Effect of intravenous lidocaine on experimental spinal cord injury

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A series of experiments was conducted to study the effect of systemic intravenous administration of lidocaine on neurological recovery after acute experimental spinal cord injury in cats. The spinal cord was injured by the rapid inflation of an epidural balloon at T-6. The physiological integrity of the spinal cord ceased within 2 seconds in all animals, as demonstrated by acute disappearance of the somatosensory evoked response (SER). There was essentially no return of the SER in the five untreated animals when monitored for 4 hours post-injury. All of the pathological specimens from these animals revealed severe central cord hemorrhage. Intravenous lidocaine was begun 15 minutes after the injury in five animals. Three of these animals had significant return of the SER. The pathological specimens from the lidocaine-treated animals revealed either mild or moderate central cord hemorrhage. The results of this experiment suggest that systemic lidocaine administration has a significant beneficial effect in the treatment of acute spinal cord injury.

KEY WORDS • lidocaine • spinal cord injury • spinal cord compression • paraplegia • evoked potentials • somatosensory evoked response

AN effective treatment for spinal cord injury is not available at present. Although much has been learned in the 70 years since Allen’s contributions regarding spinal cord injury,1 the pathophysiology and the anatomical substrate leading to immediate irreversible neurological loss remain elusive. It is still not known whether the changes in blood flow and metabolism that occur are instrumental in the neurological dysfunction or just an accompanying phenomenon, whether there is more than one critical process involved, and, most importantly, whether any of the processes are reversible.

In the past, we have studied the major mechanisms of blood flow regulation in the spinal cord,12,14–19,23,25 as well as the alterations of blood flow following experimental impact injury.13 For the last several years, we have been using a model of balloon compression of the spinal cord, rather than the impact model, so as to separate and study blood flow changes and neurophysiological changes.17,20–22,24 In the present experiments, we have used this model to study the effects of systemically administered lidocaine in acute experimental spinal cord injury. We elected to study lidocaine on the basis of earlier work in which we demonstrated a beneficial effect of systemic lidocaine in neurological dysfunction accompanying cerebral air embolism7 and in the reduction of the associated intracranial hypertension.8

Materials and Methods

Ten adult cats, ranging in weight from 2.85 to 5.9 kg (mean 3.8 ± 0.87 kg), were used for these experiments.* These cats were separated into two groups of five animals each, an untreated group and a lidocaine-treated group. Anesthesia was induced by an intramuscular injection of ketamine HCl (0.15 mg/kg), and was maintained for the duration of the experiment by an intravenous injection of alpha-chloralose (80 to 100 mg/kg) dissolved in warm saline. Chloralose anesthesia was supplemented with nitrous oxide and/or halothane as needed during surgery. After tracheal intubation, ventilation was controlled by a small-animal respirator.† After insuring that the animal had reached a surgical

* The experiments reported herein were conducted according to the principles set forth in the “Guide for the Care and Use of Laboratory Animals,” Institute of Laboratory Animal Resources, National Research Council, DHEW, Publ. No. (NIH) 78-23.
† Animal respirator manufactured by Phipps and Bird, Inc., Richmond, Virginia.
level of anesthesia, pancuronium bromide (0.1 mg/kg) was administered intravenously at appropriate intervals to control ventilation and movement artifact in the evoked response measurements. Periodic determinations of arterial pO2, pCO2, and pH were made.† These parameters were maintained within normal physiological limits by adjusting the rate and tidal volume of the respirator. Esophageal temperature was monitored and kept at 37° to 38°C by intermittent use of a heating pad and heat lamp. A right femoral cutdown procedure was performed, and catheters were inserted into the femoral artery to record blood pressure and into the femoral vein to administer drugs.

After the above preparation, the cat was positioned in a stereotaxic apparatus. To record somatosensory and visual evoked responses, the left sciatic nerve was exposed for stimulation and the right scalp was incised and retracted to allow placement of small stainless steel screws over the occipital and temporal areas. A screw placed in the frontal area of the skull served as the indifferent recording electrode. The exposed sciatic nerve was immersed in mineral oil.

To prepare for spinal cord compression, a small laminotomy at T-8 was performed, and a No. 3 French Fogarty catheter was inserted into the epidural space, with the tip resting on the right side of T-6. The spinal cord was injured by quick inflation of the water-filled balloon catheter to a volume of 0.25 cc for a period of 15 seconds. The balloon was then quickly deflated and the catheter gently removed.

Somatosensory evoked responses were obtained by applying a stimulus (8 V for 1 msec at 1 Hz) to the left sciatic nerve and recording from the temporal and indifferent (frontal) screw electrodes. Visual evoked responses were obtained by flashing a strobe light into both atropine-dilated eyes (1 flash/sec) and recording from the occipital and indifferent screw electrodes. Cortical evoked responses were amplified by a Grass differential preamplifier, further amplified and displayed by an oscilloscope, and then averaged.§ Averaged evoked responses were plotted on an x-y recorder. Records of each response were collected at the following times: immediately before injury, at 1 to 3 seconds during the 15-second balloon compression, and at 5 to 15 minute intervals for 4 hours thereafter.

The treated animals were given an infusion of lidocaine via the right femoral vein starting 15 minutes after the injury.† The lidocaine was administered ac-

† Model 713 pH and blood gas analyzer manufactured by Instrumentation Laboratory, Inc., 113 Hartwell Avenue, Lexington, Massachusetts.

§ Model P-15 differential preamplifier manufactured by Grass Instrument Co., 101 Old Colony Avenue, Quincy, Massachusetts; Model 5113 oscilloscope manufactured by Tektronix, Inc., Beaverton, Oregon; and Model 527 signal averager manufactured by Nicolet Instrument Corp., 5225 Verona Road, Madison, Wisconsin.

¶ Model 341 syringe pump manufactured by Sage Instruments, Cambridge, Massachusetts.

fig. 1. The change in mean blood pressure (MBP) after spinal cord compression in untreated (solid line) and lidocaine-treated (broken line) animals.

cording to the following schedule: 1.5 mg/kg over the initial 3 minutes, 3 mg/kg over the next 30 minutes, and 1 mg/kg every 30 minutes for the remainder of the experiment. We have found that this method of lidocaine administration in cats maintains lidocaine blood levels of 3 to 4 µg/ml. This dosage schedule was based on previous studies showing that comparable rates of infusion are effective in maintaining therapeutic blood levels of the drug in humans.30

Continuous strip-chart recordings were made of the electrocardiogram and arterial blood pressure using a Gould Brush Model 481 amplification and recording system.* Analog signals from the recording system were also sent to a computer for real-time measurement, storage, and analysis of cardiovascular, respiratory, and other parameters.

At the completion of the experimental protocol, the animals were sacrificed by an intravenous infusion of Somlethal. Spinal cord segments at points well above and below T-6 were removed for pathological examination in seven of the 10 animals and placed in Karnovsky’s solution. The fixed cord segments were sectioned serially and examined by light microscopy following routine histological preparation procedures and hematoxylin and eosin staining. Qualitative histological grading of spinal cord injuries was performed independently, and the experimental group remained unknown until grading was completed. Spinal cord injuries were graded as mild, moderate, and severe with respect to the degree of hemorrhage, which was the primary pathological finding by light microscopy.

* Model P23 1D pressure transducer and Gould Brush Model 481 amplification and recording system manufactured by Gould, Inc., 3631 Perkins Avenue, Cleveland, Ohio.
Results

In all animals, there was a marked hypertensive response concomitant with balloon inflation. A number of cardiac arrhythmias were observed, as in our previous experiments. The mean arterial blood pressure returned to control levels, and remained or was kept in the normal range for both untreated and lidocaine-treated animals during the entire experiment (Fig. 1). Lidocaine-treated animals required additional volume replacement with normal saline to keep the blood pressure in the normal range. The visual evoked response remained essentially unchanged in both groups of animals throughout the experiment, confirming preserved cortical function.

The somatosensory evoked response (SER), initiated by stimulation of the left sciatic nerve and recorded from the right side of the brain, disappeared within 1 to 3 seconds of balloon inflation and remained flat during the entire period of inflation in all animals. In four of five untreated animals, there was no return of the SER (Fig. 2), and in the fifth untreated animal there was minimal return of the SER (Fig. 3). In the lidocaine-treated group, three of the five animals had significant return of the SER. One of these animals had a return of the SER to a nearly normal pattern (Fig. 4). In this case the SER returned so near to a normal configuration that one could question the severity of the injury for this animal; however, the SER disappeared immediately upon balloon inflation and remained flat during the entire period of balloon inflation and for at least 20 minutes after balloon deflation. A strong hypertensive

![FIG. 2. Somatosensory evoked responses (SER) after spinal cord compression in an untreated animal showing no return of the SER. Times of tracings given are after the beginning of the 15-second period of spinal cord compression.](image)

![FIG. 3. Somatosensory evoked responses (SER) after spinal cord compression in an untreated animal showing minimal return of the SER. Times of tracings given are after the beginning of the 15-second period of spinal cord compression.](image)

![FIG. 4. Somatosensory evoked responses (SER) after spinal cord compression in a lidocaine-treated animal showing return of the SER to a nearly normal pattern. Times of tracings given are after the beginning of the 15-second period of spinal cord compression.](image)
FIG. 6. A representative photomicrograph of feline spinal cord segment T-6 following spinal cord compression without lidocaine treatment. Note the large central severely hemorrhagic region extending into the adjacent white matter, together with scattered petechial hemorrhages throughout the white areas. H & E, × 10.

response was noted in this animal, indicating a significant spinal cord injury. When the SER first reappeared, the latency was increased and slowly returned to a more normal pattern over 4 hours. Even at the end of the experimental period, an increase in latency remained. This model of balloon inflation spinal cord injury has been used in our laboratory for over 5 years, and includes well over 30 control animals for various projects. We have never seen a control animal, that was injured as above and that met the above criteria, have significant return of the SER. One lidocaine-treated animal had significant transient return of the SER at 60 and 90 minutes. The remaining two lidocaine-treated animals demonstrated no significant return of the SER.

Spinal cord specimens were obtained from three untreated control animals and four lidocaine-treated animals. There were striking differences between the pathology of untreated and treated animals. The three untreated animals uniformly showed severe central gray matter hemorrhage (Fig. 6), while the lidocaine-treated animals showed only mild to moderate degrees of hemorrhage (Fig. 7). The severe hemorrhage in the untreated control animals represented coalescent foci of hemorrhage that were massive and grossly apparent in the central gray region, with extension of hemorrhage into adjacent white matter. Additionally, scattered small petechial hemorrhages were identified in the peripheral white matter and scant quantities of blood were occasionally seen in the subarachnoid space. The hemorrhagic foci were localized to the region of spinal cord compression with no proximal or distal extension of hemorrhage beyond the area of compression. While hemorrhage was prominent, no marked necrosis or inflammatory infiltrate was noted at the relatively early time of sacrifice of the animals.

Spinal cord specimens from the lidocaine-treated animals showed significantly less hemorrhage in the central gray region compared to the untreated controls. The amount of hemorrhage was characterized as mild in two lidocaine-treated animals, and moderate in two others. The spinal cord of one of the two treated animals that showed no return of the SER still demonstrated only mild to moderate hemorrhage. Scattered petechial hemorrhages were seen in the white matter in these lidocaine-treated animals as well. Overall, the number of petechial hemorrhages, and the extent of central hemorrhage throughout the region of compression, appeared by histological examination to be reduced in the lidocaine-treated animals.
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FIG. 7. Representative photomicrographs of feline spinal cord segment T-6 from two animals following spinal cord compression injury and lidocaine treatment. H & E, × 10. Left: There is mild hemorrhage in the gray and white matter. Right: Moderate hemorrhage is characterized by central gray and white matter petechial hemorrhages, small to moderate in size.

Discussion

The results from this preliminary study strongly suggest that systemically administered lidocaine has a beneficial effect in treating animals with experimental acute spinal cord injury. Three of five lidocaine-treated animals demonstrated significant return of the SER, whereas none of the untreated animals demonstrated return.

Lidocaine is thought to exert its local anesthetic effect by restricting sodium flux across the neural membrane; that is, making the membrane impermeable to sodium during the action potential phase. We postulated from earlier experiments that neural membrane injury, which results in leakage of sodium through the membrane at rest and leads to a resting membrane potential that is less negative, might be the basic anatomical substrate that explains the lesion in spinal cord injury. Is it possible that lidocaine stabilizes the injured neural membrane, returning its resting membrane potential to the normal range and thereby returning its excitability? A recent study by Fink supported this notion. The study demonstrated that lidocaine, in low concentrations, preserved neural conduction in isolated nerves subjected to glucose-free solutions. Further evidence was obtained that lidocaine reduced the leak of potassium out of, and sodium into, the isolated nerves. This study provides evidence that neural conduction was preserved by the ability of lidocaine to inhibit the leak of cations across the axonal membrane. Furthermore, Astrup and colleagues produced considerable evidence that lidocaine in high doses has certain effects on cerebral metabolism similar to those induced by hypothermia. These effects include the decrease of cerebral oxygen and glucose consumption, and the decrease of potassium efflux from cells during ischemia. Astrup and Sørenson attributed the latter effect to a “membrane stabilizing” action of lidocaine that restricts the leak fluxes of sodium and potassium across membranes. With regard to the present observations, it appears likely that some of the above-mentioned actions of lidocaine are involved; however, further investigation will be required to determine the specific mechanisms that are responsible for restoration of spinal cord function.

The difference in the pathology of spinal cord specimens from the lidocaine-treated and untreated groups may also suggest possible mechanisms responsible for the beneficial effect of lidocaine. Our previous studies suggested that the development of the central hemorrhagic lesion was more of an epiphenomenon. We thought that the differences in the structure of the central area of the spinal cord, as compared to the periphery, might account for the observed pathological changes. The central cord area is comprised of a central region of cells, relatively loose neuropil, and a rich capillary supply. Surrounding this central region are bundles of myelinated axons that are longitudinally situated and have a relatively sparse blood supply. This anatomical configuration makes the central region vulnerable to injury, whether vascular or mechanical, but not necessarily in a cause and effect manner. In the present study, however, the lidocaine-treated group of animals demonstrated less central hemorrhage. With regard to the mechanisms responsible for this action, there are a number of vascular effects of lidocaine that may be relevant. For example, Luostarinen, et al., found that lidocaine prevented thrombus formation from laser-induced microvascular injury and also restored blood flow when applied after injury. These authors attributed this action to the ability of lidocaine to reduce adhesion between blood cells, and between blood cells and the endothelial wall. Lidocaine has also
been shown to reduce endothelial damage from surgical trauma by inhibiting the adhesion and invasion of leukocytes into the vessel wall. These actions of lidocaine on blood cells and blood vessels could help preserve endothelial integrity after spinal cord injury and reduce hemorrhage.

Since it is still not clear that a relationship exists between the degree of hemorrhage following trauma and the degree of neurological dysfunction, we have elected to simply describe the pathological changes in the two groups rather than attempt to quantify the amount of hemorrhage.

In evaluating the results of treatment protocols for experimental spinal cord injury, the laboratory model, severity of injury, and relevance to clinical cases of spinal cord injury are extremely important. Obviously, a very severe injury will not respond to any form of therapy and, undoubtedly, a percentage of clinical spinal cord injuries fall into this group. On the other end of the spectrum is the clinical injury that improves with time without specific therapy. The laboratory counterpart of this clinical situation is the model in which the untreated animals are not permanently paralyzed, but walk "weakly." The investigator then compares the ability to walk of the untreated group versus the treated group. We do not think this is the appropriate model to study spinal cord injury. The small group of patients who hopefully will benefit most from research on spinal cord injury is the group whose initial complete lesion is potentially reversible with appropriate treatment. Consequently, the ideal laboratory model to use is the untreated animal preparation that utilizes the least severe injury to cause permanent total neurological dysfunction. It has been shown that immediate and persistent electrical silence (absence of SER) for 4 hours after injury is associated with clinically irreversible paralysis. Although those studies employed models (weight drop and circumferential compression) different from the model used in the present experiment, nevertheless immediate loss of the SER which does not return for 4 hours does signify a serious, probably permanent, injury. We do not mean to imply that, because the SER returned in three of five treated animals, these animals would be neurologically intact. However, the present experiment does suggest that lidocaine might reverse some of the physiological dysfunction that accompanies trauma to the spinal cord, and is worthy of further study.

Conclusions

We have studied the effects of systemically administered lidocaine after experimental acute spinal cord injury. Three of five lidocaine-treated animals demonstrated significant return of the SER following post-injury lidocaine treatment. There was essentially no return of the SER in the untreated animals. While further work is necessary to confirm these preliminary findings and to clearly delineate the mechanism of action, it appears that systemic lidocaine treatment is beneficial and deserves cautious clinical trials.

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References

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