Effect of lidocaine after experimental cerebral ischemia induced by air embolism

DELBERT E. EVANS, PH.D., PHILIP W. CATRON, M.D., JAMES J. McDERMOTT, M.S., LINDA B. THOMAS, B.S., ARTHUR I. KOBRIE, M.D., PH.D., AND EDWARD T. FLYNN, M.D.

Diving Medicine Department, Naval Medical Research Institute, Bethesda, Maryland, and Department of Neurological Surgery, George Washington University Medical Center, Washington, D.C.

To investigate possible approaches to the treatment of neural damage induced by air embolism and other forms of acute cerebral ischemia, somatosensory evoked potentials (SEP's) were measured after cerebral air embolism in the anesthetized cat. Air was introduced into the carotid artery in increments of 0.08 ml until the SEP amplitude was reduced to approximately 10% or less of baseline values. Either a saline or lidocaine infusion was begun 5 minutes after inducing cerebral ischemia. In the saline-treated group, SEP amplitude was reduced to 6.7% ± 1.6% (mean ± standard error of the mean) of baseline, with a return to 32.6% ± 4.7% of baseline over a 2-hour period. In the lidocaine-treated group, SEP amplitude was reduced to 5.9% ± 1.5%, with a return to 77.3% ± 6.2% over a 2-hour period. The results suggest that lidocaine administration facilitates the return of neural function after acute cerebral ischemia induced by air embolism.

KEY WORDS: lidocaine • air embolism • somatosensory evoked potentials • cerebral ischemia • cat

Cerebral air embolism in the cat has been used to study the pathophysiology of acute cerebral ischemia.17-22 Although clinical cases of cerebral air embolism are not common, such cases can occur in individuals during deep-sea diving and in others exposed to increased atmospheric pressure.10,11,17 Cerebral air embolism has been reported during surgery and other invasive procedures when air gains entrance into the systemic circulation.7,12,41 Air embolism has also been used in animals as a model of acute stroke. In comparing the pathophysiology resulting from various forms of experimental cerebral ischemia, Fritz and Hossmann24 found that air embolism combines elements of both inflow occlusion and microembolic forms of cerebral ischemia. Thus, cerebral ischemia induced by air embolism may be relevant not only to clinical cases of air embolism, but to other forms of acute cerebral ischemia as well.

In previous studies it was found that pretreating animals with intravenous lidocaine greatly attenuated the cardiovascular and autonomic responses to air embolism.19 Because these results suggest that lidocaine was providing generalized protection from cerebral air embolism, further studies were conducted to determine if lidocaine would protect neural function against cerebral ischemia.18,20 With somatosensory evoked responses used as a measure of neural function, it was found that pretreating animals with lidocaine greatly reduced the decrement and facilitated the return of neural function as compared to untreated animals. While this study demonstrated a protective effect of lidocaine, it did not address the question of efficacy of lidocaine when given after the acute ischemic insult, an effect that would have the greatest clinical relevance. The present study was conducted to determine if lidocaine would facilitate the return of neural function when given after the onset of acute cerebral ischemia induced by air embolism. A preliminary summary of this work has been published.39

Materials and Methods

The experiments described here were conducted according to the principles set forth in the National Institutes of Health “Guide for the Care and Use of Laboratory Animals.” Male and female adult cats, each weighing 2.4 to 4.5 kg, were used for this study. Anesthesia was induced by an intramuscular injection of ketamine HCl (0.15 mg/kg) and was followed by an intravenous injection of alpha-chloralose (80 to 100
mg/kg) dissolved in warm saline. Ventilation, temperature control, and cardiovascular monitoring were performed as in previous studies. For infusion of air into the carotid circulation, the lingual artery was cannulated in a retrograde direction with a PE-50 catheter and the tip of the catheter was advanced into the left common artery to a position below the origin of the ascending pharyngeal artery. The external maxillary artery was ligated so that air would be directed into the internal maxillary and ascending pharyngeal arteries. Since the internal carotid artery is vestigial in the adult cat, these two arteries provide the main blood supply to the anterior portion of the brain. Using the lingual artery to access the carotid artery allowed air emboli to be introduced into the otherwise unobstructed blood flow to the brain.

The methods used for amplifying, recording, and measuring somatosensory evoked potentials (SEP's) were the same as in previous studies. In brief, SEP's were obtained by applying a stimulus (8 V for 0.5 msec at 1 Hz) to the right sciatic nerve and recording responses from left temporal and indifferent (frontal) screw electrodes. Each recorded response was an average of 32 SEP's obtained at 1-second intervals. The amplitude from the major positive peak (P2) to the major negative peak (MN) was used as an index of cerebral ischemia (Fig. 1). This amplitude, which has frequently been called the P2-MN amplitude, is thought to be generated by the cerebral cortex, and has been shown to correlate well with critical levels of cerebral blood flow.

To produce a standardized degree of ischemia against which drug therapy could be evaluated, 0.08-ml increments of air were infused into the carotid artery until the SEP amplitude was reduced to less than 10% during a 15-minute period. The sequence of air infusion and SEP recording is illustrated in Fig. 1. The SEP amplitude was kept below 10% for the 15-minute period by additional infusions of air, if needed.

Five minutes after the period of ischemia (20 minutes after the start of the experiment), an infusion of either lidocaine or saline was begun. The sequence of numbers from a random number table determined which of these two solutions was administered during a given experiment (even numbers received lidocaine, odd numbers received saline). The investigators conducting the experiment and measuring the SEP data were kept blinded from this information. For the lidocaine infusion, lidocaine HCl for intravenous infusion (Xylocaine, 40 mg/ml) was diluted with saline and administered by an infusion pump according to a three-step schedule of administration that has been shown to quickly achieve and maintain a therapeutic blood concentration (2 to 4 μg/ml) of lidocaine. The rate of administration was as follows: 1.5 mg/kg over the first 5 minutes, 3.0 mg/kg over the next 25 minutes, and 1.0 mg/kg every 30 minutes for the duration of the experiment. This regime has been found to produce a mean blood concentration (± standard error of the mean, SEM) of 4.13 ± 0.23 μg/ml lidocaine over a 2-hour period in cats (unpublished observations). In the control experiments, saline was administered to the animal at the same rate and volume as the lidocaine infusion.

In addition to the experiments described above, a small number of experiments were conducted to confirm the stability of the evoked response measurement over time and to determine the effect of lidocaine alone on the SEP's. These animals were subjected to the same procedure as the lidocaine- and saline-treated groups except that the lingual artery was not cannulated and air was not infused into the carotid artery.

The statistical analysis of the SEP data was performed in the following manner. First, the mean and SEM of SEP amplitudes at each measurement point were determined for both groups. These values were used to construct the illustrative figures. Second, an analysis of variance (ANOVA) with repeated measurements was performed by computer using BMDP programming to determine whether the values over the entire observation period were different for the control and lidocaine- or saline-treated groups. The statistical analysis of the SEP data was performed in the following manner. First, the mean and SEM of SEP amplitudes at each measurement point were determined for both groups. These values were used to construct the illustrative figures. Second, an analysis of variance (ANOVA) with repeated measurements was performed by computer using BMDP programming to determine whether the values over the entire observation period were different for the control and lidocaine-treated groups.
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TABLE 1
Comparisons of physical and physiological measurements between control and lidocaine-treated groups*

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Weight (kg)</th>
<th>pH</th>
<th>pO₂ (mm Hg)</th>
<th>pCO₂ (mm Hg)</th>
<th>Temp (°C)</th>
<th>Vol. of Air (cc)</th>
<th>SEP (% of baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>3.47 ± 0.18</td>
<td>7.36 ± 0.01</td>
<td>93.28 ± 3.38</td>
<td>29.68 ± 1.38</td>
<td>37.6 ± 0.03</td>
<td>0.43 ± 0.06</td>
<td>6.69 ± 1.63</td>
</tr>
<tr>
<td>lidocaine</td>
<td>3.35 ± 0.20</td>
<td>7.37 ± 0.01</td>
<td>94.34 ± 3.51</td>
<td>29.41 ± 1.26</td>
<td>37.7 ± 0.04</td>
<td>0.33 ± 0.05</td>
<td>5.88 ± 1.54</td>
</tr>
<tr>
<td>t-value</td>
<td>0.46</td>
<td>0.07</td>
<td>0.22</td>
<td>0.143</td>
<td>1.18</td>
<td>1.25</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Values are the mean ± standard error of the mean for nine animals in each group. SEP = somatosensory evoked potentials. pH, pO₂, and pCO₂ values are those immediately before air embolism. Temperature is the average of measurements taken at 5-minute intervals throughout the 2-hour experimental periods. Significance of difference by t-test is given for comparison of each measurement between control and lidocaine-treated groups.
† Significant difference (p = 0.05).

Results
Repeated infusion of small increments of air into the carotid artery produced a graded decrement of SEP amplitude in this model. Figure 1 illustrates a typical SEP obtained before and after successive infusions of air into the carotid artery. From the example given it can be seen that each air infusion did not produce a linear decrement in SEP amplitude, but that by measuring the effect of each infusion it was possible to titrate the amount of air needed to reduceSEP amplitude to a relatively standard level.

The average change of SEP amplitude for both groups over a 2-hour period is illustrated in Fig. 2. In the saline-treated (control) group, the average SEP amplitude was reduced to 6.7% of pre-air embolism value with a return to 32.6% over the 2-hour period. In the lidocaine-treated group, the SEP was reduced to an average of 5.9% of the amplitude recorded prior to air embolism with a return to 77.3% over the 2-hour period. The ANOVA revealed that the recovery of the SEP in the lidocaine-treated group was significantly greater than that in the control group (p = 0.001).

During the period of ischemia before drug infusion (from 0 to 20 minutes after the start of the experiment), the average mean blood pressure was 95.1 ± 4.6 mm Hg in the control group and 94.7 ± 3.3 mm Hg in the lidocaine group. After beginning drug infusion, the average mean blood pressure for the remaining 100 minutes was 107.9 ± 2.3 mm Hg in the control group and 97.1 ± 1.4 mm Hg in the lidocaine-treated group. Comparisons of these averages by t-test revealed no significant difference between groups during the first 20 minutes (t = 0.071, p > 0.05), but there was a significant difference of approximately 11 mm Hg over the remaining 100 minutes (t = 3.996, p < 0.05).

The two groups were comparable with regard to weight, blood gas measurements, body temperature, and amount of air infused. Table 1 gives the average of each of these measurements and the SEP amplitudes at 15, 60, and 120 minutes for both groups. Comparisons of the data in Table 1 by t-test revealed no significant differences between the control and lidocaine-treated groups except for the recovery of the SEP.

To determine the effect of lidocaine alone on the SEP without ischemia, five additional experiments were conducted. In these experiments, the SEP was measured every 15 minutes for 1 hour before and 2 hours during an infusion of lidocaine that was identical to that received by the lidocaine-treated ischemic group. During the hour before lidocaine administration, SEP amplitude averaged 94% ± 0.77% of baseline value. An ANOVA indicated no effect of time on the SEP amplitude (p = 0.276). During the 2 hours after beginning lidocaine administration, SEP amplitude averaged 92% ± 1.2% of baseline value. The ANOVA revealed no significant effect of either lidocaine infusion (p = 0.245) or time (p = 0.649) on the amplitude of the SEP.
Discussion

Use of the SEP amplitude as an index of neuronal function in this study was based on previous evidence demonstrating it to be sensitive to cerebral ischemia induced by hypotension, to hypoxia induced by decreased inspired oxygen concentration, and to spinal cord compression. Others have shown a strong correlation of this measurement with critical levels of cerebral blood flow in models using occlusion of the middle cerebral artery and in models using cerebral air embolism. In a recent editorial, Ropper discussed the usefulness and limitations of evoked potential monitoring in experimental cerebral ischemia. He noted that changes in the SEP do not reflect the fundamental pathophysiology of cerebral infarction, but can be used as indicators of reduced cerebral blood flow or metabolic impairment of brain tissue. Even with some limitations of SEP recordings, he suggested that improvement in SEP amplitude resulting from therapy would be convincing evidence of benefit.

When comparing the recovery of the SEP in both groups, it is clear that the lidocaine-treated group had a considerably greater return of neural function than did the control group, which received only saline. The effect of lidocaine in improving SEP recovery was suggested as early as 30 minutes after beginning air embolism (10 minutes after beginning lidocaine administration), but the differences between SEP recovery were not statistically different until 60 minutes (40 minutes after beginning lidocaine infusion). Other measured differences between the control and the lidocaine-treated groups were small. The control group had a slightly higher mean body weight and required slightly more air to suppress the SEP than the lidocaine-treated group, but these differences were not statistically significant. Although there were no significant differences in blood pressure before drug administration, the blood pressure of the lidocaine-treated group was significantly lower than that of the group receiving saline after beginning these infusions. It is unlikely that the slightly lower blood pressure in the lidocaine-treated group was involved in the greater return of SEP of that group.

Because it was found that lidocaine had a rapid effect on the return of the SEP after ischemia, the additional experiments were conducted to establish the stability of the SEP measurement over time and to determine whether lidocaine had any effect on that measurement. Results indicating an insignificant decrease in SEP amplitude during 2 hours of lidocaine infusion essentially ruled out a direct effect of lidocaine on the SEP measurement.

Results from this study extend previous findings, which showed that lidocaine had a protective effect on neural function when given before air embolism. The present study suggests that lidocaine is also effective in facilitating the return of neural function when given immediately after the ischemic event. The mechanisms by which lidocaine was effective is unknown. Two separate actions seem possible: an action on cerebral blood vessels or an action on neural membranes and cerebral metabolism. With regard to the first possibility, lidocaine has been shown to cause both vasodilation and vasoconstriction depending upon the dose, the method of administration, and the vascular bed being studied. However, intravenous lidocaine has been found to sharply decrease the elevated intracranial pressure induced by air embolism of the posterior cerebral circulation, an effect suggesting a vasoconstrictive action of the drug. If intravenous lidocaine causes cerebral vasoconstriction, it is unlikely that such an action would facilitate return of neural function after air embolism.

A more likely mechanism may be related to the ability of lidocaine to stabilize neural membranes and reduce cerebral metabolism. In reviewing his own and other work, Astrup has suggested that high doses of lidocaine, like hypothermia, reduce cerebral metabolism by several mechanisms. First, lidocaine decreases cerebral metabolism by inhibiting electrocortical activity with a consequent decrease in oxygen and glucose consumption. This action has been described by Astrup, et al., as a “barbiturate-like effect.” Second, lidocaine has a specific membrane-sealing or stabilizing effect that restricts the movement of sodium and potassium across the membrane and thus reduces the metabolic demand of the active transport systems for these ions. This latter effect has further been shown to reduce the extracellular accumulation of potassium in the ischemic brain. In his review, Astrup, et al., suggested that membrane failure induced by ischemia may be a key step in the irreversible damage to neural cells. Therefore, the ability of lidocaine to inhibit or delay membrane failure may be involved in protecting neurolog onal function. Astrup used high doses of lidocaine to demonstrate these effects; however, other studies have shown that, even at low doses, lidocaine has both of these effects. Perhaps most relevant to the present study is the work of Fink and Schimek, who demonstrated that lidocaine preserved neuronal conduction in isolated nerves subjected to glucose-free solutions by inhibiting the leak of potassium out of, and sodium into, the nerves. Fink also found that, after nerve excitability had been extinguished by incubation in glucose-free solutions, the addition of lidocaine to the perfusate resulted in partial return of nerve function. Both the protective and restorative effects of lidocaine occurred at a lidocaine concentration of 0.1 mmol/liter, which roughly corresponds to a blood concentration in the whole animal of 2.5 μg/ml, a level that would be obtained by intravenous lidocaine administration.

In contrast to the present findings, a recent study by Shokunbi, et al., found that lidocaine in doses sufficient to suppress or flatten the electroencephalogram had no protective effect on the severity of ischemic neuronal injury after middle cerebral artery occlusion. Histochemical and histological techniques were used to assess neuronal injury after 4 to 6 hours of artery

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occlusion in cats. It is difficult to determine the relevance of these results to the present findings because Shokunbi, et al., used high doses of lidocaine (approximately 15 times the dose used in this study), a much greater severity of ischemic injury (4 to 6 hours of occlusion), and measurement of histopathology as compared to the measurement of neural function (SEP’s). However, Gelb, et al., more recently reported the results of a preliminary study in which they found that a single bolus of lidocaine provided transient protection of the evoked potentials after middle cerebral artery occlusion in cats. In another preliminary study, Dutka and colleagues found that an infusion of lidocaine facilitates the return of somatosensory evoked responses in dogs receiving recompression therapy after air embolism and induced hypertension. In this study, SEP amplitude returned to a level greater than twice that in animals not receiving lidocaine after 3 hours 45 minutes. Although preliminary, the latter two reports tend to confirm the present findings in other models of acute cerebral ischemia.

Based on our experimental data, one of the present authors (A.I.K.) has been using intravenous lidocaine in clinical cases of suspected or potential cerebral ischemia associated with subarachnoid hemorrhage. During intracranial surgery for the obliteration of cerebral aneurysms, 100 mg of lidocaine has been given as an intravenous bolus both before the aneurysm is clipped and shortly thereafter. Although this has not been done as part of a prospective randomized study, it is the surgeon’s perception that postoperative ischemic problems have been less since this regimen has been adopted. No problems have become apparent from such use of lidocaine. Final conclusions on the merit of this modality of treatment await a more controlled statistical review of clinical experience.

In conclusion, this study has shown that intravenous lidocaine facilitates the return of neural function when administered after acute cerebral ischemia induced by air embolism. Although care must always be taken in extrapolating results from animal experiments to the clinical setting, these results suggest that administration of lidocaine may favorably alter the neurological outcome in patients suffering cerebral air embolism. Perhaps more importantly, these results provide the rationale for testing lidocaine in other models of acute cerebral ischemia to determine its efficacy in more common types of stroke. The fact that lidocaine is already a widely used and relatively safe drug heightens its clinical potential should it prove to facilitate return of neurological function after stroke.

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Address reprint requests to: Delbert E. Evans, Ph.D., Diving Medicine Department, Naval Medical Research Institute, Bethesda, Maryland 20814-5055.