Effect of Lidocaine on Somatosensory Evoked Response and Cerebral Blood Flow After Canine Cerebral Air Embolism

Andrew J. Dutka, MD; Richard Mink, MD; James McDermott, PhD; Jonathan B. Clark, MD; and John M. Hallenbeck, MD

Background and Purpose: Victims of air embolism often recover rapidly on hyperbaric treatment then deteriorate again, even if hyperbaric treatment is continued. In previous animal experiments, lidocaine has been shown to improve recovery of somatosensory evoked response amplitude after air embolism. However, animals in these experiments rarely deteriorated. We have shown that the induction of air embolism and transient hypertension in canines produces deterioration despite hyperbaric treatment, and we decided to test the effect of lidocaine on somatosensory evoked potential recovery and cerebral blood flow in this model.

Methods: Dogs were treated with repeated doses of lidocaine or equivalent volumes of saline during hyperbaric therapy after internal carotid air embolism and transient hypertension. The investigators were unaware of treatment group assignment during the experiments. The amplitude of the median nerve somatosensory evoked potential and cerebral blood flow measured with carbon-14-labeled iodoantipyrine autoradiography were used to assess effect of therapy.

Results: Lidocaine-treated dogs recovered 60±10% (mean±95% confidence limits) of the baseline somatosensory evoked potential amplitude 220 minutes after air embolism; saline-treated dogs recovered 32±10% (a significant difference at p<0.01). Lidocaine-treated dogs also had higher cerebral blood flow values than saline-treated dogs 220 minutes after air embolism.

Conclusions: Lidocaine ameliorated the delayed deterioration of evoked potential associated with air embolism and hypertension in this canine model. The improved cerebral blood flow may be a mechanism of action of lidocaine or an associated effect of improved neuronal survival. (Stroke 1992;23:1515–1521)

Key Words • cerebral blood flow • embolism • evoked potentials, somatosensory • lidocaine • dogs

Cerebral air embolism is a complication of pulmonary barotrauma in diving accidents" and can also occur as a result of medical procedures requiring central venous or arterial access, chest trauma, neurological surgery in the sitting position, or cardiac surgery.

Victims of air embolism occurring as a result of submarine escape training immediately receive hyperbaric treatment. Pressure produces an immediate relief of symptoms in most cases, but approximately 20% of victims with initial recovery will later develop increasing headache, visual changes, and worsening of the original focal deficit. This clinical course is called "late" or "secondary" deterioration and is responsible for many cases of permanent disability. The phenomenon of secondary deterioration is not confined to hyperbarically treated air embolism as a result of diving accidents, however, since it has been observed in iatrogenic cases with delayed therapy and occurs after apparent spontaneous recovery from air embolism. Any therapy that could be shown to reduce the severity or incidence of secondary deterioration when used in combination with hyperbaric oxygen would be potentially useful in the treatment of victims of air embolism.

See Editorial Comment, p 1520

Previous studies from this laboratory suggested that lidocaine in doses similar to those used for control of cardiac arrhythmias improved recovery of the somatosensory evoked potential (SSEP) amplitude after air embolism in cats. The first of these studies administered lidocaine before air embolism, the second demonstrated improved recovery with therapeutic administration but without concurrent hyperbaric treatment, and in the third lidocaine was no better than hyperbaric treatment alone.
rare in the animals in these studies, and no indicators of recovery other than SSEP were studied.

The present study was undertaken to refine the previous observations, particularly with respect to the effect of lidocaine on the phenomenon of late deterioration. We used a previously described model in which the SSEP amplitude deteriorated despite hyperbaric treatment in dogs subjected to a combination of internal carotid air embolism and a pharmacologically induced transient, severe burst of arterial hypertension. These experiments model many features of the clinical syndrome of secondary deterioration. The SSEP amplitude is affected by temperature, anesthesia, and potentially by lidocaine itself but is also a reflection of the number of functioning cells within the somatosensory cortex and is correlated with local cerebral blood flow. If the effect of lidocaine on SSEP amplitude is a result of improved neuronal survival rather than some artifactual enhancement of electrical activity, the improvement should be correlated with increased local cerebral blood flow. Lidocaine might also act as a cerebral vasodilator, and measurement of cerebral blood flow also allowed a test of this hypothetical mechanism of action.

Materials and Methods

The experimental protocol was reviewed by the institutional animal care and use committee and complies with the requirements of the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council, US Department of Health and Human Services, publication No. (NIH) 86-23.

We used male mongrel dogs (Canis familiaris) that were fasted for 12 hours before the experiment. The dogs were tranquilized with a subcutaneous injection of xylazine (1.1 mg/kg) and atropine (0.05 mg/kg), and surgical anesthesia was induced with 13.5 mg/kg pentobarbital i.v., followed in 20 minutes with 6.25 mg/kg i.v. Additional doses of 1.3 mg/kg pentobarbital were given intravenously every 20 minutes for the remainder of the surgical preparation, therapeutic recompression, and euthanasia. The animal was intubated and mechanically ventilated to maintain the expired CO₂ fraction at 4-5%.

Surgical anesthesia was induced with 13.5 mg/kg pentobarbital i.v., followed in 20 minutes with 6.25 mg/kg i.v. Additional doses of 1.3 mg/kg pentobarbital were given intravenously every 20 minutes for the remainder of the surgical preparation, therapeutic recompression, and euthanasia. The animal was intubated and mechanically ventilated to maintain the expired CO₂ fraction at 4-5%.

Additional doses of 1.3 mg/kg pentobarbital were given intravenously every 20 minutes for the remainder of the surgical preparation, therapeutic recompression, and euthanasia. The animal was intubated and mechanically ventilated to maintain the expired CO₂ fraction at 4-5%.

The responses to 40 stimuli were averaged with a Nicolet CA 1000 recording system with a bandwidth of 30–3,000 Hz to obtain the SSEP. The amplitude difference between first upward deflection (P1) and the next downward deflection was averaged from five baseline SSEPs done before air injection. All subsequent amplitude measurements were referred to the P1 latency of the baseline and are expressed as a percentage of the average baseline amplitude.

After obtaining baseline measurements and verifying backflow from the carotid catheter, 0.4 ml air was flushed into the internal carotid artery with 0.6 ml warmed saline. An SSEP was obtained 2 minutes after air; if its amplitude was >10% of control, the experiment was terminated because of inadequate suppression. After securing the door of the chamber, the therapeutic compression began with descent to 165 feet sea water (FSW, 6 atm absolute) at a rate of 75 feet per minute (FPM). During the descent, 10 μg/kg norepinephrine was injected intravenously to produce a transient burst of severe high blood pressure. SSEPs were obtained at 10-minute intervals over the next 214 minutes of a modified US Navy Treatment Table 6A schedule, consisting of 30 minutes at 165 FSW on air, three 20-minute periods of 100% oxygen breathing at 60 FSW each followed by a 5-minute air break, ascent to 30 FSW at 1 FPM on oxygen, then 1 hour of 100% oxygen breathing at 30 FSW before surfacing. The final SSEP is an average of three responses obtained at the surface after the electrodes had been cleaned of any serious fluid or blood that had accumulated while in the chamber.

For the determination of blood flow, 60 μCi/kg carbon-14–labeled iodoantipyrine in 20 ml saline was injected at a rate of 20 ml/min for 1 minute. Arterial blood samples were collected every 5 seconds during the infusion of tracer for determination of the concentration curve; the animal was immediately killed with rapid injection of KCl into the right ventricle. The brain was frozen in freon or isopentane at −60°C then grossly sectioned into thirds, from which representative 20-μ sections containing respectively the caudate, thalamus, and posterior hippocampus were prepared for autoradiography. The sections were sealed in roentgenographic phosphor cassettes with Kodak SB-5 film, and 14C-methylmethacrylate standards were calibrated against those used in Dr. L. Sokoloff's laboratory at the National Institute of Mental Health (courtesy of Dr. J. Jehle). After 10-day exposure, the films were developed and 12 gray matter areas and nine white matter areas were identified in sections from the anterior, middle, and posterior thirds of the right and left sides of the brain in each dog. A technician who was unaware of the treatment group assignment read the optical density of each area manually with a Macbeth photodensitometer with 1-mm-diameter aperture. Blood flow was calculated from the observed concentration curve and the densitometry according to the equation of Sakurada et al. 14

The treatment group received lidocaine 1.5 mg/kg in 15 ml saline i.v. when the blood pressure first returned to <200 mm Hg systolic after norepinephrine. This loading dose was followed by lidocaine 1 mg/kg every 10 minutes for three doses, then 1 mg/kg every 30 minutes for the remainder of the experiment. This intermittent administration was necessary because no pump that could maintain a constant flow rate against the hyperbaric chamber pressures was available. Control animals received saline in boluses on the same schedule as the lidocaine-treated animals. The order of treatments was random, and the experimental team did not know which animal received lidocaine during the experiment.
This study required 42 dogs. Seven dogs were eliminated before the air injection for reasons such as bloody cisternal puncture with unrecordable evoked response (four dogs), inability to record evoked responses (two dogs), and baseline blood pressure >3 standard deviations above the mean for the groups (one dog). Five dogs were not studied further when the air bolus failed to reduce the 2-minute evoked response <10% of baseline amplitude. A preliminary unblinded study was performed in four lidocaine-treated and three saline-treated dogs. Lidocaine was administered without air embolus to three dogs to study the effects of lidocaine alone on the evoked response. The data reported below are based on eight dogs receiving lidocaine and 12 dogs receiving saline with the experimental crew unaware of the treatment.

All results are reported as mean±95% confidence limits of mean (CL). Statistical analyses were performed using the SOLO statistics program, version 3.0, for the IBM personal computer (BMDP Statistical Software, Los Angeles, Calif.).

Results

The values of selected physiological variables recorded in the baseline period before air, during hyperbaric treatment, and just before the end of the experiment are presented in Table 1. Separate analyses of variance (ANOVA) with repeated measures for each variable found no differences between groups; however, cerebrospinal fluid pressure and PO₂ increased after air embolism and during hyperbaric treatment. The PO₂ values in the treatment and final phases of the study reflect the hyperbaric oxygen treatment but are not accurate measures of PO₂ because of the detection limits of the oxygen electrode.

The peak mean arterial pressure recorded after the injection of norepinephrine was 265±12 mm Hg in the saline-treated group and 282±21 mm Hg in the lidocaine-treated group. The blood pressure was >200 mm Hg systolic after norepinephrine for 169±19 seconds in the saline-treated group and 198±22 seconds in the lidocaine-treated group. The cerebrospinal fluid pressure rose to a peak of 48±8 mm Hg in the saline-treated group and 46±16 mm Hg in the lidocaine-treated group. These indexes of the severity of the hypertensive stress are statistically similar in the two groups (Wilcoxon rank sum). The time between the air injection and the beginning of hyperbaric treatment was statistically the same in the two groups (5.7±0.5 minutes for the saline-treated group and 5.9±0.9 minutes for the lidocaine-treated group). The amplitude of the first evoked response recorded after air embolism was also identical in the two groups (lidocaine-treated group, 2.9±2.7% of baseline; control group, 5.3±2.2% of baseline). The accumulation of serous fluid while the animal is inaccessible in the chamber causes electrical bridging of the two electrodes. At the 220-minute mark the electrodes have been cleaned, thus accounting for the increase in amplitude from the 210-minute mark; however, the 210-minute recovery is significantly better in the lidocaine group by Wilcoxon rank sum analysis as well (p<0.02). Lidocaine-treated dogs recovered significantly more (64±29%, n=4) than did saline-treated dogs (27±11%, n=3) at 220 minutes in a preliminary unblinded study.

In the unembolized dogs treated with lidocaine, the evoked response deteriorated while in the chamber and improved after surfacing and cleaning electrodes; the final response was 86±12% of baseline values. Average cerebral blood flow values in gray and white matter areas for six lidocaine-treated and seven saline-
Discussion

Lidocaine administered after ischemic injury in conjunction with hyperbaric oxygen results in improvement in an electrophysiological measure of brain function and increases blood flow after cerebral air embolism and hypertension. Lidocaine thus partially reverses the poor recovery of SSEP and reduction in blood flow despite hyperbaric treatment produced in previous experiments by the combination of intracarotid air and transient arterial hypertension.13 In the previous experiments, hypertension alone produced no change in the SSEP amplitude, and hyperbarically treated animals with air embolus but without hypertension recovered 58% of the baseline evoked response amplitude.13

The degree to which improvement in SSEP amplitude is correlated with clinical recovery is debatable. Its use as an outcome measure in studies of humans with stroke is limited by the difficulty of controlling for the confusing effect of factors such as body temperature, drug effects, and the occurrence of ischemia in brain areas far from those involved in generating the SSEP.15 The Pco2, blood pressure, and recording site are constant in the laboratory situation, and in previous unreported experiments from our laboratory SSEP amplitude did not decrease until rectal temperature reached 36.3°C with deliberate cooling. The cells that generate the SSEP are certainly ischemic, because any animal that does not lose more than 90% of the initial SSEP amplitude after air embolus is rejected from the study. We often note a shortening of latency to the peak of the positive response after air embolism, possibly due to uncovering unaffected far field generators of the SSEP previously buried in the upgoing slope of the response. We therefore refer the amplitude measurement from the latency of the baseline peak to the next most negative peak; this amplitude has been shown to correlate with cerebral blood flow of 0.1–0.2 ml/g tissue per minute16,17 and with the metabolic rate of glucose utilization.18 The loss of amplitude of the SSEP also correlates with poor prognosis for clinical recovery after stroke in primates.19 After clamping the rat middle...
cerebral artery, SSEP amplitude correlates better with white matter edema; this may be due to the pattern of collateral flow in those models and would not apply to the situation of multiple microemboli.20 Our impression is that the improved electrophysiological recovery with lidocaine is physiologically significant and suggestive of possible functional benefit.25

To demonstrate any possible artificial enhancement of evoked response amplitude with lidocaine, the effect of lidocaine infusion and hyperbaric treatment without air embolism was tested in three animals. A slight loss in baseline amplitude over the course of the treatment was observed. A slight loss of SSEP amplitude over time has been reported previously as a consequence of prolonged hyperbaric exposure.21 This loss of amplitude would tend to bias the results against finding a benefit from lidocaine, and we found no evidence that lidocaine enhanced SSEP amplitude under nonischemic conditions.

Lidocaine improved overall blood flow after air embolism in this experiment. The cerebral blood flow in the right hemisphere gray matter, where we would expect most of the damage from the air, is, however, not significantly different from that of control. Air embolism resulted in a multifocal insult in which areas of very low flow are juxtaposed to areas of high flow. The heterogeneity of blood flows in the area of maximum embolic damage caused increased scatter that reduced the power of the statistical test used to find a significant difference between groups. The overall increase in postischemic blood flow supports the notion that the recovery of SSEP amplitude might be associated with functional recovery and is a possible mechanism for the action of lidocaine. Increased cerebral blood flow has not previously been observed with infusions of lidocaine. Lidocaine doses in the range that cause the burst-suppression EEG pattern on the electroencephalogram (EEG) reduce blood flow in cortical areas in nonischemic animals by autoradiography.22 Others have observed no effect on flow in uninjured animals with a combination of lidocaine at 15 mg/kg and isoflurane anesthesia.23 We used a lidocaine dosage schedule modified from a three-step infusion method that has been tested in various ischemic models with conflicting results. Lidocaine has a complex dose-response profile. Antiarrhythmic doses of lidocaine similar to those used in this study block the transmembrane sodium current.25 As the dose of lidocaine is increased, there is activation of the cortical EEG progressing to seizures and then suppression of cerebral metabolism and electrical activity.26,27 Shokunbi et al28 reported that lidocaine did not reduce histological evidence of infarction in a rat middle cerebral artery clipping model. However, these authors titrated the dose of lidocaine to the point of producing a burst-suppression EEG pattern, and this EEG pattern is associated with increased metabolism in hippocampal neurons,22 thus increasing their vulnerability to ischemia. When similar experiments were repeated with a lower dose of lidocaine, preservation of evoked responses, a reduction in infarct size, and improved blood flow were observed.29 Prophylactic lidocaine given at mean doses of 23.5 mg/kg to produce a "preepileptogenic" spike pattern on EEG failed to protect hippocampal neurons from infarction in a model of global ischemia.30 This dose is close to that causing increased metabolism in hippocampal neurons.22 Pretreatment with 5 mg/kg lidocaine led to preservation of electrocortical activity after global ischemia in rabbits31 and some reduction in hippocampal neuron loss after forebrain ischemia in rats.32 It appears that lidocaine may reduce ischemic damage at the lower doses used for cardiac arrhythmias and that this beneficial effect is lost at higher doses associated with preepileptogenic or burst-suppression EEG patterns, perhaps because the increased metabolic demand of neurons generating the EEG activation decreases their resistance to ischemia. At very high doses lidocaine suppresses electrocortical activity, but the doses used in this study do not approach those needed for cerebral suppression.27 The mechanism of the beneficial effect is therefore unlikely to be similar to that of barbiturates. Blockade of the inward sodium current through the voltage-gated sodium channel at the low doses used might contribute to a reduction in the amount of depolarization of neurons induced by ischemia. By limiting depolarization, lidocaine would limit the release of excitatory amino acids and might also enable postsynaptic cells to resist depolarization induced by sodium and calcium entry through the channels opened by excitatory amino acids.33 The calcium entry provoked by excitatory amino acids leads to cell death34; blunting of this process by lidocaine might therefore account for the electrophysiological recovery.

Patients receiving lidocaine infusion for cardiac disease have leukocytes that are less susceptible to activation.34 Leukocytes are major determinants of blood flow in the microcirculation,35 and we have recently shown that leukocytes participate in the production of reduced microvascular perfusion after air embolism.36 Lidocaine could prevent leukocyte activation, thus accounting for the improved blood flow and possibly improved neuronal survival.

Lidocaine is a familiar drug with a known spectrum of side effects that may have promise for the treatment of cerebral ischemia.

Acknowledgments

The authors wish to thank Mr. Ed Sloan, Ms. C.J. Jones, Mr. Melvin Routh, HM2 A. Winton, HM3 D. Lehman, HM2 James Velasquez, HM2 M. Pasion, and Mr. J. DeJesus for expert technical assistance and S. Cecire and J. Gaines for editorial assistance.

References

Lidocaine has long been considered a candidate as a neuroprotective agent against cerebral ischemia. The compound reduces metabolic rate and stabilizes cellular membranes by inhibiting ionic flux through sodium channels. Several investigations have explored the potential for lidocaine to either ameliorate pathophysiological changes associated with ischemia or improve neurological/histological outcome from global or focal ischemic events. Although the experimental results have been mixed, the work presented by Dutka et al. adds to a growing body of evidence that lidocaine may have some clinically relevant cerebroprotective properties. Given the broad clinical experience and margin of safety associated with lidocaine, it is tempting to conclude that this work indicates the use of lidocaine as a therapeutic agent specifically in the context of air emboli. Such a conclusion may be premature for important reasons. First, Dutka et al. have demonstrated only an improved physiological state that has yet to be associated with either improved neurological or histological outcome. Second, the dose of lidocaine administered is apparently important with respect to obtaining therapeutic benefit. Using a model of cat middle cerebral artery occlusion, Gelb et al. also observed improved posts ischemic somatosensory evoked potential (SSEP) recovery in animals prophylactically treated with lidocaine. This improved neurophysiological end point was not associated with a reduction in infarct size. In their later work, when smaller doses of lidocaine were administered, the same group was able to produce a reduction in infarct size that was attributed to the lower dose’s having less severe hemodynamic side effects. This lesson suggests caution in directly associating improved SSEP recovery with improved neurological/histological outcome. Extension of the work by Dutka et al. to the human scenario of air emboli should be greeted with caution.
Effect of lidocaine on somatosensory evoked response and cerebral blood flow after canine cerebral air embolism.
A J Dutka, R Mink, J McDermott, J B Clark and J M Hallenbeck

Stroke. 1992;23:1515-1520
doi: 10.1161/01.STR.23.10.1515

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/23/10/1515

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/