

Effect of sevoflurane concentration on visual evoked potentials with pattern stimulation in dogs

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(Received 2 July 2014/Accepted 1 October 2014/Published online in J-STAGE 5 November 2014)

ABSTRACT. The purpose of this study was to investigate the effects of sevoflurane concentration on canine visual evoked potentials with pattern stimulation (P-VEPs). Six clinically normal laboratory-beagle dogs were used. The minimum alveolar concentration (MAC) of sevoflurane was detected from all subjects by tail clamp method. The refractive power of the right eyes of all subjects was corrected to -2 diopters after skiascopy. For P-VEP recording, the recording and reference electrode were positioned atinion and nasion, respectively, and the earth electrode was positioned on the inner surface. To grasp the state of CNS suppression objectively, the bispectral index (BIS) value was used. The stimulus pattern size and distance for VEP recording were constant, 50.3 arc-min and 50 cm, respectively. P-VEPs and BIS values were recorded under sevoflurane in oxygen inhalational anesthesia at 0.5, 1.0, 1.5, 2.0, 2.5 and 2.75 sevoflurane MAC. For analysis of P-VEP, the P100 implicit time and N75-P100 amplitude were estimated. P-VEPs were detected at 0.5 to 1.5 MAC in all dogs, and disappeared at 2.0 MAC in four dogs and at 2.5 and 2.75 MAC in one dog each. The BIS value decreased with increasing sevoflurane MAC, and burst suppression began to appear from 1.5 MAC. There was no significant change in P100 implicit time and N75-P100 amplitude with any concentration of sevoflurane. At concentrations around 1.5 MAC, which are used routinely to immobilize dogs, sevoflurane showed no effect on P-VEP.

KEY WORDS: canine, minimum alveolar concentration, P100 implicit time, pattern stimulated visual evoked potentials, sevoflurane

doi: 10.1292/jvms.14-0345; *J. Vet. Med. Sci.* 77(2): 155-160, 2015

The visual evoked potential (VEP) test is a method for detecting brain wave signals from the visual cortex induced by a light stimulus. VEP is affected by the function of all regions in the visual pathway. If VEP is recorded, the subject reacted to the stimulation [5, 6]. VEP is classified into pattern-stimulated VEP (P-VEP), which uses a contrast-reversing checkerboard pattern stimulus, and flash-stimulated VEP (F-VEP), which uses a flash stimulus. The P-VEP test requires gazing at a stimulating monitor. The F-VEP test is useful when a subject has poor vision and/or cooperates poorly. The visual cortex is more sensitive to a stimulus with figures of different contours and contrast than a flash stimulus, in which the entire retina is stimulated uniformly. Thus, P-VEPs are less variable in waveform and timing than F-VEPs [5].

P-VEP is used to support the diagnosis of optic neuritis and multiple sclerosis, and P-VEP abnormalities have been reported in patients with Parkinson disease and Alzheimer disease in human medical science [10, 19]. In veterinary

medical science, there are very few reports about P-VEP. There are some reports indicating that P-VEP is applicable to visual function testing in dogs [18]. In recent years, Itoh *et al.* showed the possibility of using canine P-VEP for objective evaluation of visual acuity [11].

P-VEP recording in dogs is difficult because the subjects are often uncooperative, and sedation or general anesthesia is required. However, general anesthesia has a depressive effect on the central nervous system (CNS). Therefore, general anesthesia is expected to affect VEP, which is one component of an electroencephalograph (EEG). In human medical science, some reports have investigated the effects of injectable and inhalational anesthetics on VEP [3, 12, 15, 16, 20, 21], while in the veterinary field, no report has investigated the influence of sevoflurane, which is an inhalational anesthetic, on VEP.

The bispectral index (BIS) is a derived from the EEG and has been used to demonstrate the state of CNS suppression objectively. This parameter is obtained to continuously measure brief periods of electroencephalographic activity. The EEG signal is converted to a digital signal, and then quantitative variables of the signal are calculated and transformed in a proprietary algorithm that yields a single value termed the BIS. A BIS value is represented as an integer between 0 and 100, with zero indicating a loss of cerebral activity and 100 indicating a conscious state. A patient is maintained at a depth of anesthesia that yields a BIS value between 40 and 60 in general surgery. Greene investigated the relation-

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ship between BIS and inhalational sevoflurane concentration in the range used clinically (1.36–4.8%) during surgical anesthesia in dogs [8]. They reported that the BIS value decreases with increases in sevoflurane concentration. Thus, it is thought that BIS might be useful as an index of CNS suppression in dogs. In the human medical field, BIS monitoring is often used clinically as an indicator of the hypnotic state under general anesthesia. There are some reports about the usefulness of BIS monitoring [4, 7, 13, 22, 25].

In this study, we recorded P-VEP with a constant stimulus pattern size and stimulus distance and with changing concentrations of sevoflurane in oxygen inhalational anesthesia and recorded BIS to grasp the state of CNS suppression. We investigated the effects of sevoflurane concentration on P-VEP.

MATERIALS AND METHODS

Subjects and Animals: Six 5 to 7 years old (mean: 6 years) clinically normal beagle dogs (three males and three females) with body weights of 11 to 15 kg (mean: 14 kg) were used in this study. In addition, the right eye of each dog was selected for use in this study. The dogs had no abnormalities on neurologic and ophthalmic examinations before the study, including pupillary light reflex, menace response, tonometry, slit-lamp biomicroscopy, ophthalmoscopy and electroretinography. The dogs received no food or water for 8 hr before the experiment. This study was conducted according to the guidelines of the Experimental Animal Research Committee of Rakuno Gakuen University.

Methods of anesthesia: Each dog was administered sevoflurane in oxygen (OS) anesthesia using a mask and was intubated with an endotracheal tube that could accommodate a sampling endotracheal gas tube (8 Fr, 100 cm; Feeding tube, Terumo, Tokyo, Japan) at the tip, and then, OS anesthesia was started with the dog in the right lateral recumbent position with a vaporizer for sevoflurane (Sevoflurane ASV-5, Kimura Medical Instrument, Tokyo, Japan; Ohmeda Sevotec 3, Datex-Ohmeda, Tokyo, Japan) set to 3%. For OS anesthesia, an inhaler equipped with a vaporizer for sevoflurane (Siesta 21, Kimura Medical Instrument) as an outside circuit vaporizer and a rebreathing circuit were used. After administering anesthesia, a 22 or 24 gauge intravascular indwelling catheter was placed in the cephalic vein.

1) Measurement of minimum alveolar concentration (MAC). The MAC of sevoflurane was measured by the tail clamp method in all dogs [14, 26], according to the previous method reported by Ko [14].

Each dog was allowed to equilibrate for 30 min at an end-tidal sevoflurane concentration (ETSEV) of 2.4%. The hair was clipped from a section of the dog's tail with a diameter approximately equivalent to the diameter of a standard Backhaus towel clamp (Backhaus Towel Clamp, Mizuho, Tokyo, Japan). After equilibration for 30 min, a towel clamp was placed around the dog's tail and closed to the third ratchet. The clamp was left in place for 60 sec or until the dog showed any gross purposeful movement. Purposeful movement was defined as substantial movement of the head or extremities and did not include coughing, chew-

ing, swallowing or increased respiratory effort. The clamp circumscribed the tail and did not puncture the skin of the dog, thereby producing a blunt force on the tail [14, 26]. If the dog exhibited any purposeful movement in response to tail clamping, the ETSEV was increased by 0.2%. If the dog did not exhibit any purposeful movement in response to tail clamping, the ETSEV was reduced by 0.2%. After changing the ETSEV, the dog was allowed to re-equilibrate for 20 min. The dog was retested after re-equilibration. Testing continued until the lowest ETSEV at which the dog did not demonstrate purposeful movement in response to tail clamping was determined. MAC was calculated as the mean of the ETSEV at which the dog did not demonstrate any purposeful movement and the next lower concentration tested (i.e., the highest concentration at which the dog still demonstrated purposeful movement in response to tail clamping). The MAC for each dog was determined in triplicate.

2) Anesthesia while recording P-VEP. All dogs were administered OS anesthesia using a mask and intubated with an endotracheal tube. Subsequently, OS anesthesia was started at the concentration of sevoflurane for 1.25 MAC. While recording P-VEP, dogs were changed to the prone position. During anesthesia, heart rate, blood pressure, body temperature, ETSEV, partial pressure of carbon dioxide (PaCO₂) and percutaneous oxygen saturation (SpO₂) were monitored by using a patient medical monitor (COLIN BP-508, OMRON COLIN Co., Ltd., Kasugai, Japan). Respiration was controlled by IPPV (respiration rate, 12 times/min; inspiration/expiration ratio, 1:2) using a volume-controlled respirator. Blood pressure was maintained above 60 mmHg. PaCO₂ was maintained at 35 to 40 mmHg. Intravenous infusion of lactated Ringer's solution was started at a continuous rate of 10 ml/kg/hr via the catheter placed in the cephalic vein of the right forefoot. The body temperature of all dogs was kept at 37.5 to 38.0°C using a warm air blanket (AD-J200, Mitsubishi Electric Home Appliance Co., Ltd., Fukaya, Japan). While recording P-VEP, the position of the eye was fixed by administration of rocuronium bromide (Eslax, MSD, Tokyo, Japan). Continuous intravenous infusion of rocuronium bromide was performed at 0.2 to 2.0 mg/kg/hr from a catheter placed in the saphenous vein using a syringe pump.

BIS recording: BIS recording was performed at each concentration of sevoflurane. BIS was recorded with a BIS monitor (A-2000XP, Aspect Medical Systems, Natick, MA, U.S.A.) and spiral electrodes. A reference electrode was positioned at the center point of the left and right medial canthus. One of the recording electrodes was positioned in the parietal region, and the other was positioned 2 cm behind the right lateral canthus on the zygomatic process. The BIS value and suppression ratio (SR) were recorded. SR was the proportion of flat waveforms in a 60-sec EEG recording.

P-VEP recording:

1) Correction of refractive power of eye. The refractive power of the recorded eyes, the right eyes of all dogs, was measured by skiascopy. All measured eyes were corrected to -2 diopters (D) using soft contact lenses (PremiO, Menicon, Nagoya, Japan).

2) Setting of P-VEP recording. Mydriasis and cycloplegia

of the recorded eye were obtained by instillation of cyclopentolate hydrochloride eye drops (Cyplegin 1%, Santen Pharmaceutical Co., Ltd., Osaka, Japan) 20 min before P-VEP recording at each concentration of sevoflurane. P-VEP was recorded with a portable VEP system (LE-3000, Tomey, Nagoya, Japan) and pattern stimulus display (PS-410, Tomey). For P-VEP recording, needle electrodes (VEP needle electrodes, Mayo Co., Nagoya, Japan) were positioned at theinion (external occipital protuberance) as the recording electrode and the nasion (nasal point) as the reference electrode. A plate type electrode (LE ear electrode, Mayo) was positioned on the inner surface of the right auricle as an earth electrode. The positions of the electrodes are shown in Fig. 1. Dogs were placed in a lighted room during equalization of anesthesia. Then, the light was turned off, and P-VEP was recorded from the right eye under dim lighting. An eye speculum was used to keep the eyelids open, and physiological saline eye drops were instilled for corneal hydration. The left eye was occluded with a bandage to avoid stimulation. The testing distance, which was the distance from the cornea to the display, was 50 cm, the stimulus pattern size was 7.31 mm, and the visual angle was 50.3 arc-min. The stimulation rate was 3 reversals/sec. The P-VEP signal was averaged from 128 repetitions. P100 implicit time and N75-P100 amplitude were estimated according to a standard determined by the ISCEV.

P-VEP and BIS recording was started after maintaining 1.25 MAC of OS anesthesia for 20 min. We also recorded P-VEP without pattern stimulation as a negative control in dog No. 1 at 1.25 MAC. After recording at 1.25 MAC, P-VEP and BIS were recorded at 0.5, 1.0, 1.5, 2.0, 2.5 and 2.75 MAC for each dog. When the VEP waveform disappeared, we stopped recording VEP and BIS at deeper depths of anesthesia.

Statistical analysis: The P100 implicit times and N75-P100 amplitudes obtained at concentrations of sevoflurane for 0.5, 1.0, 1.5 and 2.0 MAC were analyzed by ANOVA. The statistical significance of differences was determined with $P < 0.05$ as the minimum level of acceptable significance.

RESULTS

MAC of sevoflurane and refractive power of the eye: The

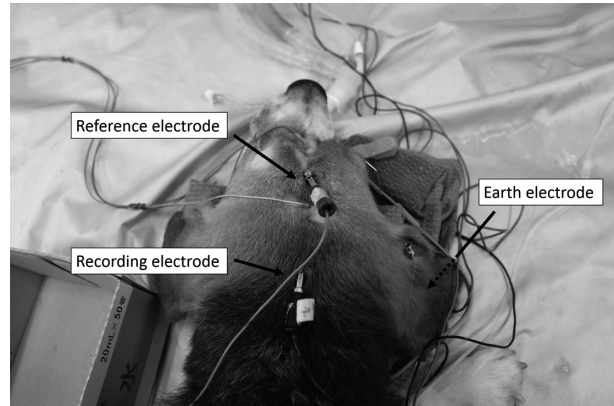


Fig. 1. Positions of the electrodes for P-VEP recording.

Table 1. MAC of sevoflurane and refractive power of the eyes in each dog

Dog No.	End-tidal sevoflurane concentration at 1.0 MAC (%)	Refractive power of eyes by skiascopy (D)
1	1.95	+1.0
2	2.87	+2.0
3	2.33	+1.0
4	2.85	+2.0
5	2.05	+0.5
6	2.65	+3.0

MAC of sevoflurane and refractive power of the eye for each dog are shown in Table 1.

P-VEP: The P100 implicit times and N75-P100 amplitudes at each concentration of sevoflurane are shown in Table 2, and P-VEP waveforms obtained from all dogs at each sevoflurane concentration are shown in Fig. 2. Graphs for the P100 implicit time and MAC and the N-75-P100 amplitude and MAC are shown in Figs. 3 and 4, respectively. P-VEP was recorded in all dogs at 0.5 to 1.5 MAC. It disappeared at 2.0 MAC in four dogs and at 2.5 and 2.75 MAC in one dog each.

The P100 implicit time at each concentration of sevoflurane is shown in Table 2. Although there was no significant

Table 2. P100 implicit time, N75-P100 amplitude, BIS value and SR at each concentration of sevoflurane

MAC of sevoflurane	P100 implicit time (msec)	N75-P100 amplitude (μV)	BIS value	SR (%)
0.5	104.3 \pm 7.8	2.29 \pm 0.57	73.8 \pm 2.6	0
1.0	113.1 \pm 13.1	3.34 \pm 1.92	56.2 \pm 4.0	0
1.25	109.3 \pm 24.0	2.67 \pm 0.96	56.0 \pm 5.4	0
1.5	110.9 \pm 24.2	2.70 \pm 0.96	55.5 \pm 14.2	5.2 \pm 10.8
2.0	104.4 \pm 2.2	3.44 \pm 1.99	43.0 \pm 32.3	37.7 \pm 39.5
2.5	87.2	1.60	25.0 \pm 2.8	43.5 \pm 2.1
2.75	not-recordable	not-recordable	88.0	9.0

Data are shown as the mean \pm standard deviation. P-VEP responses were obtained in 6 dogs at 0.5 to 1.5 MAC, in 2 dogs at 2.0 MAC and in one dog at 2.5 MAC. P-VEP responses were not obtained at 2.75 MAC, and the BIS value and SR were recorded in 6 dogs at 0.5 to 2.0 MAC, in 2 dogs at 2.5 MAC and in one dog at 2.75 MAC.

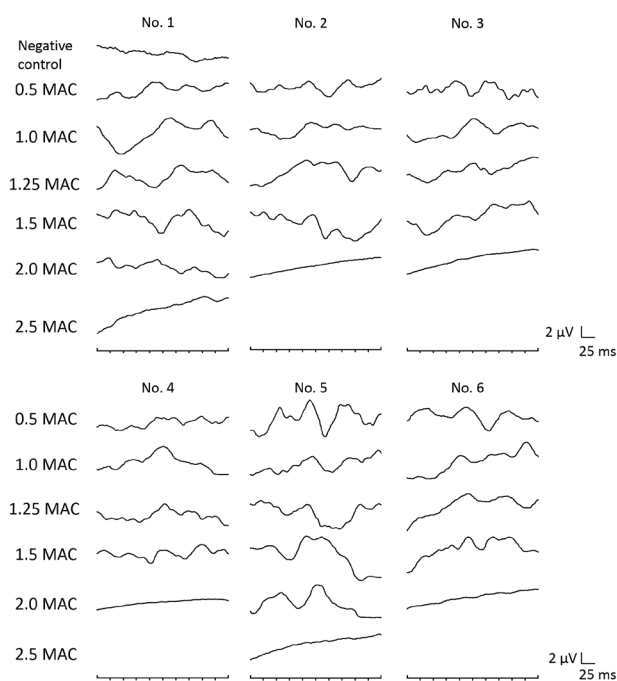


Fig. 2. P-VEP waveforms obtained from all dogs at each sevoflurane concentration and negative control of dog No. 1 at 1.25 MAC.

change in P100 implicit time at any of the concentrations of sevoflurane, the P100 implicit time showed a tendency toward prolongation with increasing concentrations of sevoflurane.

The N75-P100 amplitude at each concentration of sevoflurane is shown in Table 2. No significant change in N75-P100 amplitude was recognized at any of the concentrations of sevoflurane.

BIS value and SR: The BIS value and SR at each concentration of sevoflurane are shown in Table 2. BIS value and SR recording were performed in all dogs at 0.5 to 2.0 MAC, in two dogs at 2.5 MAC and in one dog at 2.75 MAC, because P-VEP responses disappeared at 2.0 MAC in four dogs and at 2.5 MAC in one dog.

DISCUSSION

In this study, P-VEP was recorded in all dogs from 0.5 to 2.0 MAC of sevoflurane, and there was no significant influence of different sevoflurane concentrations on P100 implicit time. Therefore, sevoflurane showed no effect on P-VEP at the concentrations normally used to produce immobilization and surgical anesthesia as demonstrated in P-VEP recording in the present study.

In the dogs in this study, the BIS value decreased from 56 to 43, and the SR began to appear and increased from 5.2 to 38%, which coincided with the decrease in BIS when the sevoflurane concentration increased from 1.5 to 2.0 MAC. At the same time, burst suppression began to appear beginning at 1.5 MAC of sevoflurane. SR and burst suppression

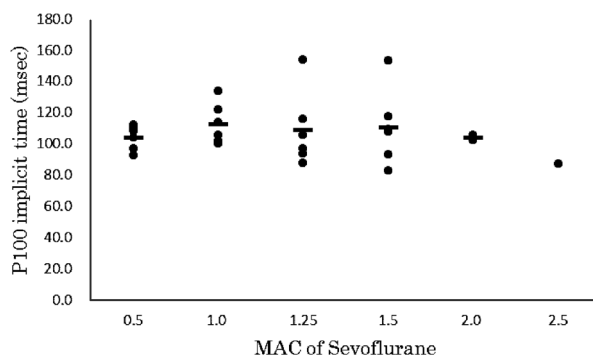


Fig. 3. The graph shows the correlation between the P100 implicit time of each dog and different MAC concentrations of sevoflurane. The plots show the P100 implicit times of each dog, and the bars show the means.

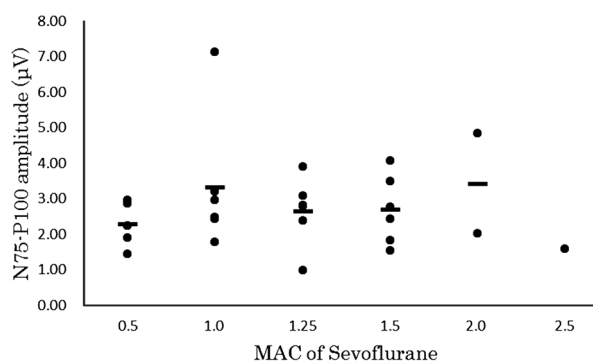


Fig. 4. The graph shows the correlation between the N75-P100 amplitude of each dog and different MAC concentrations of sevoflurane. The plots show the N75-P100 amplitude of each dog, and the bars show the means.

occur when the CNS is suppressed [1]. Thus, it is suggested that strong CNS suppression starts at 1.5 MAC of sevoflurane. In this study, a flat EEG was observed, and BIS values decreased rapidly when the sevoflurane concentration was greater than 1.5 MAC. Further increasing sevoflurane to 2.0 MAC resulted in strong suppression of the CNS as well as the visual cortex, resulting in disappearance of the VEP.

There was no significant change in P100 implicit time associated with the changes in sevoflurane concentrations. In F-VEP recording in humans, it has also been reported that prolongation of the positive peak implicit time and disappearance of the VEP signal were observed depending on the concentration of an inhalational anesthetic like sevoflurane and isoflurane [3, 12, 16]. It has been reported that a P100 implicit time is 100 msec after stimulation when visual recognition of a subject to a stimulation pattern was appropriate. But, disappearance of a VEP signal or prolongation of the P100 implicit time would be observed when a subject could not well recognize a stimulation pattern in humans [2, 23, 24]. In this study, the rights eyes of all dogs were corrected to -2 D according to the results of skiascopy to focus the

stimulus pattern after administration of a cycloplegic drug, and the effect of blur on P100 implicit time was minimized. However, no prolongation of the P100 implicit time in beagle dogs depending on the concentration of sevoflurane was observed, which is different from the report for F-VEP in humans. It was suggested that the visual function of a dog was maintained until the VEP disappeared.

There was no significant change in N75-P100 amplitude with increasing sevoflurane concentrations. It was difficult to compare the N75-P100 amplitude between dogs in this study, because the amplitudes of N75-P100 in each dog varied significantly. In F-VEP recording in humans, there are some reports showing that the N75-P100 amplitude was reduced with increasing isoflurane or sevoflurane concentrations during general anesthesia [3, 12, 16]. In contrast, it has also been reported that fluctuations of the N75-P100 amplitude varies from person to person. Even in the same subject, the values varied under light anesthesia or no anesthesia in P-VEP recording in humans [2]. Many factors, e.g., illumination in the laboratory room, the condition of the optic media, fixation to the stimulus device and drowsiness, affect the amplitude of VEP [2], thus making it difficult to evaluate the amplitude of N75-P100 in dogs as a result of the large variation [17]. At present, a consensus concerning evaluation of the amplitude of VEP has not been obtained. It would be necessary to investigate the factors affecting the amplitude further.

Sevoflurane is widely used in veterinary medicine. Based on our results, sevoflurane does not affect P-VEP recording when the concentration of sevoflurane was within the general percentages normally used for immobilization and surgical anesthesia. A number of studies have investigated the effects of various anesthetics on VEP in human medicine [3, 12, 15, 16, 20, 21]. Prolongation of the P100 implicit time in F-VEP recording is observed depending on the dosage of anesthetic [3, 12, 16], and F-VEP is useful as an index of depth of anesthesia [9]. In this study, the VEP responses of the dogs were recorded at 0.5 to 1.5 MAC. The P100 implicit time stayed at approximately 100 msec, and no significant change was recognized. A normal VEP waveform was observed up to an anesthetic depth just before VEP disappeared. Although P-VEP in dogs cannot be used as an index of the precise depth of anesthesia, the anesthetic concentrations at which P-VEP disappeared were greater than 1.2 to 1.5 MAC, which is normally the range for concentrations of sevoflurane that produce surgical anesthesia. In other words, the result of this study suggested that P-VEP is a useful indicator to determine whether a patient is too deeply anesthetized or not.

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