Effects of Midazolam on the Threshold of Lidocaine-induced Seizures in the Dog

—Comparison with Diazepam—

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The anticonvulsive effect of midazolam was compared with that of diazepam in ten dogs. Lidocaine-induced seizure waves on the electroencephalogram were used to observe the suppressive effect of the drugs. Midazolam, 0.2 $mg \cdot kg^{-1}$, was found to possess a stronger suppressive effect against lidocaine-induced seizures than the same dose of diazepam. These two drugs showed to possess similar effects on cerebral and systemic circulations and cerebral metabolism during seizures.
(Key words: midazolam, diazepam, lidocaine, seizures)

(Horikawa H, Tada T, Sakai M et al.: Effects of midazolam on the threshold of lidocaine-induced serizures in the dog. J Anesth 4: 265–269, 1990)

Benzodiazepine compounds have been used for the prevention and treatment of convulsions of various nature, including one induced by local anesthetics. Midazolam, being a benzodiazepine, can be expected to possess an anticonvulsive property. We observed effects of this drug on the electrical threshold of lidocaine-induced seizures in the dog, and compaired them with those of diazepam.

Experimental Methods

1) Material of the Experiment

Ten healthy mongrel dogs of both sexes, with a mean body weight of 11.7 kg, were divided into two groups of five animals each; midazolam group and diazepam group.

2) Anesthesia

Anesthesia was induced with intravenous (i.v.) ketamine 5 $mg \cdot kg^{-1}$, and the trachea was intubated after i.v. pancuronium 0.1 $mg \cdot kg^{-1}$. Anesthesia was maintained with ketamine 2 $mg \cdot kg^{-1} \cdot hr^{-1}$ and pancuronium 0.1 $mg \cdot kg^{-1} \cdot hr^{-1}$. Using pure oxygen, the animal's lungs were ventilated mechanically in order to maintain a Pa_{CO_2} level of 35–40 mmHg. Under these anesthetic conditions preparatory operations were carried out as described below.

3) Preparatory Operations

A cannula was inserted into the abdominal aorta through a femoral artery for blood pressure monitoring and blood sampling. Cannulae were placed in a femoral vein and a foreleg vein for the administration of lidocaine and benzodiazepines, respectively.

A cannula was inserted into the superior sagittal sinus for the measurement of the cerebral cortical blood flow (CBF), according to the method of Michenfelder et al[1]. The venous blood from the superior sagittal sinus was returned to the left external jugular vein through a perivascular electromagnetic flow probe. Prior to the placement of this cannula heparin 1 $mg \cdot kg^{-1}$ was given i.v. and the same amount was given every one hour thereafter.

Metal electrodes were screwed into the

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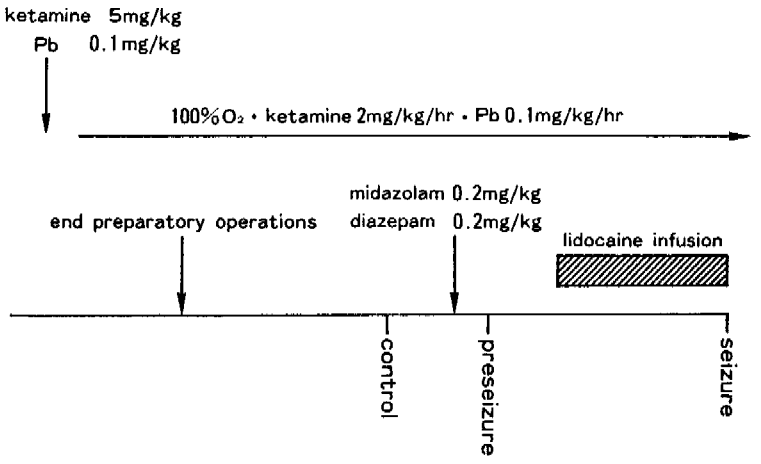

Fig. 1. Protocol of the experiment.

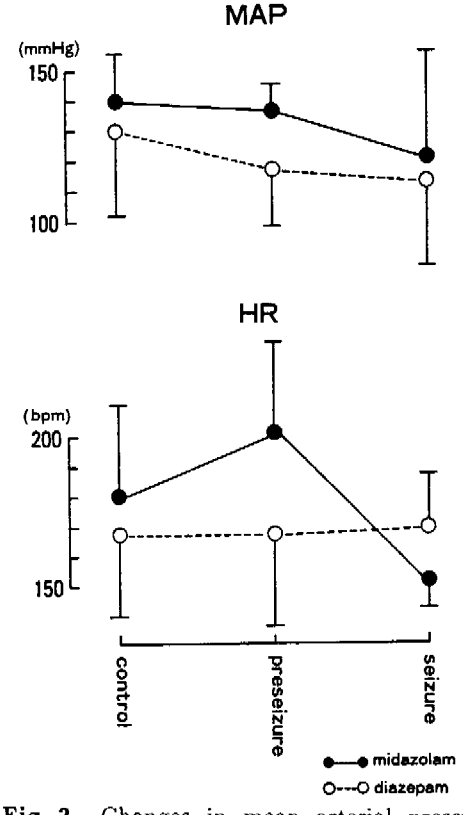

Fig. 2. Changes in mean arterial pressure (MAP) and heart rate (HR). There are no significant differences.

frontal and temporal bones in order to record bipolar electroencephalogram (EEG). A 20-gauge teflon cannula was placed in the cisterna magna for the sampling of cerebrospinal fluid (CSF). A thermal blanket was used to control the esophageal temperature within a range of 37.5–38.5°C.

4) Administration of Benzodiazepines and Induction of Lidocaine-Seizures

Following the above preparatory operations an hour was allowed to pass in order to stabilize the general condition of the animal. Following this stabilization period the dogs were randomized to midazolam 0.2 $mg \cdot kg^{-1}$ or diazepam 0.2 $mg^{-1} \cdot kg^{-1}$ given i.v. as a bolus injection.

Twenty minutes after the administration of midazolam or diazepam an i.v. infusion of lidocaine was started at a rate of 2.5 $mg \cdot kg^{-1} \cdot min^{-1}$. It was kept running until five consecutive burst-suppressions were observed on the EEG, which was regarded as the onset of seizures.

5) Monitoring, Sampling and Measurements

The blood sampling, measurement and analyses were carried out three times: (1) one hour after the end of the preparatory operations ("control"), (2) five min after the injection of either midazolam or diazepam ("preseizure"), and (3) at the time when seizure waves were observed on the EEG ("seizure"). The experimental protocol is shown in figure 1.

Mean arterial blood pressure (MAP), heart rate (HR), ECG (II lead), EEG and CBF were displayed continuously and recorded intermittently as necessary. Arterial and superior sagittal sinus blood were

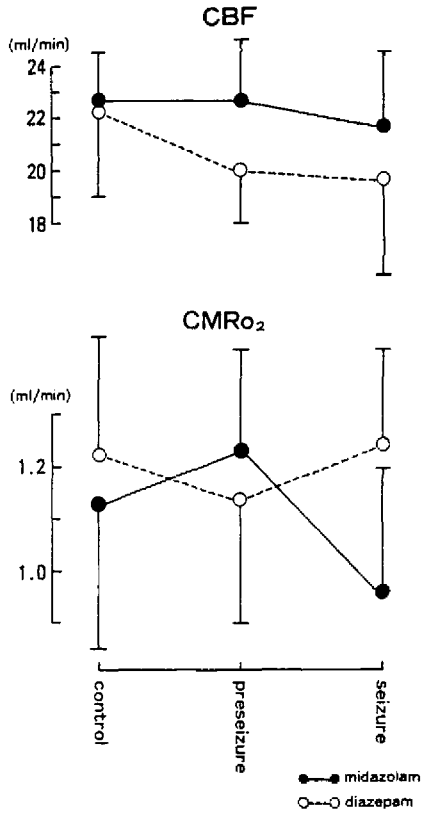

Fig. 3. Changes in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRo_2$). There are no significant differences.

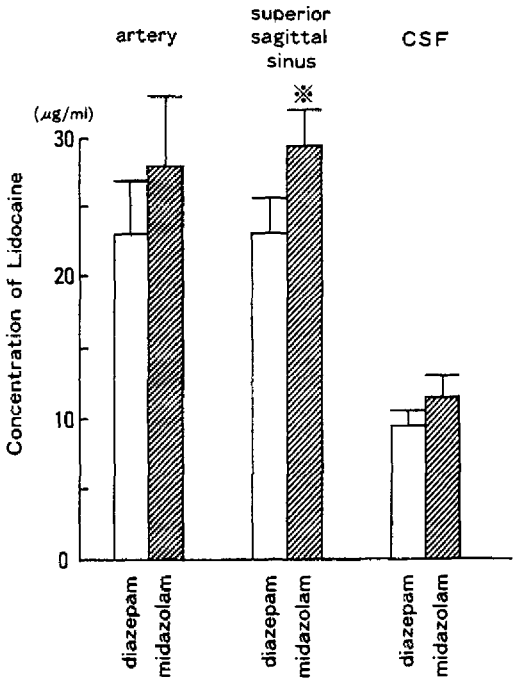

Fig. 4. Lidocaine concentrations in arterial blood, superior sagittal sinus blood and cerebrospinal fluid (CSF).

*Significant difference between midazolam group and diazepam group ($P < 0.01$).

sampled simultaneously and analyzed for pH, P_{CO_2}, P_{O_2} and O_2 content (Lex O_2 Con, Lexington). Lidocaine concentrations were measured by fluorescence polarization immunoassay (FPIA) (TDX System, Dainabot) from arterial blood, superior sagittal sinus blood and CSF which were sampled simultaneously. Cerebral metabolic rate for oxygen ($CMRo_2$) was calculated as a product of arterial-sagittal O_2 difference and CBF.

6) Statistical Analysis

Analysis of variance was used for statistical analysis and the difference was deemed significant when $P < 0.01$.

Results

MAP and HR showed no difference between the two groups at any time during the course of the experiment (fig. 2). Neither CBF or $CMRo_2$ showed any difference (fig. 3). Time required for induction of seizure waves on the EEG was 735 ± 73.6 (mean ± SD) sec for diazepam and 1071 ± 94.1 sec for midazolam, the difference being significant ($P < 0.01$). Lidocaine concentrations at the time of seizures are shown in figure 4. In the midazolam group the lidocaine concentration in the superior sagittal sinus blood was significantly higher than in the diazepam group.

Discussion

Concentrations of a local anesthetic in various compartments of the body at the time of manifestation of seizure waves on the EEG may be influenced by several factors, including 1) species, 2) anesthetics, 3) Pa_{CO_2}, 4) cerebral blood flow, 5) temperature, 6) acid-base status, etc. Some of these factors were the same (1,2) or were meticu-

lously controlled (3,5,6) in the present study.

The cerebral effects of local anesthetics are generally thought to be biphasic. At low concentrations they are anticonvulsive and at higher concentrations they provoke convulsions. Sakabe et al.[2] substantiated this concept in an electrophysiological and cerebral metabolic study in the dog. They found that $CMRo_2$ decreased to 70% of control value immediately prior to the manifestation of seizure waves on the EEG, and it increased to 112% of control value once the seizures started. Seo et al.[3] observed the behavior and electrical activity of the midbrain multineuronal reticular system of the rat during i.v. infusion of lidocaine at 1 $mg \cdot kg^{-1} \cdot min^{-1}$. They found that basic pattern of lidocaine effect has four stages: initial depression, excitation, late depression and convulsion. The present study was carried out to observe the modifying effect of benzodiazepines on the terminal EEG events induced by lidocaine, i.e., seizures.

The focus of convulsions induced by local anesthetics has been identified in many species as the limbic system. Ingvar et al.[4] observed regional cerebral glucose utilization in the rat. They found that prior to the advent of seizure waves on the EEG glucose utilization increased to a level of 3.4 times the control value in the Ammon's horn of the hippocampus. Correspondingly Tommasino[5] also found in the rat that glucose utilization increased 2 to 4 times in the Ammon's horn, CA1, CA3 and amygdala during seizures.

Benzodiazepine compounds, diazepam in particular, have been used both prophylactically and therapeutically against local anesthetic-induced convulsions. Several studies have focused on the location of the action of benzodiazepines. Eidelberg et al.[6] observed in the cat, using spectrum analysis of subcortical EEG, that the spectrum in the amygdala has a peak around 40 Hz which disappeared by the administration of diazepam. Wale et al.[7] found in the cat that lidocaine-induced seizures recorded on the EEG can be attenuated by the prior injection of diazepam in the hippocampus. In the rat diazepam has been found to decrease regional glucose utilization in the subcortical area including the hypothalamus, hippocampus and amygdala by 20–40%[8,9]. These studies seem to indicate that the focus of the action of diazepam is the limbic system of the brain. The proximity of the locus of action of the two substances, local anesthetics and benzodiazepines, may be one of the main reasons why the action of the former is suppressed by the latter.

Diazepam has been found, besides its anticonvulsive effect, to inhibit increases in CBF and $CMRo_2$ during lidocaine-induced seizures[10]. In the present study the anticonvulsive effect of midazolam was compared with that of diazepam. Midazolam, like diazepam, in the dose of 0.2 $mg \cdot kg^{-1}$, was found to suppress completely increases in CBF and $CMRo_2$ during lidocaine-induced seizures. Neither HR or MAP was significantly suppressed by midazolam, as well as by diazepam, during lidocaine-induced seizures.

As the infusion time for the development of seizure waves was longer during midazolam than during diazepam it can be concluded that a larger amount of lidocaine was necessary to induce EEG changes in the midazolam group than in the diazepam group. This is supported by the finding of a higher concentration of lidocaine in the superior sagittal sinus blood at the onset of seizures when midazolam was administered compared to when diazepam was given.

From the results of the present study it is suggested that, in the dog, 0.2 $mg \cdot kg^{-1}$ midazolam probably possesses a stronger suppressive effect against lidocaine-induced seizures than the same amount of diazepam and that the two drugs possess similar effects on cerebral and systemic circulations and cerebral metabolism during seizures.

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