Diazepam Treatment of Local Anesthetic-induced Seizures

Edwin S. Munson, M.D.,* and Irving H. Wagman, Ph.D.†

The effects of diazepam on seizure activity induced by several amide-type local anesthetic agents in rhesus monkeys have been evaluated. Lidocaine, mepipvacaine, and bupivacaine were administered intravenously at a constant rate of infusion until seizure activity began. A single intravenous bolus injection of diazepam, 0.1 mg/kg, rapidly terminated electrical seizure activity in every monkey. After brief periods of behavioral depression, the animals recovered without sequelae. Moderate respiratory and metabolic acidosis occurred in some. Heart rates and arterial blood pressures remained stable throughout the experimental period. Our findings indicate that diazepam is an effective anticonvulsant agent in dosages which have only minimal effects on ventilation and circulation. (Key words: Diazepam; Lidocaine; Mepipvacaine; Bupivacaine; Seizures; Primates; Local anesthetic toxicity.)

Diazepam (Valium), a benzodiazepine-related drug, has been used with increasing frequency in the clinical treatment of prolonged seizure activity.1-3 The administration of diazepam to laboratory animals has also been shown to protect against the development of local anesthetic-induced seizures.4-7 de Jong and Heavner8 recently reported that pretreatment of cats with diazepam (0.25 mg/kg) administered intramuscularly afforded significant protection against the convulsive effects of intravenous injection of lidocaine. As a result of their findings, they recommend that diazepam be used clinically as a premedicant for patients who will receive local anesthetics. This suggestion is appealing, since diazepam in the dosage used produced only minimal behavioral effects and did not alter cerebral electrical activity. The combination of diazepam (0.25 mg/kg) and lidocaine (less than 10 mg/kg) produced minimal cardiovascular or respiratory changes, a finding in contrast to the depression often seen following treatment of local anesthetic-induced seizures with barbiturates.9 However, the clinical usefulness of diazepam would be enhanced if, in addition to its protective effect against the development of local anesthetic-induced seizures, it could be shown that it also was effective in arresting or attenuating seizure activity without severely depressing the respiratory and circulatory systems.

We have evaluated the anticonvulsant effects of diazepam on seizure activity induced by the amide-type local anesthetic agents, lidocaine, mepipvacaine, and bupivacaine. Our findings indicate that diazepam is an effective anticonvulsant agent in dosage which has only minimal effects on ventilation and circulation.

Methods†

Twenty-seven experiments were performed on five male Macaca mulatta ranging in weight from 3.9 to 4.9 kg. For each experiment, the monkey was positioned supine in a monkey-restraining chair without prior medication. Oxygen was delivered at a rate of 5 l/min into a transparent hood (volume 2 liters) that covered the animal’s head. Inspired oxygen concentrations were not measured. Electrical activity was monitored by means of...
chronically implanted electrodes placed in the cortex and at various subcortical depths by stereotaxic techniques. Brain areas sampled included the amygdala, caudate nucleus, midbrain reticular formation, hippocampus, and precentral cortex. A single-lead ECG was also recorded.

In each monkey, a cannula was inserted into a superficial forearm vein for the continuous infusion of a glucose-balanced electrolyte solution. Local anesthetic solutions, without epinephrine, were administered with a constant-volume infusion pump through this cannula until electrical seizure activity began. On separate occasions, each monkey received both lidocaine and bupivacaine, in random order. Two animals also received meipivacaine. Intervals between experiments ranged from one to eight weeks. Lidocaine and mepivacaine were delivered at a rate of 4 mg/kg/min and bupivacaine at a rate of 1 mg/kg/min. Seizure dosage is defined as the dose of drug (expressed in mg/kg body weight) needed to evoke electrical seizure activity. With the onset of seizure, local anesthetic infusion was terminated, and diazepam, 0.05 or 0.1 mg/kg,
was administered intravenously in single, bolus injections at intervals ranging from 0.5 to 8 minutes (mean 2.5 minutes) after the onset of seizure activity. In only two instances was this interval longer than 4.5 minutes. Diazepam was always administered in the presence of generalized tonic-clonic seizures, characterized by bursts of electrical activity interspersed with electrically silent periods.

In eight experiments the saphenous artery was surgically cannulated following infiltration of the tissues with dilute local anesthetic solution. The cannula permitted continuous monitoring of blood pressure (Statham transducer), as well as intermittent withdrawal of blood. Specimens were obtained at the onset of seizure activity and, thereafter, at various intervals of 10 minutes or less, for the analysis of plasma concentrations of lidocaine and bupivacaine and arterial blood-gas and pH values. Analyses of lidocaine and bupivacaine were performed by R. N. Boyes and G. T. Tucker, respectively, using gas chromatographic methods. Measurements of $P_{aCO_2}$, $P_{aO_2}$, and $pH_a$ were made with appropriate electrodes. The base excess of arterial blood was calculated by the method of Andersen and Engel. All monkeys survived the experimental procedure without apparent sequelae. Verification of electrode placements by necropsy was subsequently made in two animals. The three remaining animals are still alive.

Results

Infusion of local anesthetic drugs induced generalized electrical seizure activity accompanied by tonic-clonic motor activity in all monkeys. As we previously had found in monkeys, there was no evidence to substantiate seizure foci with any drug. Behavioral and electroencephalographic changes with lidocaine and mepivacaine in the preseizure and postseizure periods were similar to our earlier findings.

Diazepam (0.1 mg/kg) produced rapid termination of seizure activity caused by lidocaine, bupivacaine, or mepivacaine in all animals within a minute (fig. 1). This dosage of diazepam produced mild, transitory sedation. Three animals received a smaller dose of diazepam (0.05 mg/kg), which was ineffective in rapidly terminating seizure activity. Mean seizure dosage for each drug and the duration of seizure activity after administration of diazepam are shown in table 1. In six other experiments in which animals were allowed to recover spontaneously without diazepam therapy, local anesthetic-induced seizure activity lasted 5 to 22 minutes (mean 11 minutes). The duration of this untreated seizure activity is consistent with our previous observations.

Respiratory blood-gas data before and after the administration of local anesthetics in eight experiments are shown in table 2. During the control period, moderate respiratory alkalosis ($P_{aCO_2}$ 29.6 torr) was observed. The $P_{aCO_2}$ values returned toward normal (37.4 torr, $P < 0.05$) during the infusion of local anesthetic drug prior to the onset of seizure activity. Ten minutes after administration of diazepam and cessation of seizure activity, a decreased base excess was observed in every monkey (mean change 2.9 mEq/l, $P < 0.05$). In three animals, base excesses decreased more than 9 mEq/l. No correlation between duration of seizure activity and degree of metabolic acidosis was observed.

Arterial plasma concentrations of lidocaine

### Table 1. Effects of Diazepam (0.1 mg/kg) on Duration of Local Anesthetic-Induced Seizures in Five Rhesus Monkeys*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Experiments</th>
<th>Seizure Duration (mg/kg)</th>
<th>Duration of Seizures after Diazepam (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>18</td>
<td>22.6 ± 2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>2</td>
<td>21.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>7</td>
<td>4.9 ± 1.3</td>
<td>0.4–0.5</td>
</tr>
</tbody>
</table>

* Mean weight 4.2 kg.

† Durations of seizures before administration of diazepam ranged from 0.5 to 8.3 minutes (mean 2.5 minutes). In six control animals durations of untreated seizure activity ranged from 5 to 22 minutes.

Figures represent mean and SD or range values.
Table 2. Blood-Gas and pH Values during Lidocaine- and Bupivacaine-Induced Seizures

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Seizure Onset before Diazepam</th>
<th>Ten Minutes after Diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Pressure of Carbon Dioxide (Pco₂) (torr)</td>
<td>280 ±81</td>
<td>283 ±90</td>
<td>308 ±118</td>
</tr>
<tr>
<td></td>
<td>200-400</td>
<td>131-400</td>
<td>130-420</td>
</tr>
<tr>
<td>Partial Pressure of Oxygen (Poa₂) (torr)</td>
<td>29.6 ±3.0</td>
<td>31.4 ±6.0</td>
<td>26.0 ±4.0</td>
</tr>
<tr>
<td></td>
<td>25.4-43.4</td>
<td>31.0-46.0</td>
<td>20.0-47.0</td>
</tr>
<tr>
<td>pHa</td>
<td>7.49 ±0.12</td>
<td>7.39 ±0.12</td>
<td>7.23 ±0.12</td>
</tr>
<tr>
<td></td>
<td>7.40-7.55</td>
<td>7.33-7.49</td>
<td>7.20-7.24</td>
</tr>
<tr>
<td>Base excess (mEq/l)</td>
<td>1.3 ±0.5</td>
<td>-0.9 ±0.5</td>
<td>-1.0 ±1.0</td>
</tr>
<tr>
<td></td>
<td>±0.0-6.0</td>
<td>±0.0-7.0</td>
<td>±0.0-13.0</td>
</tr>
</tbody>
</table>

* Data represent mean ± SD, and range values from eight experiments on five monkeys.
† Significant difference between groups, P < 0.05.

Diazepam is effective in reducing the severity of seizures induced by lidocaine or bupivacaine. The table shows the blood-gas and pH values before and after administration of diazepam.

Discussion

The use of benzodiazepine-related drugs in controlling seizure activity may be based on their ability to depress specific portions of the limbic system. In addition, the molecular structure of diazepam resembles that of diphenhydantoin. The Camerons believe this similarity indicates a steric basis for the anticonvulsant activities of these drugs. Most evaluations of diazepam, as well as chlor-diazepoxide (Librium), have considered this action important, in light of the observations that lidocaine-induced seizures in cats and rabbits have been shown to be preceded, and possibly initiated, by specific changes of electrical activity in the amygdala–hippocampal complex. It is of interest in this regard that our studies in rhesus monkeys have been unable to demonstrate amygdala specificity for lidocaine or other amide-type local anesthetics. If diazepam exerts its effect primarily by virtue of its action on the limbic system, its effectiveness in limiting seizure activity may be reduced when it is administered after the onset of diffuse epileptic electrical patterns. In contrast, we have shown that diazepam possesses an immediate and effective action in relatively low dosage in the treatment of local anesthetic-induced seizures. We speculate that this may indicate that the action of diazepam is due, at least partially, to a more generalized depressant action, similar to that observed with the barbiturates and inhalation anesthetics such as nitrous oxide (unpublished data). This conclusion is supported by Swinyard and Castellion, who showed diazepam and chlordiazepoxide to be effective anticonvulsants to electroshock and pentylene-tetrazol-induced seizures in mice. Sharer and Kutt also found diazepam to be capable of altering peripheral motor responses produced by intracortical penicillin foci. In experiments in the cat, during electrical stimulation of the amygdala, hippocampus, and motor cortex, Hernandez-Peon et al. found that diazepam had a generalized depressant action.

Diazepam pretreatment of laboratory animals has been shown by numerous investigators to be effective in elevating seizure thresholds to local anesthetic agents of both the ester- and amide types. Feinstein et al. showed that the intravenous administration of diazepam, 0.3 mg/kg, to cats effectively antagonized seizure activity induced by procaine. However, the combination of diazepam and a relatively high dose of procaine (250 to 300 mg/kg) given intraperitoneally resulted in a mortality rate of 23 per cent. de Jong and Heavner also reported increased morbidity, which included ataxia, apnea, and circulatory depression, in cats given the combination of
0.25 mg/kg diazepam pretreatment and a relatively large dose of lidocaine (20 mg/kg). Our observations, as well as those of others, indicate that convulsant doses of local anesthetics alone have no deleterious effects on the circulation if an adequate PaO₂ is maintained. We believe the absence of significant respiratory depression in the present study is related to the relatively low dose of diazepam used (0.1 mg/kg) and the brief duration of administration of local anesthetic.

Studies in humans with various degrees of uncontrollable epilepsy indicate a rapid intravenous action of diazepam (within one minute of intravenous injection) which, in dosage 3.5 times that used in the present study, is accompanied by rapid recovery and minimal side-effects. These observations are consistent with the lipophile nature of the drug and its rapid uptake by the brain. In our monkeys, the relatively short period of infusion of local anesthetic allowed for rapid redistribution and decrease in plasma levels when drug administration was terminated at the onset of seizures. However, during clinical practice, absorption of local anesthetics from injection sites may continue after the onset of seizure activity, with further increases in plasma drug concentration. The anticonvulsant action of diazepam and its effects on ventilation and circulation in this circumstance may not necessarily be the same as those described under the conditions of this study. Although diazepam dosage of 0.05 mg/kg was ineffective in terminating seizure activity, the possibility that diazepam in dosages less than 0.1 mg/kg might modify seizure activity cannot be excluded.

Our finding of moderate respiratory alkalosis in restrained, unanesthetized, apprehensive monkeys is consistent with the observations of others. However, with the onset of sedation and a state of light analgesia following infusion of local anesthetic drug, PaCO₂ values increased toward normal in each animal. Mean PaCO₂ values at the time of seizure onset and 10 minutes after diazepam therapy were similar to those previously reported to be normal for calm, unanesthetized, trained rhesus monkeys. The development of moderate respiratory and metabolic acidosis during relatively short periods of seizure activity is consistent with our earlier reports. The lack of correlation between the duration of seizures and the degree of acid-base disturbance, even when seizure activity is of relatively short duration and with inhalation of supplemental oxygen, emphasizes the importance of careful acid-base assessment in the clinical treatment of seizures. We believe diazepam is an effective therapeutic agent for the treatment of local anesthetic drug-induced seizures in dosages which have only minimal side-effects on ventilation and circulation.

The authors gratefully acknowledge the assistance of: Messrs. Richard W. Martucci and Perry Pugno for technical assistance; R. N. Boyes, Ph.D., and Geoffrey T. Tucker, Ph.D., for their analyses of drugs; and Jerome H. Modell, M.D., for his helpful advice in preparing the manuscript. Lidocaine (Xylocaine) for this study was supplied by the Astra Pharmaceutical Company; bupivacaine by the Sterling-Winthrop Research Institute.

References


---

**Respiration**

**ABSENT HYPOXIC PULMONARY VASOCONSTRICTION AND HEPATIC CIRRHOSIS** Evidence that patients with hepatic cirrhosis have increased pulmonary blood flow, arterial oxygen desaturation, decreased pulmonary vascular resistance, and hyperventilation has been presented. Although many explanations for arterial hypoxemia are available, none has been accepted. The shift to the right in the oxyhemoglobin-dissociation curve is not sufficient to explain the degree of desaturation. Common findings include a normal diffusion capacity, an increased alveolar–arterial oxygen tension gradient, and inability to saturate arterial blood fully during breathing of oxygen. These findings, and the results of various isotope gas studies, all favor venous admixture as the fundamental cause of the arterial hypoxemia. However, necropsy studies of patients with hepatic cirrhosis have revealed intrapulmonary arteriovenous anastomoses or portopulmonary venous communications in only a few patients. It has recently been theorized that, in the absence of a ventilatory defect, the arterial hypoxemia might be due to inappropriate distribution of pulmonary flow relative to ventilation. If the pulmonary system were not able to regulate perfusion, then the combination of arterial hypoxemia and low pulmonary vascular resistance might occur. The authors postulate that impairment of pulmonary hypoxic vasoconstriction might be responsible for both the low pulmonary vascular resistance and the resulting arterial hypoxemia in these patients. Therefore, the effects of low fractional inhalation concentrations of oxygen were studied in patients with cirrhosis, normal subjects, and finally, patients with clinical features similar to cirrhosis, i.e., increased pulmonary flow, anemia, and chronic debilitating illness. Ten patients with alcoholic hepatic cirrhosis breathed 10 per cent oxygen in nitrogen, but failed to demonstrate an increase in pulmonary vascular resistance. However, four patients with functional murmurs, three patients with hyperkinetic heart syndrome, six patients with normal pulmonary arterial pressures and intracardiac left-to-right shunts, and five patients with renal failure and anemia all increased their pulmonary vascular resistances when they breathed 10 per cent oxygen in nitrogen. These findings suggest that in hepatic cirrhosis the normal regulating mechanism of the pulmonary vascular bed, hypoxic vasoconstriction, may be impaired, resulting in failure of the lung to match perfusion to ventilation. (Daoud, F. S., Reeves, J. T., and Schaefer, J. W.: Failure of Hypoxic Pulmonary Vasoconstriction in Patients with Liver Cirrhosis. J. Clin. Invest. 51: 1076–1080, 1972.)