Lidocaine Accelerates Neuroelectrical Recovery After Incomplete Global Ischemia in Rabbits

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The use of high-dose lidocaine for cerebral protection during ischemia has produced varied results. Our study uses a new, single carotid artery preparation in the rabbit to produce incomplete global ischemia by graded carotid occlusion; specific electroencephalographic changes are used as the end point for the extent of blood flow reduction sustained during 20 minutes. We monitored arterial pressure, intracranial pressure, and internal carotid blood flow that were recorded with an electromagnetic flowmeter after surgical ligation of the opposite internal and the two vertebral arteries, and we studied the electroencephalogram and somatosensory-evoked potentials elicited by stimulation of the sciatic nerve. Low-dose lidocaine (0.2 mg/kg/min) infused throughout the experiment significantly accelerated the time course of the return of electroencephalographic and evoked-potential amplitudes toward control. Deep halothane anesthesia alone elicited the slowest recovery, suggesting that the action of lidocaine was independent of its general anesthetic effect. There were very small differences among the groups in the measured arterial pressure, intracranial pressure, and cerebral blood flow, suggesting that lidocaine changed recovery rate without markedly modifying any characteristic of the postischemic cerebral perfusion. The protective effect of lidocaine may be the result of a specific blockade of Na⁺ channels or a decrease in excitatory neurotransmitter release, either of which would cause a delay in the onset of the events that lead to neuronal damage during ischemia. (Stroke 1990;21:929-935)

Cerebral ischemia is a potential complication of neurosurgical procedures that may occur transiently as during deliberate hypotension or with the temporary clipping of a large blood vessel. High-dose barbiturates or etomidate are used to provide some degree of brain protection in those situations.1-4

In an animal model of brain ischemia, Astrup et al5,6 described the cerebral protective action of lidocaine. This agent was used by other authors,7-9 who described beneficial effects after air embolism, experimental spinal cord injury, and focal brain ischemia. In contrast, other studies10,11 failed to show the protective effects of this agent on histologic changes in experimental models of focal ischemia.

To evaluate these contradictory findings, we tested the effect of lidocaine by using a moderate level of blood flow reduction defined by changes in the electroencephalogram (EEG) comparable with those studied by Gregory et al12 and Graham et al,13 who reported no neuropathologic alterations after 20 minutes of incomplete global ischemia. We tested a low dose of the drug, expecting some central nervous system beneficial action because lidocaine has a significant effect at low concentrations in other excitable tissue; one of these effects is the suppression of cardiac arrhythmias.14 The effect was assessed by monitoring the time course of the recovery of the EEG and the evoked potentials. These temporal changes have been shown to constitute a reliable index of neurologic restoration in both experimental15 and clinical16,17 settings. However, early neuroelectrical recovery may be followed in some ischemic conditions by later deterioration and the "maturation" of histopathologic changes18; thus, acceleration of electrophysiologic recovery may not represent true brain protection.

Materials and Methods

Studies were successfully performed in 32 rabbits with an average weight of 3.2 kg and were in accordance with the "Guide for the Care and Use of Laboratory Animals" of the National Institutes of
were cannulated for arterial pressure and blood gas monitoring and for drug injection, respectively.

One common carotid artery was dissected free for placement of a 1.5-mm noncannulating flowmeter probe and a miniature hydraulic occluder. All branches were then isolated and tied off; only the internal carotid was left intact. The baseline blood flow was measured with a Biotronex 310 unit (Biotronex Laboratory, Inc., Kensington, Massachusetts) and the preparation continued if the flow was higher than 1.3 ml/min. The opposite common carotid artery and its branches were tied off. The course of the vertebral arteries at the level of C-1 was exposed, and the vessels were coagulated with electrocautery long enough for the thrombosis to extend to the junction with the anterior spinal artery. When this occurred, occlusion of the patent internal carotid artery changed the background EEG into isoelectric within 20 seconds. In these conditions, the electromagnetic probe measured almost "total" cerebral blood flow with little extracerebral contamination.

Flow was measured in milliliters per minute per 100 g by weighing the cerebrum after removal from the rabbit.

Electroencephalogram and evoked potentials were monitored from three stainless steel screws placed on the skull. The active electrode was located over the parietal region, 2 mm lateral to midline and 2 mm caudal from the coronal suture. The reference electrode was placed at the midline over the maxillary bone, and the ground electrode was placed over the parietal bone. Pressure in the cisterna magna was recorded through a small needle. Finally the sciatic nerve contralateral to the skull electrodes was exposed and mounted on two platinum hooks. The evoked potentials were processed after 100 pulses to the nerve at 5/sec for 1 msec at 2–3 V (supramaximal stimulation), and the responses were averaged with a Cadwell 5200 A unit (Cadwell Laboratories, Inc., Kennewick, Washington). After a pilot study, we characterized the voltage, latency, and generators of the evoked waveform represented in Figure 1. It consistently showed a small positive peak (P1) with an average latency of 2.0±0.4 msec (apparently originating in the cervical spinal cord or medulla), a negative peak (N1) with an average latency of 18.5±0.5 msec (apparently of thalamic origin15), and another positive peak (P2) with an average latency of 35±3.0 msec (apparently of cortical origin).

After the preparation was completed, arterial pressure, EEG, "total" brain blood flow, end-expired CO2, and cisternal pressure were continuously monitored on a polygraph (model 7, Grass Instrument Co., Quincy, Massachusetts). After stabilization for 1 hour, the rabbits were included in the study if the internal carotid blood flow was at least 80% of the preisolation level or if the arterial pressure was greater than 75 mm Hg. Most commonly, the "total" brain blood flow doubled or tripled; greater increases occurred when the initial value was lower, and lower increases occurred when the initial value was higher. If hypotensive, the rabbits developed progressive acidosis, hyperkalemia, and marked slowing of the EEG.

We assigned the rabbits to one of six different groups. Groups 2, 4, and 6 were the ischemic groups, and groups 1, 3, and 5 were their respective control groups. Group 1 (control-control, n=3) rabbits were maintained at 1% halothane in an O2-air mixture, and EEG and somatosensory-evoked potentials were recorded during 75 minutes without ischemia. Group 2 (control-ischemia, n=11) rabbits were anesthetized in a manner similar to group 1 and subjected to 20 minutes of incomplete ischemia and 40 minutes of postischemic evaluation. Group 3 (lidocaine-control, n=3) rabbits were managed in a manner similar to group 1 and subjected to 2 minutes of incomplete ischemia and 40 minutes of postischemic evaluation. Group 4 (lidocaine-ischemia, n=8) rabbits were managed in a manner similar to group 3 and, in addition, an infusion of 0.2 mg/kg/min lidocaine was started 15 minutes before the baseline recording and continued for 60 minutes without inducing ischemia. This dose of the agent was chosen after a pilot study showed that it had minimal effects on the baseline neuroelectrical activity. Group 5 (halothane-control, n=3) rabbits were maintained at 1% halothane in an O2-air mixture, and the record-
ings were performed for 75 minutes without inducing ischemia. Because of the higher anesthetic concentration, most rabbits required cardiovascular support with 3–5 μg/kg/min phenylephrine. Group 6 (halothane-ischemia, n=4) rabbits were maintained as in group 5. Otherwise, the protocol for recording during ischemia and reperfusion was similar to groups 2 and 4.

We induced incomplete global ischemia by gradually occluding the patent carotid artery until the baseline EEG changed from the control 6–10/sec background to a pattern of prominent slow (1–4/sec) high-voltage waves with suppression of the 6–10/sec background activity. The extent of the occlusion was finely adjusted to compensate for the reflex changes in arterial pressure that followed the initiation of cerebral ischemia.

The results of the arterial pressure, "total" blood flow, and intracranial pressure measurements were represented for the following intervals: baseline (average of three measurements), ischemia (average of four measurements, 5 minutes apart), early reperfusion (immediately after release of the occlusion), middle reperfusion (20 minutes after release of the occlusion), and late reperfusion (40 minutes after release of the occlusion).

The EEG was analyzed during the periods of control and ischemia and during two stages of reperfusion: 1) early recovery, represented by the return of the fast activity (6–10/sec) background at a low voltage and 2) late recovery, defined by the increase in the voltage of the fast activity background and the display of a more complex pattern with theta waves, comparable with the baseline recording. The somatosensory-evoked potential amplitudes of the N₁ and the P₂ potentials were calculated at baseline, every 5 minutes during occlusion, 2 minutes after release of the occlusion, and every 5 minutes thereafter for 40 minutes.

The mean±SEM of the cerebral blood flow and arterial and intracranial pressures was calculated, and the differences from control within groups were analyzed by paired t tests. The differences in those parameters and in the EEG recovery times were compared among groups by analysis of variance (ANOVA) and Dunnett’s procedure.

The amplitudes of the evoked potential peaks N₁ and P₂ at the different intervals were expressed as percent of control, and the means at each interval for groups 2, 4, and 6 were compared with their respective control groups. Groups 1 and 2, control; groups 3 and 4, lidocaine; groups 5 and 6, halothane.

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>Control</th>
<th>Ischemia</th>
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<th>40 minutes</th>
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<td>94±7</td>
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<td>CBF (ml/min/100 g)</td>
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<td>51±8</td>
<td>50±9</td>
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<td>127±6*</td>
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<td>CBF (ml/min/100 g)</td>
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<tr>
<td>3</td>
<td>MAP (mm Hg)</td>
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<td></td>
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<td>75±5*</td>
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<tr>
<td></td>
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<td>6.6±0.8*</td>
<td>5.1±0.6</td>
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</tbody>
</table>

Values are mean±SEM. MAP, mean arterial pressure; CBF, cerebral blood flow; ICP, intracranial pressure. Groups 2, 4, and 6 are the experimental ischemic groups, and groups 1, 3, and 5 are their respective control groups. Groups 1 and 2, control; groups 3 and 4, lidocaine; groups 5 and 6, halothane.

*p<0.05 vs. control of each group.

†p<0.05 vs. group 2.
TABLE 2. Time Course of Electroencephalogram Recovery After Ischemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial recovery (min)</th>
<th>Complete recovery (min)</th>
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<tbody>
<tr>
<td>2</td>
<td>4.5±0.6*</td>
<td>18±1.6*</td>
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<tr>
<td>4</td>
<td>2.8±0.6*</td>
<td>8±1.6*</td>
</tr>
<tr>
<td>6</td>
<td>5.2±1.2</td>
<td>22±2.8</td>
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</table>

Values are mean±SEM. Group 2, control; group 4, lidocaine; group 6, halothane.

*p<0.05 vs. group 2.

Results

The baseline values of cerebral blood flow, mean arterial pressure, and intracranial pressure were similar in all rabbits (Table 1). There were no significant differences among the experimental groups during ischemia. Cerebral blood flow was decreased to 20–25% of control to achieve the EEG end point designated by the protocol. Intracranial pressure significantly diminished, and arterial pressure markedly increased.

During reperfusion, cerebral blood flow and intracranial pressure rapidly increased in all groups while the arterial pressure rapidly returned to normal. Initially, the extent of the hyperemia was very similar in all the groups; however, the intracranial pressure increased more in group 2. Later in the reperfusion period, cerebral blood flow and intracranial pressure decreased gradually. In group 2, the cerebral blood flow was lower, and the intracranial pressure was higher. These differences were small but statistically significant. The arterial pressures were not significantly different among the groups, and the time course of ischemic hypertension and postischemic return to baseline was similar in all groups.

The most important finding was the marked difference among groups in the time course of recovery of the EEG and evoked potentials. The return of the EEG toward baseline varied, and the time for both initial and complete recovery was significantly faster in group 4 and slowest in group 6 (Table 2).

The changes in Nt and P2 amplitudes are represented in Figures 2, 3, and 4. In the control studies, the peaks were stable in groups 1 and 3 but progressively declined in group 5. In the ischemic groups, the course of the Nt potential differed markedly (Figure 2). In group 2, the average amplitude was reduced during ischemia to 43% of the baseline. This was followed by a gradual return to 83% of the initial amplitude after 25 minutes of reperfusion, with a significant decrease thereafter. In group 4, the wave amplitude was reduced during occlusion to 63% of the baseline, with recovery to 98% of the control after 5 minutes of reperfusion. The amplitudes were significantly different from group 2 during ischemia and most of the recovery. In contrast, the differences in amplitude between groups 4 and 6 were significant throughout the observation period, because in group 6 the Nt potential was reduced to 21% with no return to baseline during the 40 minutes of reperfusion. The time course of the P2 potential was different (Figure 3). Its average amplitude was reduced during ischemia to 25% and 12% of the control values in groups 2 and 6, respectively. These amplitudes recovered only partially during reperfusion. In contrast,
group 4 the amplitude of $P_2$ declined to only 48% of the baseline during carotid occlusion and returned to 81% after 20 minutes of reperfusion. This value was not different from the control at 25 minutes but differed significantly from group 6 at 15 minutes. The differences in the course of the EEG and evoked potentials are represented in Figure 4, which illustrates the differences among ischemic groups.

Discussion

The results show that the single internal carotid preparation in the rabbit was stable during control conditions and that a reliable episode of incomplete global ischemia was elicited while "total" brain blood flow and neuroelectrical changes were continuously monitored.

There are potential difficulties with this experimental model, especially with the collateral circulation from extracerebral vessels. A previous study showed that the two internal carotid and the two vertebral arteries join in a circle of Willis with very small collaterals from the external carotid artery that may join the ophthalmic artery through the orbit. More importantly, there is a well-defined anastomosis between the vertebral and the anterior spinal arteries. The extent of coagulation at this junction was based on the rapid change of the EEG into isoelectric after carotid clamping. EEG suppression occurs when cerebral blood flow is very low, and it does not indicate that the brain perfusion is completely interrupted. In our preparation, some residual blood flow in the circle of Willis may result from the opening of anastomosis with the external carotid system because of the decrease in arterial pressure within the internal carotid system during ischemia. This potential blood flow could not be measured by the flowmeter placed in the carotid artery, and it may have varied among the rabbits. However, the end point of the ischemia was not the measured flow, but the EEG pattern. Because the pattern was very similar in the three ischemic groups, it was assumed to represent an identical level of ischemia.

The neuroelectrical changes were observed when the carotid blood flow reached 20–25% of the baseline, corresponding to 12–14 ml/min/100 g. Residual blood flow was comparable with the values measured around cortical neurons by Heiss et al when those cells decreased or stopped their spontaneous firing and were able to recover after persistence of the ischemia for up to 30 minutes. Similar values were reported by Symon in a model of middle cerebral artery occlusion, which was recorded in the cerebral region subjected to an "ischemic penumbra" where changes in somatosensory-evoked potentials comparable with ours were observed.

If we assume that the degree of ischemia was similar in the experimental groups, our most important finding was that the EEG and amplitudes of the evoked potentials showed a reliable recovery that was significantly faster during lidocaine infusion. Interestingly, we observed a faster and more complete recovery of the thalamic compared with the cortical potential, especially in group 4. These observations do not support the concept that the changes in the cortical waves of the somatosensory-evoked potential observed during ischemia represent deafferentation.
secondary to alteration in conduction along the brain stem andthalamic pathways.23 Rather, they favor the hypothesis that various neuronal groups differ in their sensitivity to ischemia or hypoxia.24 Our results showed a faster recovery of the EEG compared with the somatosensory-evoked potentials; these findings confirm the experience of other authors12,25 and emphasize the higher sensitivity of the somatosensory-evoked potential to the remaining cerebral effects of an ischemic episode.26

At least three mechanisms relate to the effect of lidocaine in our preparation: 1) depth of anesthesia, 2) "total" cerebral blood flow, and 3) neurotransmitter or ionic changes. Lidocaine infusion may have increased the depth of anesthesia used during the study, as reported in other clinical situations,27 which could then improve postischemic recovery through the protective mechanism proposed for deep inhalation anesthesia.28 However, this possibility is not supported by others29–31 or by our experiments, in which lidocaine infusion did not evoke an EEG pattern consistent with deeper anesthesia and in which the animals in group 6 showed the slowest neuroelectrical recovery. These findings imply that the lidocaine may be more detrimental for recovery after ischemia; the effects of halothane are different from the effects of intravenous anesthetics such as barbiturates or etomidate, which protect the brain in conditions of experimental or clinical ischemia.1–6

The variations in cerebral blood flow and intracranial pressure between groups were very small and may not explain the differences in recovery rate on the basis of a direct vascular effect of lidocaine or, indirectly, by a decrease in intracranial pressure that could improve cerebral perfusion pressure. However, in our preparation, we did not measure the extent that the anastomosis contributed to the remaining cerebral blood flow during ischemia and thus cannot say whether lidocaine had a unique effect when this unmeasured fraction was increased selectively.

The observed action of lidocaine may result from a direct brain "protective" characteristic. This protective action has been reported when a high dose of this drug was used and was characterized by a barbiturate-like action, which decreased cerebral metabolism,3 and by a delaying effect in the K+-efflux initiated by ischemia.6 This latter event is very important and, according to Bures and Buresova32 and Astrup,33 a delay of the early ionic changes could also slow the progression of the events that lead to irreversible membrane failure. Another mechanism, compatible with the low dose of lidocaine used, relates to the hypothesis that at the beginning of ischemia an altered disposition (e.g., excessive release) of excitatory neurotransmitter, such as glutamate, may trigger a persistent opening of the Na+ channels, followed by an increase in intracellular water and an opening of the K+ channels.34 Lidocaine could act at this early stage by blocking Na+ channels, which is the mechanism of action that explains the local anesthetic effect of the drug35 and also its cardiac antiarrhythmic effect.36 This mechanism was proposed by Fink37 to explain the protective effect of low-dose lidocaine on nerve conduction and more recently by Prenen et al.,38 who demonstrated in a rat model that tetrodotoxin, a Na+ channel blocker, delayed ion shifts secondary to ischemia.

Lidocaine could also directly decrease the release of excitatory neurotransmitter, acting perhaps at the presynaptic level. This mechanism may operate in the heart, where lidocaine decreases the release of noradrenaline from cardiac sympathetic nerve endings during ischemia.39 We observed an accelerated rate of neuroelectrical recovery by lidocaine after a moderate blood flow reduction. This effect may not represent strict cerebral protection, because in our preparation 20 minutes of incomplete global ischemia may not lead to histopathologic changes and because early recovery may be followed by late histologic deterioration.18

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