Diazepam Prevents and Aborts Lidocaine Convulsions in Monkeys

Rudolph H. de Jong, M.D.,* and James E. Heavner, D.V.M., Ph.D.†

Prophylaxis of local anesthetic convulsions in six rhesus monkeys was gauged by bracketing seizure-producing lidocaine doses before and after diazepam premedication. The control median intravenous convulsant dose (CD₅₀) of lidocaine was 12.5 mg/kg. Sixty minutes after 0.25 mg/kg diazepam (im) the CD₅₀ had risen by two-thirds to 21.1 mg/kg. Thirteen other monkeys were given lidocaine, iv, until status epilepticus was induced. Small iv doses of diazepam (0.05 mg/kg) consistently attenuated the intensity and duration of seizures, but terminated them in only half the cases. Larger doses of diazepam (0.1 mg/kg, iv) consistently aborted lidocaine-induced seizure activity. Diazepam both prevents and terminates lidocaine-induced convulsions in nonhuman primates; it may prove similarly effective in man. (Key words: Anesthetics, local; lidocaine; Anticonvulsants; diazepam; Hypnotics: diazepam; Complications: convulsions.)

PHYSICIANS have long relied on nonselective central nervous system (CNS) depressants such as barbiturates to prevent or treat local anesthetic-induced convulsions. Newer studies show that diazepam (Valium) instead may be the drug of choice for countering the CNS toxicity of local anesthetics.1-7 Because these newer studies deal either with diazepam’s therapeutic properties in one species, or with its prophylactic properties in another, there still is no direct basis for comparing relative dose levels. Yet such information is important to the clinician who will need guidelines, however rough, for tailoring diazepam dosages to man. To establish these guidelines, we have used lidocaine in the present study as the drug challenge, since it is a popular local anesthetic, and we have used rhesus monkeys as an animal model, since they are primates like man. A further advantage of using monkeys is that lidocaine convulsions in this species are long-lasting, so assuring a sharp therapeutic endpoint.

Our data show that intramuscular (im) premedication of nonhuman primates with 0.25 mg/kg diazepam increases tolerance to lidocaine by two-thirds, and that 0.1 mg/kg diazepam intravenously (iv) consistently arrests established lidocaine-induced convulsions.

Methods

SEIZURE PROPHYLAXIS

Six healthy male Macaca mulatta weighing 4.0 to 5.3 kg were fasted 12 hours, then positioned supine on a cross-shaped restraining frame. A 23-gauge butterfly needle was inserted into a leg or arm vein and 8.0 to 15.8 mg/kg lidocaine injected at a rate of 1 mg/kg/sec. Lidocaine dosage was increased or decreased by 0.05 log units at weekly intervals to bracket the doses that just produced and just did not produce convulsions. The 2 per cent lidocaine solution was prepared by dissolving lidocaine HCl crystals in distilled water, then bringing the pH to 7 with NaOH; no preservative was added. Generalized tonic-clonic contractions of limb and body muscles were taken as evidence of convulsions—Munson et al.8 showed these muscular signs to bear a one-to-one relationship to epileptiform bursts in the monkey’s EEG.

Next we evaluated the seizure protection afforded by diazepam (Valium; marketed by Hoffman-La Roche as a 0.5 per cent solution containing 40 per cent propylene glycol, 10 per cent alcohol, and preservatives). One or more weeks after the control studies, the monkeys were given 0.25 mg/kg diazepam, injected into

* Professor of Anesthesiology and Pharmacology.
† Assistant Professor of Anesthesiology.
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DIAZEPAM IN LIDOCAINE SEIZURES

Fig. 1. Dose–response lines of unprotected (left) and diazepam-treated (right) monkeys. Lidocaine dose (logarithmic scale) on the abscissa, cumulative frequency of convulsions (probit scale) on the ordinate. The median convulsant dose (CD₅₀) is interpolated from the lines at the 50 per cent response level. Control data points are shown as closed circles; open circles represent observations after diazepam treatment.

the thigh muscles. Forty-five minutes later they were positioned on the restraining frame and at 60 minutes lidocaine was injected intravenously. Initially, one and a half to two times the control lidocaine seizure dose was given. In subsequent weeks, the fixed dose of diazepam was followed one hour later by smaller or larger doses of lidocaine until the post-diazepam seizure threshold was bracketed.

The median convulsant dose (CD₅₀) of lidocaine was computed by probit analysis from the quantal (seizure, no seizure) observations of the control and diazepam-treated groups. Log dose–probit lines were plotted from the probit equations.

SEIZURE THERAPY

A plastic catheter was inserted into the saphenous or femoral vein of 14 additional rhesus monkeys (4.2 kg average weight) anesthetized briefly with halothane. Both legs were then wrapped with elastic bandages to prevent dependent edema, and the animals seated in a restraining chair. The indwelling catheter was kept patent by trickling 5 per cent glucose solution through it (100–120 ml/day) with a Sigmamotor pump.

Three to seven days after surgery, 20, 25, or 31.6 mg/kg of the 2 per cent lidocaine solution were injected through the catheter at a rate of 1 mg/kg/sec while the animal breathed oxygen from a plastic hood. Lidocaine was increased at 3- to 5-day intervals until it caused protracted convulsions lasting at least 7 minutes. Time of seizure onset and seizure duration, along with intensity and frequency of clonic episodes, were noted to appraise the duration and severity of untreated convulsions. (Some seizures had to be terminated with diazepam because of the animal’s deteriorating condition.)

One week later the convulsant lidocaine dose was repeated. After seizures started we waited one minute to let them become fully established, then gave 0.05 or 0.1 mg/kg diazepam (commercial 0.5 per cent Valium diluted with propylene glycol to 0.1 per cent) as an intravenous bolus. The effects of
TABLE 1. Control Observations

<table>
<thead>
<tr>
<th>Lidocaine Dose (mg/kg, iv)</th>
<th>Protracted Seizures (No. of Monkeys)</th>
<th>Mean Seizure Duration* (Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0</td>
<td>5/9</td>
<td>&gt;15</td>
</tr>
<tr>
<td>25.0</td>
<td>12/13</td>
<td>&gt;21</td>
</tr>
<tr>
<td>31.6</td>
<td>1/1</td>
<td>&gt;24</td>
</tr>
</tbody>
</table>

* Several prolonged convulsions had to be terminated prematurely because of the animal’s deteriorating physical condition. Durations of untreated convulsions thus are minimum estimates.

repeated 0.05 mg/kg doses of diazepam were studied in four animals.

Respiratory depression or apnea was treated by ventilating the lungs with oxygen, delivered via a self-inflating bag and mask set. If the heart sounds became faint, external cardiac massage was applied till the heart beat strongly again.

Results

SEIZURE PROPHYLAXIS

Every untreated monkey convulsed after a sufficient intravenous dose of lidocaine. The control lidocaine \( CD_{25} \) was 12.8 mg/kg, with 95 per cent fiducial limits of 11.3 to 14.4 (fig. 1).

Intramuscular injection of 0.25 mg/kg diazepam had no noticeable effect on animal behavior during the one-hour observation period preceding lidocaine administration. Nevertheless, this dose of diazepam provided significant protection against lidocaine-induced seizures. Only one of six diazepam-treated monkeys convulsed when 17.8 mg/kg of lidocaine were injected intravenously, compared with a 100 per cent seizure incidence (6/6) when given to untreated animals. The post-diazepam \( CD_{25} \) was 21.1 mg/kg, with 95 per cent fiducial limits of 19.3 to 23.1 (fig. 1). The 65 per cent increase over the control \( CD_{25} \) was significant at the .01 level. With or without diazepam treatment, seizure onset progressed in similar fashion. First the monkeys developed nystagmus and looked stunned; next they blinked their eyelids rapidly, and the scalp and facial muscles began to twitch. Then tonic–clonic contrac-

tions of limb and trunk muscles began, increasing in intensity, duration and frequency during the first minute. Time to onset of seizures after lidocaine injection was not significantly altered by diazepam treatment—in untreated animals seizures started within 14 to 54 seconds (mean = 31.4), in diazepam-treated animals within 7 to 90 seconds (mean = 38.9). However, seizures were less violent when the monkeys were pre-treated with diazepam.

SEIZURE THERAPY

To produce the status epilepticus-like state with which to test diazepam’s anticonvulsant properties, more lidocaine had to be given than in the preceding series. Though nine monkeys convulsed after a 20 mg/kg bolus of lidocaine, the seizures terminated spontaneously within 7 minutes in four of the nine (table 1). On the other hand, all but one monkey (which required 31.6 mg/kg) convulsed for 10 minutes or more when given 25 mg/kg lidocaine. Convulsions usually began as the lidocaine injection was finished, and continued at a rate of 6 to 10 per minute. Ictal periods lasted 2–5 seconds, each preceded by facial twitching, muscle stiffening, nystagmus, and pupillary dilation. The accompanying chest-wall spasm impeded respiration, and when seizures lasted beyond 4 to 6 minutes the mucosal membranes often turned bluish pale, preoxygenation notwithstanding. Part of the problem seemed to result from accumulation of oropharyngeal secretions.

As seizures continued, muscle spams gradually weakened. The end of gross seizure activity was heralded by “pill-rolling” pronator movements of the upper limbs. Twitching of the ears, blinking of the eyelids, and concomitant pupillary dilation persisted beyond that for another 1 to 3 minutes.

Table 2 condenses the observations made when diazepam was given shortly after the onset of lidocaine-induced convulsions. Though 0.05 mg/kg diazepam aborted convulsions induced by 20 mg/kg lidocaine, it was effective only in slightly more than half the instances where 25 mg/kg was given. Even though this small dose of diazepam did not always stop convulsions, it always reduced the severity
of the fits and lengthened the interictal interval.

The 0.1 mg/kg dose of diazepam always aborted convulsions. Even if it did not immediately stop a seizure, the next ictal attack consistently was less severe than the one just before diazepam. That is, gross motor movements after 0.1 mg/kg diazepam were less pronounced, the attack itself was briefer (lasting 2–3 seconds at most) and the interictal interval lengthened progressively. The diazepam bolus, though it often further emphasized interictal muscle weakness, improved the animal’s appearance as soon as seizures stopped. Respiration rapidly strengthened and color returned to normal. Troublesome oral secretions also were reduced by diazepam.

While 0.1 mg/kg diazepam immediately abated seizure intensity, a few minutes usually lapsed before seizures stopped altogether. (Only once did 0.1 mg/kg diazepam immediately halt seizures.) As is evident in Table 2, this latency to full effect (time from diazepam injection to complete cessation of seizures) was the longer the larger the lidocaine dose.

In the four cases where 0.05 mg/kg diazepam did not stop convulsions induced by 25 mg/kg lidocaine, we gave a second dose of diazepam 2½ to 5 minutes later. The second dose further decreased the intensity and duration of the ictal periods, terminating seizures altogether in three monkeys. The fourth monkey required a third 0.05 mg/kg dose of diazepam before seizures were arrested.

The circulatory and respiratory effects of the large doses of lidocaine used were profound. Whereas the nine monkeys which received 20 mg/kg lidocaine required nothing more than oxygen inhalation, five of 13 monkeys given 25 mg/kg lidocaine needed ventilatory assistance and external cardiac compression. Four of ten monkeys given 25 mg/kg lidocaine followed by 0.1 mg/kg diazepam required cardiac massage; results for one which died subsequently are eliminated from the series.

**Discussion**

The efficacy of diazepam both in preventing and in terminating lidocaine-induced convulsions in a single species (monkeys) is evident from the present report. Our findings, combined with those of others, seem to justify generalization of diazepam’s anticonvulsant actions to local anesthetics as a class. Seizure prophylaxis, for instance, has already been demonstrated for procaine, cocaine, tetra- cocaine, lidocaine, and mepivacaine$^{1,2,3}$; seizure therapy for procaine, tetracaine, lidocaine, mepivacaine, and etidocaine.$^{1,2,4}$ It also has been shown that diazepam prophylaxis produces fewer undesirable side effects than an equiprotective dose of barbiturate,$^{1,2,5}$ and that diazepam therapy of convulsions has only minimal effects on ventilation and circulation.$^{1}$

As might be expected, the longer the delay between onset of convulsions and diazepam injection, the more rapidly seizures terminated. Likewise, seizure activity persisted longest when diazepam was given as soon as convulsions began. We attribute the relationship between seizure duration and anticonvulsant latency to the decrease in local anesthetic blood (and presumably brain) level with time. Supporting this view is the additional observation that the larger the dose of lidocaine, the greater the latency of diazepam effect.

How diazepam controls local anesthetic-induced convulsions is by no means settled yet. We$^{1}$ have proposed that diazepam exerts its effect by quieting the limbic seizure focus that is generated by local anesthetics in cats.

dogs, rabbits and rats. Munson et al.,\textsuperscript{4} conversely, unable to pinpoint a similar seizure focus in monkeys, attributed diazepam’s anticonvulsant properties to a general cerebral depressant effect in this species. Tseng and Wang,\textsuperscript{10} on the other hand, presented evidence for a brainstem reticular formation site of action of diazepam. Their assumption is strengthened by the work of Wale and Jenkins,\textsuperscript{2} who demonstrated that diazepam prevents lidocaine seizures consistently only when injected directly into the brainstem reticular formation.

Diazepam’s potential role in treating local anesthetic-induced convulsions in man can only be weighed against this experimental background. The work by Usubiaga and colleagues\textsuperscript{11} established that local anesthetic-induced convulsions impede respiration in man. This, along with the lowered seizure threshold and prolonged seizure activity that accompany respiratory and metabolic acidosis,\textsuperscript{9,12} makes assisted or controlled ventilation with oxygen the mainstay in treating a toxic reaction. And oxygen alone is often ampler therapy.\textsuperscript{13}

But what if seizures persist? Usubiaga et al.,\textsuperscript{4,11} though finding in their patients no adverse effect of brief seizures properly treated, nevertheless recommended anticonvulsant therapy for prolonged local anesthetic-induced seizures in man. Current practice is to inject a barbiturate (often thiopental) to stop seizure activity. Experimentally, however, equi-prophylactic doses of pentobarbital potentiate the cardiorespiratory depressant effects of local anesthetics more than does diazepam.\textsuperscript{1,4,5,7} This, combined with its minimal CNS effects under the same conditions, gives diazepam an apparent therapeutic edge over oxybarbiturates. Although the adverse systemic effects of equitherapeutic doses of thiopental and diazepam remain to be compared, Munson and Wagman\textsuperscript{6} certainly showed those of diazepam to be minimal.

As diazepam seems to be as effective in prophylaxis as it is in therapy of toxic CNS reactions to local anesthetics, it has much to recommend it to the clinician using these drugs in his practice.

References