEP at a sevoflurane concentration between 1.0× and 1.5× MAC was evident in our study. Although monitoring BIS appeared to be more sensitive than MLAEP recordings for detection of graded changes in sevoflurane concentration in dogs,\textsuperscript{30} it should be emphasized that the BIS is empirically derived from human data, making it less than completely reliable for application in dogs. Published studies investigating BIS in dogs and other animals are scarce, but BIS has been found to be an unreliable indicator of CNS depression in isoflurane-anesthetized horses\textsuperscript{31} and during anesthesia with propofol or sevoflurane in pigs,\textsuperscript{32} suggesting that the current BIS monitoring technology may not be reliable in animal species.

A potential limitation of our study is that MAC sevoflurane was not individually determined in each dog before MLAEP recording; it is possible that dogs were not at equivalent depths of anesthesia, although the end-tidal concentrations of sevoflurane were identical. The sevoflurane concentrations were approximately 1.1× MAC (a concentration too low to provide anesthesia sufficient for surgery to be performed) and 1.5× MAC (a concentration that would be expected to be sufficient for surgery to be performed in dogs anesthetized with sevoflurane alone). Therefore, the concentrations should have been sufficiently different from each other to allow differences in the MLAEP waveform to be identified should they occur with graded changes in sevoflurane concentration.

The EEG and cerebral blood flow are usually both correlated with cerebral activity and metabolism, and changes in cerebral blood flow may also affect the EEG.\textsuperscript{33} Cerebral perfusion pressure is one of the major extracerebral physiological factors contributing to global cerebral perfusion and is determined by the difference between cerebral blood flow and intracranial pressure. In a study in dogs, Werner et al\textsuperscript{34} determined that mean arterial blood pressure < 49 mm Hg was associated with a shift of the EEG to lower frequencies. Administration of sevoflurane, in common with other inhalant anesthetic agents, is associated with dose-
dependent cardiorespiratory depression. Arterial blood pressure was not monitored in the dogs in the present investigation, but the concentrations of sevoflurane administered would be unlikely to result in mean arterial blood pressure < 50 mm Hg in healthy animals.\textsuperscript{33,34} There was also no indication from other variables monitored to ensure safe anesthetic episodes, such as heart rate or expired carbon dioxide concentration, that hypotension occurred. Therefore, it is unlikely that hypotension influenced the MLAEP results in our study.

To the authors' knowledge, this is the first study in which the MLAEP in dogs was recorded during anesthesia with sevoflurane, and our findings indicate that the MLAEP changes are qualitatively similar to those that occur in sevoflurane-anesthetized humans. These changes were maximal in dogs administered sevoflurane at 1.1X MAC, suggesting that the effects of sevoflurane resemble those of isoflurane in terms of CNS responsiveness during MLAEP and EEG recording in anesthetized dogs. As a result of relative CNS unresponsiveness, Antunes et al\textsuperscript{19} recommended that halothane be administered instead of isoflurane when EEG tracings are made during research projects involving inhalation anesthesia. The results of the present study allow this recommendation to be extended to include the choice of halothane over sevoflurane in research investigations, despite the advantage associated with the latter of a more rapid induction and recovery from anesthesia. The rapid, maximal depression of the MLAEP waveform during administration of sevoflurane also suggests that the MLAEP is not a suitable tool with which to monitor anesthetic depth during sevoflurane anesthesia in dogs.

References


