The Effects of Sevoflurane on Lidocaine-induced Convulsions

Fujio KARASAWA

The influence of sevoflurane on lidocaine-induced convulsions was studied in cats. The convulsive threshold (mean ± SD) was 41.4 ± 6.5 mg · l^{-1} with lidocaine infusion (6 mg·kg^{-1}·min^{-1}), increasing significantly to 66.6 ± 10.9 mg · l^{-1} when the end-tidal concentration of sevoflurane was 0.8%. However, the threshold (61.6 ± 8.7 mg · l^{-1}) during 1.6% sevoflurane was not significant from that during 0.8% sevoflurane, indicating a celling effect. There was no significant difference in the convulsive threshold between sevoflurane and enflurane. The rise in blood pressure became less marked when higher concentrations of sevoflurane or enflurane were administered and the blood pressure at convulsions decreased significantly in 1.6% sevoflurane, and in 0.8% and 1.6% enflurane. However, there was no significant difference in the lidocaine concentrations measured when the systolic blood pressure became 70 mmHg. Apamin, a selective blocker of calcium-dependent potassium channels, was administered intracerebroventricularly in rats anesthetized with 0.8% sevoflurane to investigate the mechanism of the anticonvulsive effects. Apamin (10 ng) had a tendency to decrease the convulsive threshold (21.6 ± 2.2 to 19.9 ± 2.5 mg · l^{-1}) but this was not statistically significant. It is suggested that sevoflurane reduces the convulsive effect of lidocaine toxicity but carries some risk due to circulatory depression. (Key words: sevoflurane, enflurane, lidocaine, convulsions, apamin)

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Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether) has been reported to possess favorable pharmacological properties[1–3] but many more features of sevoflurane have yet to be elucidated. Although it has been reported that enflurane has anticonvulsive effects in cat models (amygdaloid kindled, penicillin and bicuculline)[4], it is not clear whether sevoflurane has such effects. Furthermore, there are few reports of the anticonvulsive effects of volatile anesthetics on local anesthetic-induced seizures[5].

Lidocaine acts as an anticonvulsant at lower doses but it also causes convulsions at higher concentrations[6] because local anesthetics are generally believed to inhibit neural activity on both excitatory and inhibitory pathways and the former are more resistant than the latter[7]. Recent study has proposed that the inhibition of gamma-aminobutyric acid (GABA) release from synaptosomes is the mechanism of lidocaine-induced convulsions[8].

In contrast to the anticonvulsive action of barbiturates which has been suggested to be hyperpolarization by enhanced GABA-mediated chloride conduction[9], inhalational anesthetics must have different mechanism(s) of anticonvulsive effects because they have no GABA-like effects[10].

Department of Anesthesia and Resuscitation, School of Medicine, Gunma University, Maebashi, Japan

Address reprint requests to Dr. Karasawa: Department of Anesthesia and Resuscitation, School of Medicine, Gunma University, 3-39-22, Showa-machi, Maebashi, Gunma 371, Japan

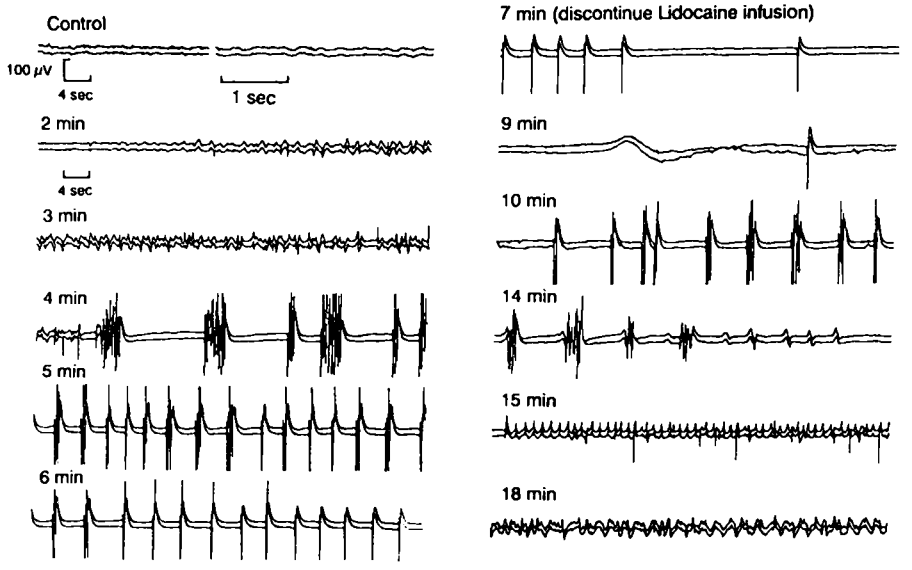

Fig. 1. The typical EEG (right and left fronto-occipital recordings) of lidocaine-induced convulsions. In this case 0.8% sevoflurane was administered. Traces are not continuous but show the entire pattern from the time of lidocaine injection until after the convulsions stopped.

A hypothesis was advanced by Godfraind[11] that the increase of calcium-dependent potassium conductance is the mechanism of volatile anesthetics in the CNS. Electrophysiological studies[9,12] have demonstrated that most volatile anesthetics induce hyperpolarization which is generated as a result of increased calcium-dependent potassium conductance which would result in decreased neuronal excitability. It has been also reported that afterhyperpolarization due to calcium-dependent potassium potential may be of importance in preventing seizure development[12]. Therefore it should be reasonable to consider that apamin, an inhibitor of the calcium-dependent potassium channel[13], may inhibit the anticonvulsive effects of inhalational anesthetic agents.

In the present study, the effects of sevoflurane and ·enflurane on lidocaine-induced seizures, and their effects on the circulatory system, were investigated in cats. The influences of apamin, administered intracerebroventricularly, were also studied in rats to investigate the mechanism of anticonvulsive effects of sevoflurane.

Methods

Experiment 1

The threshold of lidocaine-induced convulsions and corresponding cardiovascular changes were investigated in fourteen cats of either sex (weights 3.0 ± 0.5 kg). Animals were anesthetized with sevoflurane in oxygen and tracheal intubation was performed with the aid of pancuronium (initial dose 1 $mg \cdot kg^{-1}$, supplemented as required). Ventilation was controlled with a volume-limited ventilator (Harvard Pump Model No. 607). A cannula was inserted into the femoral artery to permit the monitoring of arterial blood pressure and the withdrawal of blood for blood-gas analysis and measurement of concentration of lidocaine and its metabolites. Blood-gas analysis (ABL300, Radiometer) was performed to maintain Pa_{CO_2} and arterial pH values between 34–44 mmHg and 7.33–7.44 respectively by adjustment of the tidal volume and/or administration of sodium hydrogen carbonate. Plasma proteins were also measured by refractionometer (Tsukasa) and cats whose plasma proteins

were less than 5.0 $g \cdot dl^{-1}$ were excluded from the experiment. Heart rate was monitored by the electrocardiogram (ECG). Silver chloride electrodes for EEG recording were attached bilaterally onto the frontal and occipital region with EEG paste. The ground electrode was placed over the frontal sinus. A cannula was also inserted into the radial cutaneous vein for the administration of fluid and drugs. Rectal temperature was maintained between 37–38.5°C with a heating lamp.

After preparation was completed, the end-tidal sevoflurane concentration was adjusted to either 0.4, 0.8 or 1.6 per cent using gas-chromatography (Shimazu, GC-7A, C-71B) and animals were assigned to groups of S_1, S_2 and S_3 respectively. Lidocaine was infused at least forty minutes later. In another group (S_0) the end-tidal concentration of sevoflurane was less than 0.02% when lidocaine infusion was started more than one hour after discontinuation of anesthesia.

Lidocaine for injection (4.3% solution) was made by dilution of lidocaine hydrochloride (10% Xylocaine, Fujisawa) with distilled water. Lidocaine was injected into the radial cutaneous vein at a rate of 6 $mg \cdot kg^{-1} \cdot min^{-1}$ by an infusion pump. A two channel EEG monitor (Neuropack II, Nihon Kohden) was used in the 0.3–100 Hz bandpass mode. Generalized convulsions induced by lidocaine (fig. 1) was identified by high-voltage epileptiform spike bursts on the EEG appearing synchronously in both leads and alternating with electrically quiet periods[14]. Blood samples were withdrawn 5 to 12 times during each experiment, centrifuged and the supernate frozen at minus 20°C for later analysis. The last withdrawing of blood was followed by cessation of lidocaine infusion to finish the experiment when the systolic blood pressure decreased to less than 70 mmHg. Fluid and vasopressor agents were then given to increase the blood pressure. Plasma concentrations of lidocaine and its metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX) were measured by high-performance liquid chromatography (Waters Model 510, Lambda-Ma Model 481, LC Photometer and 3390A Integrator, Hewlett Packard). Experiments were not repeated in the same cat at intervals of less than two weeks.

The same protocol was used for enflurane. Groups in which the end-tidal concentration was 0.4, 0.8 and 1.6 per cent were assigned to groups of E_1, E_2 and E_3 respectively and corresponded to the sevoflurane groups. E_0 was a group in which enflurane was discontinued after cannulation.

Experiment 2

The protocol of experiment 2 consisted of determining the effect of apamin on lidocaine-convulsion threshold during sevoflurane anesthesia. Sixteen male Wistar rats (weights 250–280 grams) anesthetized with sevoflurane in oxygen were intubated with special endotracheal tubes. Ventilation was controlled with a ventilator (Harvard Apparatus Rodent Respirator) under muscle relaxation with pancuronium (0.2 $mg \cdot 100g^{-1}$, intraperitoneally). A cannula was inserted into the femoral artery to permit blood pressure monitoring and the withdrawal of blood samples. Heart rate was monitored by the ECG. The scalp was incised and a hole of two mm diameter was made with a drill according to the atlas of Paxinos and Watson[15] (0.8 mm behind the Bregma and 1.5 mm laterally). A needle of 0.47 mm diameter was inserted gently by using a stereo-fixation apparatus (Johnson Scientific Instrument Company). Apamin was dissolved in 1 N acetic acid and diluted by physiological saline to be 10 $mg \cdot ml^{-1}$. Ten microliters of apamin (Sigma, St. Louis) or saline was injected by gravity into the cerebral ventricle[16]. The inspired concentration of sevoflurane was reduced to 0.8% just before the intracerebroventricular injection, and lidocaine was infused at a rate of 4 $mg \cdot kg^{-1} \cdot min^{-1}$ ten minutes later. The EEG was monitored in the same way as in experiment 1 but subcutaneous needle electrodes were used. When seizures were recognized on the EEG monitor screen, blood was withdrawn for blood-gas analysis and measurement of the concentration of lidocaine and its metabolites.

Differences between sevoflurane and en-

Table 1. Circulatory changes and lidocaine concentrations

Group (n)		Convulsions mean BP (%)	Convulsions HR (%)	Convulsions Lidocaine ($mg \cdot l^{-1}$)	Hypotension Lidocaine ($mg \cdot l^{-1}$)
A_0	(10)	113.6 ± 12.6	79.8 ± 13.5	41.4 ± 6.5	101.5 ± 14.2
S_1	(6)	100.9 ± 12.4	84.3 ± 16.8	54.5 ± 6.9!!	103.3 ± 12.3
S_2	(6)	100.6 ± 11.0	80.0 ± 9.2	66.6 ± 10.9!!	121.0 ± 26.9
S_3	(6)*	81.5 ± 13.7!!	75.7 ± 7.9	61.6 ± 8.7!!	99.1 ± 23.2
E_1	(6)	111.2 ± 26.5	79.2 ± 12.0	46.7 ± 6.7	111.6 ± 9.7
E_2	(6)	85.1 ± 15.2!!	77.8 ± 14.0	65.7 ± 11.9!!	106,4 ± 15.7
E_3	(6)*	84.5 ± 10.0!!	79.8 ± 9.7	64.7 ± 18.3!	97.9 ± 25.4

The symbols, ! and !!, show significant deferences ($P < 0.05$ and $P < 0.01$ respectively) versus group A_0. The symbol, *, shows that data at convulsions were tallied on n = 5.

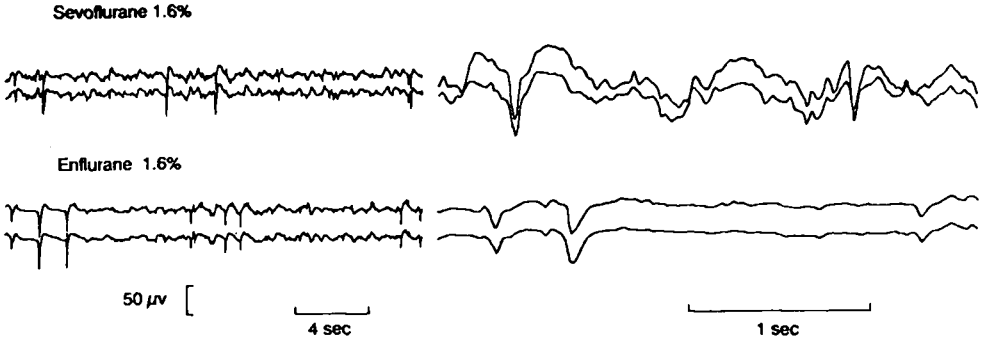

Fig. 2. Small spikes were monitored in 1.6% sevoflurane (upper) and enflurane (lower). Pa_{CO_2} was 42 and 34 mmHg respectively.

flurane groups in table 1 were tested by two-way analysis of variance (ANOVA) and other differences between the mean values were determined by Student's t-test. Results were considered statistically significant at value $P < 0.05$.

Results

Changes of the convulsive threshold

Groups of S_0 and E_0 had no significant difference in any parameters and were therefore combined as group A_0 and used in subsequent analysis (table 1). In both group S_3 and E_3 there was an animal in which the blood pressure decreased so abruptly by the intravenous lidocaine infusion that the EEG became flat without convulsions. These data were excluded in statistical analysis of convulsions in table 1.

The convulsive threshold for lidocaine was 41.4 ± 6.5 $mg \cdot l^{-1}$ in group A_0. It increased in sevoflurane groups, the highest at 66.6 ± 10.9 $mg \cdot l^{-1}$ when the end-tidal concentration of sevoflurane was 0.8% (S_2). The threshold was 61.6 ± 8.7 $mg \cdot l^{-1}$ in the 1.6% sevoflurane group (S_3), not significant by difference from the S_2 group. During administration of 1.6% Sevoflurane spontaneous low-voltage spikes (range 25 – 90 microvolts) appeared in two cats of six (fig.2), followed by epileptiform EEG after intravenous lidocaine infusion. When enflurane was administered, the threshold increased significantly to 65.7 ± 11.9 and 64.7 ± 18.3 $mg \cdot l^{-1}$ in groups E_2 and E_3 respectively. There was no significant difference between S_2, S_3, E_2 and E_3. Similar low-voltage spikes to in 1.6% sevoflurane group appeared in two cats of six in E_3

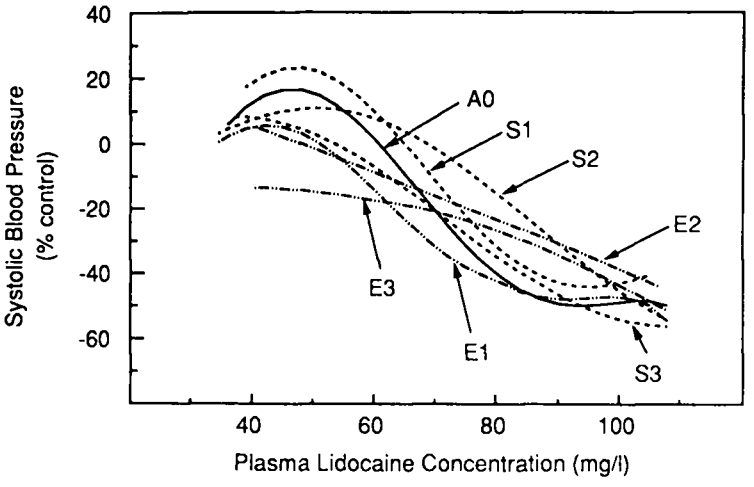

Fig. 3. The correlation between the plasma concentration of lidocaine and the systolic blood pressure derived by the least square method. Group symbols are described in text.

Table 2. Circulatory changes and lidocaine concentrations in groups of apamin (A) and saline (S)

Group (n)	mean BP (%)	HR (%)	Lidocaine ($mg \cdot l^{-1}$)
A(8)	89.9 ± 14.2	64.9 ± 6.0	19.9 ± 2.5
S(8)	91.6 ± 14.7	71.1 ± 8.6	21.6 ± 2.2

There is no significant difference between apamin group versus saline group.

before lidocaine infusion.

Cardiovascular Changes

When convulsions were identified in the EEG, the mean blood pressure increased significantly in A_0 but it decreased significantly in S_3 and E_3. There were significant differences in E_2, E_3 and S_3 versus A_0 (table 1). Heart rate decreased significantly in every group at the time of convulsions but there was no significant difference between the groups.

In figure 3 the correlation between the lidocaine concentration and systolic blood pressure is represented graphically by fourth or fifth order polynomial derived from 30.1 ± 8.1 points (range 23 – 47) using the least square method ($R > 0.81$ in every group). In A_0, S_1 and S_2 blood pressure increased typically for a while as the concentration of lidocaine increased and then it decreased gradually. The rise in blood pressure had a tendency to become less marked as higher concentrations of sevoflurane were administered. In enflurane groups the rise was less clear.

The mean concentration of lidocaine, measured when the systolic blood pressure became 70 mmHg, was 105.5 $mg \cdot l^{-1}$, having no significant differences between the groups (table 1). The concentrations of lidocaine metabolites, MEGX and GX were less than 2 $mg \cdot l^{-1}$.

There was no significant difference between any of the groups in either blood-gas analysis or the plasma protein concentrations.

Influences of apamin

The convulsive threshold for lidocaine during 0.8% sevoflurane administration was 21.6 ± 2.2 $mg \cdot l^{-1}$ in saline administered rats and 19.9 ± 2.5 $mg \cdot l^{-1}$ in apamin administered ones (table 2). This difference was not significant. The concentrations of MEGX at convulsions were 2.31 ± 0.47 and 2.15 ± 0.30 $mg \cdot l^{-1}$ in the apamin and saline groups respectively. Summations of lidocaine and MEGX concentrations, recommended as a threshold of lidocaine-induced convulsions[17], had no significant difference between saline and apamin groups. The concentrations of GX were less than 1.3 $mg \cdot l^{-1}$ in both groups, having little effect compared to lidocaine because it has only a tenth the convulsive activity of lidocaine[17]. There was

no significant difference between the groups in the mean blood pressure at convulsions. Heart rate decreased significantly in both groups but there was no significant difference between the groups.

In the apamin and saline groups arterial pH values were 7.34 ± 0.03 and 7.37 ± 0.05 respectively and Pa_{CO_2} values were 41.4 ± 2.3 and 39.7 ± 6.4 mmHg respectively, indicating controlled acid-base balance.

Discussion

In this study the threshold lidocaine concentration for convulsions in cats was 41.4 $mg \cdot l^{-1}$. The lidocaine was infused at a rate of 6 $mg \cdot kg^{-1} \cdot min^{-1}$, a rate determined in a preliminary experiment so that seizures could be induced within 15 min and changes of the circulatory system could also be measured. Others have reported the convulsive threshold of lidocaine to be 8 to 26 $mg \cdot l^{-1}$ in experiments designed to induce seizures within 5 to 20 minutes[6,18,19]. This difference in the threshold is probably due to different species and different infusion rates which will in themselves alter the threshold[20]. As acid-base balance also affects toxicity, Pa_{CO_2} and arterial pH were kept normal with a ventilator and sodium hydrogen carbonate in the present study.

About a 60% increase of the convulsive threshold concentration for lidocaine was produced by low concentrations of sevoflurane and enflurane. As the MAC of sevoflurane has been reported to be 2.58% in cats[21], similar to that of enflurane, it is apparent that sevoflurane suppresses lidocaine-induced seizures similarly to enflurane.

The circulatory changes in this study are considered to be due to the cardiovascular effects of both lidocaine and inhalational anesthetic agents[2,22]. The blood pressure rises initially due to the effects of lidocaine on the central autonomic centers[20]. Electrical excitation of the CNS induced by lidocaine is observed during pre-convulsive periods, as well as at convulsions[23]. At this stage inhalational anesthetic agents seem to attenuate the rise in blood pressure because the tendency of the rise was less marked when higher concentrations of volatile anesthetics were administered. On the other hand lidocaine directly affects the heart resulting in a decrease of electrical excitability, conduction rate and force of contractility[20]. Thus hypotension and bradycardia occurs finally as lidocaine concentrations increase. Hypotension observed in this study was associated with the high concentrations of lidocaine, suggesting that circulatory collapse may be caused by lidocaine rather than inhalational anesthetics although the latter might affect the pharmacokinetic profile of the former through cardiovascular changes[24].

Apamin, a bee venom polypeptide of 18 amino-acids, is known to block selectively the calcium-dependent potassium channel in the CNS[13]. It has been reported that apamin shows not only electrophysiological evidence of blocking calcium-dependent potassium channels but also behavioral evidence such as a decrease of anesthesia duration induced by ethanol[25]. However, apamin, administered to block calcium-dependent potassium channels in this study, had no significant influence on the anticonvulsive effect of sevoflurane. The dose of apamin was the same as reported to produce changes in behavior[25]. Although the dose is close to the toxic dose[26], larger doses of apamin could perhaps be used as apamin toxication was not observed in this study. Further studies are required to fully determine the mechanism of the anticonvulsive effects of inhalational anesthetic agents.

Although one should be cautious in extrapolating these animal data to humans, it is suggested that lidocaine-induced convulsions would be suppressed during sevoflurane or enflurane anesthesia, but the circulatory depression would likely to occur if lidocaine is absorbed continuously. Furthermore, for the treatment of seizures induced by rapid absorption of lidocaine, sevoflurane would be better than enflurane because sevoflurane produces a more rapid induction.

The author concludes that sevoflurane has an anticonvulsive effect on lidocaine-induced convulsions, and has a similar potency to enflurane. It is suggested that sevoflurane may be useful for the treatment of seizures

when administration via the respiratory system is the only route immediately available, and that sevoflurane may be better than enflurane because of more rapid induction of anesthesia. However care will be needed because of possible changes in lidocaine pharmacokinetics and effects on the circulatory system.

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