Laboratory Investigation

Isoflurane indirectly depresses middle latency auditory evoked potentials by action in the spinal cord in the goat

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Purpose: The auditory evoked potential (AEP) has been proposed as a method to determine depth of anesthesia, as AEPs are generated in the thalamus and cerebral cortex. Because general anesthesia, in part, relies on anesthetic action in the spinal cord, we hypothesized that isoflurane would have indirect depressant effects on the AEP because of its action in the spinal cord.

Methods: Six goats were anesthetized with isoflurane and the jugular veins and carotid arteries isolated to permit cerebral bypass and differential delivery of isoflurane to the head and torso. The AEPs were determined by delivering binaural clicks at 9Hz, and measuring the evoked response from electrodes placed in the skull and scalp. Isoflurane was maintained at 0.8% in the head while the torso isoflurane was alternated between 0.3% and 1.3%, and the AEP determined at each torso concentration.

Results: At isoflurane 0.3% delivered to the torso, the peak-to-trough amplitude of the mid-latency AEP waves designated as N14/P24 was $0.337 \pm 0.185 \mu V$ and the N36 wave amplitude was $0.115 \pm 0.054 \mu V$. When torso isoflurane was 1.3%, these waves decreased to $0.297 \pm 0.186 \mu V$ and $0.066 \pm 0.037 \mu V$, respectively ($P < 0.05$). The latency of the N14 wave increased slightly (from 13.7 ± 2.6 msec to 14.4 ± 2.8 msec, $P < 0.05$) but the latencies of the other waves were unchanged.

Conclusions: Isoflurane action in the spinal cord indirectly alters the AEP; however, the effect is small. These data suggest that isoflurane can depress the transmission of afferent information from the spinal cord to thalamus, mid-brain and cerebral cortex.

Objectif : Le potentiel évoqué auditif (PEA) a été proposé pour déterminer la profondeur de l'anesthésie, puisque les PEA sont générés dans le thalamus et le cortex cérébral. Comme l'anesthésie générale dépend, en partie, de l'action de l'anesthésique sur la moelle épinière, nous avons émis l'hypothèse que l'isoflurane avait des effets dépressifs indirects sur les PEA, puisqu'il agit sur la moelle épinière.

Méthode : Six chèvres ont reçu une anesthésie à l'isoflurane, et les veines jugulaires ainsi que les artères carotides ont été isolées pour permettre la dérivation cérébrale et l'administration différentielle d'isoflurane à la tête et au thorax. Les PEA ont été déterminés par l'administration de clics binaux de 9 Hz et les réponses mesurées au moyen d'électrodes placées sur le crâne et le cuir chevelu. L'isoflurane a été maintenu à 0,8 % au niveau cérébral mais alternait entre 0,3 % et 1,3 % au thorax et les PEA étaient déterminés pour chaque nouvelle concentration.

Résultats : Sous une concentration d'isoflurane à 0,3 % administré au thorax, l'amplitude de la crête à la base des ondes PEA de latence moyenne, désignées comme N14/P24, était de $0.337 \pm 0.185 \mu V$ et l'amplitude de l'onde N36 était de $0.115 \pm 0.054 \mu V$. Quand la concentration d'isoflurane thoracique était à 1,3 %, ces ondes ont diminué à $0.297 \pm 0.186 \mu V$ et à $0.066 \pm 0.037 \mu V$, respectivement. ($P < 0.05$). La latence de l'onde N14 a augmenté légèrement (de $13,7 \pm 2,6$ ms à $14,4 \pm 2,8$ ms, $P < 0,05$) mais les latences des autres ondes n'ont pas changé.

Conclusion : L'action, quoique faible, de l'isoflurane sur la moelle épinière modifie indirectement les PEA. L'isoflurane pourrait donc diminuer la transmission de l'information afférente de la moelle épinière vers le thalamus, le mésencéphale et le cortex cérébral.

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THE sites and mechanisms of anesthetic action are unknown. Recent evidence suggests that the spinal cord is the site where anesthetics, specifically isoflurane, suppress the movement that occurs as the result of a noxious stimulus.^{1,2} The other end-points of general anesthesia (unconsciousness, amnesia) are, likely, the result of anesthetic action in the brain at sites unknown. Nonetheless, anesthetics could indirectly affect memory and consciousness by reducing the orderly transmission of somatosensory stimuli through the spinal cord and to the brain.³ The auditory evoked potential (AEP) that arises from the background of electroencephalographic activity has been used with some success to measure indirectly the effect of anesthetics on memory and consciousness, as it appears to correlate with these two processes.⁴⁻⁶ We hypothesized that the action of isoflurane in the spinal cord could indirectly depress the AEP. We used a method by which we could differentially deliver isoflurane to the head and to the body of the goat, thereby maintaining a constant isoflurane concentration in the brain and altering the isoflurane concentration in the spinal cord.²

Methods

The study was approved by the local animal care and use committee. Six adult goats (39 ± 7 kg, mean, standard deviation) were anesthetized by mask with isoflurane. After tracheal intubation, bilateral neck dissection was performed and the jugular veins and carotid arteries isolated.⁷ The occipital arteries were ligated to prevent systemic blood from perfusing the brain, as previously described.^{2,7} This isolation method prevents systemic blood from perfusing the brain rostral to the caudal medulla.⁷ Two Y-cannulae were placed into the jugular veins to permit cranial venous blood to drain either back into the body or into a bubble oxygenator. A cannula was placed into a carotid artery to permit arterialized blood from the oxygenator to perfuse the head and brain using a roller pump. An isoflurane vaporizer was placed in line with the gas flow (O_2 95%/CO₂ 5%) to the oxygenator. The isoflurane concentration in the oxygenator arterial blood was estimated from the isoflurane concentration in the oxygenator exhaust.^{2,7,8} The end-tidal and exhaust isoflurane concentrations were determined using two calibrated anesthetic agent analyzers. An intravenous catheter was placed for administration of lactated Ringer's solution and pancuronium (0.1 - 0.2 mg·kg⁻¹, and 0.05 - 0.1 mg·kg⁻¹ every one to two hours). A catheter was placed into a carotid artery and directed towards the heart to measure systemic arterial blood pressure and for determination of glucose, blood gases and hematocrit. An

18-gauge catheter was inserted into the other carotid artery and directed towards the head to determine cranial blood pressure during bypass. Bypass was initiated by diverting cranial venous blood to the oxygenator and reinfusing the arterialized blood into the cranial circulation via the carotid cannula. The other carotid artery was ligated to prevent systemic blood from perfusing the brain. Blood flows during bypass were 200 - 500 ml·min⁻¹. Rectal and nasopharyngeal temperatures, maintained with heating lamps and the heating exchange of the bypass unit, were $36.5 \pm 0.5^\circ\text{C}$ and $36.3 \pm 0.6^\circ\text{C}$, respectively. During bypass, systemic and cranial blood pressures were 103 ± 23 and 41 ± 9 mmHg, respectively.

The AEPs were measured using a Cadwell Excel neuromonitoring machine (Bellingham, WA). Stainless steel screws (in four animals) were placed into the skull at the Cz position and at each mastoid process, with a ground electrode placed into the scalp. In the remaining two animals, needle electrodes (Grass Instruments, West Warwick, RI) placed into the scalp were used. Impedances were < 4 kOhms. Bandpass filters were set at 100 Hz to 3000 Hz. The auditory stimulus was a click (95 decibals above human hearing threshold, 0.1 msec) delivered to the ears of the goat at 9 Hz. The AEP (100 msec epoch, sampling rate 96 kHz) was the average of 1000 artifact-free sweeps. Artifacts were automatically detected and eliminated (1-3% of sweeps) using the manufacturer's default settings. At least one more set of 1000 sweeps was obtained to acquire reproducible waveforms. The AEP was displayed and recorded and the latencies and amplitudes of the resulting

TABLE I Isoflurane and auditory evoked potentials

	Torso isoflurane 0.3%	Torso isoflurane 1.3%
N14/P24		
Amplitude (μV)	$0.337 \pm 0.185^*$	0.297 ± 0.186
N36 Amplitude (μV)	$0.115 \pm 0.054^*$	0.066 ± 0.037
N14 Latency (msec)	$13.7 \pm 2.6^*$	14.4 ± 2.8
P24 Latency (msec)	23.5 ± 3.0	24.4 ± 4.3
N36 Latency (msec)	35.6 ± 5.1	37.5 ± 6.6

* $P < 0.05$ compared to value at 1.3%

TABLE II Hematocrit, glucose and blood gas values.

	TORSO	HEAD
pHa	7.33 ± 0.08	7.23 ± 0.05
PaCO ₂ (mmHg)	39 ± 6	47 ± 3
PaO ₂ (mmHg)	417 ± 174	500 ± 66
Base excess (mEq·L ⁻¹)	-5 ± 4	-8 ± 4
Glucose (mg·dl ⁻¹)	85 ± 32	87 ± 53
Hematocrit (%)	25 ± 5	26 ± 4

FIGURE 1 Replicate auditory evoked potentials in one animal with torso isoflurane equal to 0.3% and 1.3%. The N14/P24 amplitude was measured from the peak of the N14 wave to the trough of the P24 wave. The amplitude of the N36 wave was measured from the peak of the wave to the return to baseline. Latencies were measured at the respective peaks and troughs (arrows). Note that the N14/P24 wave was depressed at the greater isoflurane concentration. The N36 wave was slightly depressed. The latencies were slightly prolonged when torso isoflurane was 1.3%. The brainstem auditory evoked potential can be seen in the first 7 msec.

waveforms measured when the isoflurane concentration was 0.8% to the head, and the torso isoflurane concentration was 0.3% and 1.3%. At least 15 min elapsed after a change to a new end-tidal isoflurane concentration.

Data are presented as mean and standard deviation. The amplitudes and latencies of the mid-latency waves occurring after the brainstem AEP were averaged for each of the two torso concentrations, and the averages compared at the two torso isoflurane concentrations (0.3 and 1.3%) using a paired *t* test. Significance was assumed with a *P* value < 0.05.

Results

The mid-latency AEP consisted of three waves whose peaks generally occurred around 14, 24 and 36 msec, and are designated as N14, P24 and N36 waves. An example is shown in Figure 1. When the torso isoflurane was increased from 0.3% to 1.3%, while maintaining the brain isoflurane at 0.8%, the amplitude of each wave decreased. The data for all goats combined reveals that the amplitudes of the N14/P24 and N36 waves were depressed by increasing the torso isoflurane from 0.3 to 1.3% (Figure 2, Table I). Increasing the torso isoflurane prolonged the N14 latency; the P24 and N36 latencies were not prolonged. Hematocrit, glucose and blood gas values are shown in Table II.

FIGURE 2 Average of auditory evoked potentials from all animals. Note that the N14/P24 and N36 amplitudes were depressed when the torso isoflurane was increased from 0.3% to 1.3%.

Discussion

The midlatency AEP arises from the medial geniculate and the auditory cortex.^{9,10} The present study offers evidence that isoflurane action at the level of the spinal cord slightly depresses the AEP. Because the AEP appears to correlate with the level of consciousness and mental processing, these data further suggest that isoflurane, by its action in the spinal cord, indirectly affects the brain and its ability to assimilate and process information. What central nervous system pathways might be affected? Isoflurane has depressant effects on the spinal cord, including the dorsal horn and on the transmission of noxious and innocuous stimuli.¹¹ Decreased afferent stimulation to the thalamus, midbrain reticular formation and cerebral cortex could then decrease the level of consciousness.^{12,13} Although we did not investigate the direct cerebral effects of isoflurane on the AEP, it is likely that direct effects would dominate an indirect, spinal cord action of isoflurane.¹⁴

We do not believe that peripheral effects of isoflurane influenced the present results. Anesthetics such as isoflurane and halothane sensitize peripheral nociceptors,^{15,16} and we speculate that these actions, if anything, would tend to increase the amplitude of the AEP, opposite to what we found. Anesthetics have minimal effects on peripheral nerve conduction, and thus any effect on nerves would be minimal.¹⁷ Our use of pancuronium probably did not affect our data as non-depolarizing neuromuscular blockade has no effect on AEPs.¹⁸ The experimental preparation separates systemic circulation from the bypass circulation

at the level of the caudal medulla or upper cervical spinal cord.⁷ Thus, the present data are not likely to be affected by systemic blood reaching the midbrain, thalamus or cortex.

Kasaba *et al.* examined the effect of epidural anesthesia on early brainstem evoked responses.¹⁹ Although they did not examine mid-latency AEPs, they did find some amplitude depression and latency prolongation in the early brainstem evoked response.¹⁹ Thornton *et al.* determined that a noxious stimulus (skin incision) enhanced the midlatency AEP.²⁰ Eappen and Kissin found that spinal anesthesia decreased thiopental requirements for abolishment of responses to innocuous and noxious stimuli applied to the face and eye.²¹ Their study suggests that anesthetic blockade in the spinal cord, by depressing afferent transmission from the periphery to the central nervous system, can indirectly affect the level of consciousness.

Thiopental has depressant effects on the AEP. Schwender *et al.* administered 4 mg·kg⁻¹ thiopental and found that mid-latencies AEP were increased by approximately 50%, while amplitudes were decreased by 50%.⁶ The return of the AEP to control values coincided with return of purposeful movement. Thus, AEPs appear to correlate with consciousness when an intravenous anesthetic such as thiopental is used.

In summary, we have found that isoflurane indirectly affects the midlatency AEP but the effect is small. Because the AEP reflects mental processing, these data suggest that isoflurane action in the spinal cord might indirectly affect consciousness and memory.

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