An Evaluation of the Effect of Lidocaine in Experimental Focal Cerebral Ischemia


SUMMARY In order to determine the effect of lidocaine on focal cerebral ischemia, the left middle cerebral artery was transorbitaly occluded in twenty cats. Eleven received lidocaine hydrochloride intravenously. The infusion was begun half an hour prior to clip occlusion and the rate was adjusted to maintain an isoelectric EEG. Nine cats served as controls, receiving an equivalent volume of 5% dextrose 0.2% saline. Thirteen animals (7 lidocaine-treated and 6 control) were sacrificed after six hours of left middle cerebral artery occlusion without reperfusion. In the remaining seven cats, the vessel was occluded for four hours prior to sacrifice. Ischemic neuronal alteration was assessed by both histochemical and histological examination. With both durations of ischemia, there was no significant difference in the extent and severity of neuronal alterations between the lidocaine-treated and control groups of animals.

Stroke Vol 17, No 5, 1986
by 50 mls of a 2% solution of 2,3,5-triphenyl-2H-tetrazolium chloride (TTC). The brain was immediately removed from the intracranial cavity and the cerebrum sectioned coronally into two halves at the level of the optic chiasm. A 5 mm thick coronal slice obtained from the posterior end of the anterior half was incubated for 30 minutes at 37°C in 50 mls of a 2% solution of TTC. The distribution of color change (see results section) on the posterior surface of the slice was photographically recorded. The area of pallor in the ischemic cerebral cortex was calculated as a percentage of the total cross-sectional area of the hemisphere. The entire brain was fixed in formalin for at least 72 hours prior to paraffin processing. The histological changes of ischemia were independently evaluated, in a blinded manner, by microscopic examination of whole mounts of 8 micron-thick coronal sections of the cerebrum, stained with hematoxylin and eosin. These sections were obtained at the level of the optic chiasm. Ischemic neuronal damage was graded according to previously established criteria. For each grade or severity of ischemic neuronal change, the area of cerebral cortex was calculated as a percentage of the total cross-sectional area of the grey matter of the hemisphere. The results (control and treatment) were analyzed using the Wilcoxon's rank sum test. An p value less than 0.05 was considered statistically significant. The contralateral hemisphere was also examined for neuronal alterations.

### Results

1. **Physiological Parameters**

Pulse, blood pressure and temperature were maintained within normal limits in the control group of cats. In the lidocaine treated animals, hypotension sometimes occurred with the infusion. This was readily corrected by temporarily decreasing the rate of infusion and then administering neosynephrine intravenously if necessary. Mean arterial blood pressure was kept within 10-20 mm Hg of control value. Metabolic acidosis was corrected with intravenous sodium bicarbonate. The end-tidal pCO₂ correlated positively with the arterial pCO₂ and was a reliable guide to the adequacy of ventilation. It was maintained between 30-35 mm Hg.

2. **EEG Changes (fig 1)**

The EEG pattern in the unoperated anesthetized cat consisted of low voltage waves of mixed frequencies, the majority of which were in the alpha range. There was no significant difference between the two hemispheres. In the control group, occlusion of the left middle cerebral artery consistently resulted in a slight reduction of voltage and mild slowing of EEG activity over the ischemic hemisphere. This persisted throughout the duration of the experiment. The EEG pattern in the lidocaine-treated cats was profoundly altered within minutes of the start of the infusion. The initial change was that of burst suppression, which usually progressed to complete flattening of the EEG. This change was present bilaterally and was maintained to the time of sacrifice. With the dose schedule and mode of administration of lidocaine utilized in this study, seizure activity was not observed. The effect of the drug on the EEG was not significantly altered by changes in arterial blood pressure within the range observed during the experiment. Serum lidocaine levels were in the toxic range (>21.4 μmol/l) during EEG suppression (see table 1). The toxic level is the plasma concentration above which significant cardiovascular depression and seizures may be seen.

3. **Gross Pathological Findings**

The superolateral surface of the left hemisphere was pale, compared to the rest of the brain, which exhibited an intense red coloration due to the presence of the colored formazan product of the TTC reaction (see Discussion). The area of pallor corresponded to the territory of the left middle cerebral artery and confirmed occlusion of this vessel. The external appear-

![Figure 1. EEG changes with lidocaine infusion. Frank electrographic seizures were not observed. Following lidocaine administration (50 mg bolus IV and 50 mg/kg/hr), voltage suppression was consistently observed. This effect was independent of blood pressure. Serum lidocaine levels exceeded 21.4 μmol/l.](http://stroke.ahajournals.org/content/6/6/963_MO)
ane of the fresh uncut brain was otherwise unremarkable.

The area of infarction was better demarcated by incubation of the 5 mm slice of cerebrum in TTC. Incubation improved exposure of the cerebral tissue in the ischemic area to the compound, so that the post-incubation area of pallor was more representative of the area of infarction in the slice. Although the mean area of pallor in the lidocaine treated cats slightly exceeded that of the control, the difference was not statistically significant (table 2). The results were similar for both durations of ischemia.

4. Histology

The neuronal alterations in the cerebral cortex that resulted from occlusion of the middle cerebral artery are similar to those described in previous studies. Mild or Grade 1 change consisted of slight neuronal shrinkage with loss of Nissl substance. In severely altered neurons (Grade 3), there was severe shrinkage, bright cytoplasmic eosinophilia and nuclear pyknosis. The intermediate gradation (Grade 2 moderate change) was that of moderate neuronal shrinkage and increased nuclear basophilia without pyknosis.

The mean cross-sectional areas, expressed as percentages of the total cross-sectional area of the grey matter of the hemisphere are summarized in table 3. After six hours of ischemia, the mean total area of the cerebral cortex exhibiting ischemic neuronal alterations was similar in both treated (40 ± 17%) and untreated cats (37 ± 12%). Although the extent of severe neuronal alterations (Grade 3) in the lidocaine treated cats (mean = 8 ± 9%) was less than that of the control group (mean = 15 ± 10%), this difference was not statistically significant. Similarly, comparison of the other subgroups of severity (Grades 1 and 2) revealed no significant differences. In the animals subjected to 4 hours of left MCA occlusion, the results were comparable to those just described, with no statistically significant difference between treated and untreated groups. There was minimal ischemic neuronal alterations in the contralateral hemisphere.

Discussion

It has recently been suggested that lidocaine hydrochloride may confer protection on cerebral tissue during episodes of ischemia. This conclusion was based on the results of several metabolic and biochemical studies. Potassium efflux, which has been shown to occur from cortical neurons during ischemia, was decreased by massive doses of intravenous lidocaine during global ischemia. The dose required to achieve this effect also flattened the EEG and reduced oxygen and glucose consumption in the brain. As well, during periods of glucose lack, the addition of lidocaine hydrochloride to vagus nerve preparations decreased axonal permeability to potassium and sodium ions. It appeared, therefore, that lidocaine, by stabilizing membranes, reduced energy expenditure and delayed the onset of irreversible structural damage. This expectation is not confirmed by the results of the present investigation.

In support of a protective effect of lidocaine, Evans et al. observed that neurological function (as assessed by cortical somatosensory evoked response) was substantially preserved following cerebral air embolism in the animals that received a single prophylactic dose (5 mg/kg) of lidocaine. Considering that in dogs, this dose produced less than a 30% reduction in CMR02, the reported effect on SER's appeared dramatic and in excess of what can be predicted from neurochemical studies. It is pertinent to emphasize that cerebral air embolism in cats only transiently interrupts flow through small cerebral arteries and reperfusion occurs usually within a half hour, following dissipation of the embolus. Although the blood-brain barrier remains intact, intracranial pressure is often elevated. The salutary effect of lidocaine on neurological function during cerebral air embolism may partly be attributable to reduction in intracranial pressure. The model of focal cerebral ischemia utilized in the present study

Table 1

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Serum lidocaine concentration (μmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
</tr>
<tr>
<td>0-3</td>
<td>63.1 ± 22.96</td>
</tr>
<tr>
<td>3-6</td>
<td>42.0 ± 10.14</td>
</tr>
</tbody>
</table>

SE = standard error of mean.

Serum lidocaine levels were measured in five cats subjected to six hours of left MCA occlusion. The values exceeded the toxic level (21.4 μmol/l).

Table 2

<table>
<thead>
<tr>
<th>Duration of ischemia (hours)</th>
<th>Lidocaine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>(n = 7)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td>7 ± 6</td>
<td>57 ± 19</td>
<td>46 ± 11</td>
</tr>
<tr>
<td>4</td>
<td>(n = 4)</td>
<td>(n = 3)</td>
</tr>
<tr>
<td>49 ± 21</td>
<td>43 ± 19</td>
<td></td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Duration of ischemia (hours)</th>
<th>Severity of ischemia</th>
<th>% Area of cerebral cortical infarction (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lidocaine</td>
<td>Control</td>
</tr>
<tr>
<td>6</td>
<td>Grade 1</td>
<td>(n = 7)</td>
</tr>
<tr>
<td></td>
<td>10 ± 8</td>
<td>7 ± 6</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>22 ± 14</td>
</tr>
<tr>
<td></td>
<td>15 ± 12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>8 ± 9</td>
</tr>
<tr>
<td></td>
<td>15 ± 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All grades</td>
<td>40 ± 17</td>
</tr>
<tr>
<td></td>
<td>37 ± 12</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Grade 1</td>
<td>(n = 4)</td>
</tr>
<tr>
<td></td>
<td>13 ± 15</td>
<td>16 ± 17</td>
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<tr>
<td></td>
<td>Grade 2</td>
<td>9 ± 8</td>
</tr>
<tr>
<td></td>
<td>20 ± 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>6 ± 4</td>
</tr>
<tr>
<td></td>
<td>2 ± 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All grades</td>
<td>28 ± 18</td>
</tr>
<tr>
<td></td>
<td>38 ± 23</td>
<td></td>
</tr>
</tbody>
</table>
consisted of major vessel occlusion (middle cerebral artery) for 6 hours without reperfusion. Significant disruption of the blood-brain barrier occurred and the duration of ischemia was long enough to allow histologic changes to be apparent. The lack of benefit in the lidocaine-treated cats may well be a reflection of the severity and extent of the ischemic injury which exceeded that resulting from air embolism.

It is appropriate to further speculate on why lidocaine failed to provide benefit in the present investigation. Haschke and Fink have shown that the addition of lidocaine to porcine brain mitochondria markedly inhibited oxygen consumption. Specifically, this resulted from enzyme blockade in the electron transport system and was similar to the effect of anoxia. Previously, Geddes and Questel had observed that potassium-stimulated increases in the respiration of slices of rat brain cortex were considerably inhibited by lidocaine. Thus, in addition to membrane-stabilizing properties, high concentrations of lidocaine appear to possess the property of impairing cellular respiration and ATP production in a specific manner. The savings in oxygen and glucose consumption reported by Astrup et al. may partly be consequent on this. If these results can be extrapolated to in vivo situations, the availability of high energy substrates may be jeopardized by substantial doses of lidocaine. However, concentrations in excess of those used in this study would probably be required to produce such effects.

The extent and severity of ischemic neuronal alterations were not reduced by dosages of lidocaine high enough to abolish the EEG. A beneficial effect was similarly not observed when the duration of ischemia was shortened to four hours. Although there was a numerical trend toward a lesser percentage of grade 2 injury in the lidocaine group, this did not approach statistical significance (p = 0.25). Furthermore, the numerical trend was towards a larger percentage of grade 3 injury in the lidocaine treated animals. The inter-animal variation was such that it seemed highly unlikely that by enlarging this group by a few more animals that we would alter our conclusions. We cannot however exclude the possibility that lidocaine may be protective when used with shorter periods of focal ischemia.

The histological findings were corroborated by the results of TTC reaction. In the presence of intact mitochondrial enzymes, 2'-3'-4'-triphenyl-2H-tetrazolium chloride is reduced to a red colored formazan. This color change was absent in regions where irreversible tissue damage had occurred suggesting that this technique is a reliable histochemical indicator of cerebral infarction.

Lidocaine at high dose (plasma concentrations >25.5 μmol/l), exerts significant hemodynamic effects. This is associated with increased cerebrovascular resistance and reduced cerebral blood flow. Although reduction in cerebral blood flow might contribute to a reduction in intracranial pressure, it might also be harmful to the substrate supply of damaged dysautoregulated cerebral tissue. Hypotensive episodes responsive to pressor agents occurred in all animals after lidocaine administration. It is conceivable that these episodes, even though brief, contributed to the severity of ischemic alterations observed in the lidocaine-treated cats. The use of a smaller dose of lidocaine may avoid this complication.

The optimal dose required to suppress the EEG without inducing seizures has yet to be determined. Some investigators have emphasized the dual effect of this drug: EEG suppression in low doses and potent convulsant effect in 10–20 mg/kg dose range. Because of cardiotoxic effects, doses beyond this have seldom been evaluated until Astrup et al. showed that a single bolus of 160 mg/kg, rapidly administered, abolished the EEG. The corresponding peak plasma lidocaine level was 108 ± 16 mg/l. (≈ 432 ± 64 μmol/l). The EEG remained flat for up to 45 minutes after the bolus. The dose was much in excess of that required to produce cardiovascular toxicity in dogs, which were, however, on extracorporeal circulation during the experiments. By administering a 50 mg bolus IV followed by a continuous infusion of lidocaine at a rate slightly below 1 mg/kg/min, it was possible in our study to achieve prolonged EEG suppression.

The dose of lidocaine required to produce maximum reduction in cerebral metabolic rate is also not known. The EEG has been used in this study as an end point of treatment. However, in dogs pretreated with pentobarbital to the point of EEG suppression, lidocaine administration resulted in additional reduction of cerebral metabolic rate. This observation suggests that EEG suppression may not be the appropriate end point for lidocaine treatment, so that the amount infused during this study may have been inadequate for cerebral protection. However, as noted above, larger doses are associated with unacceptable cardiovascular depression.

Conclusion

In doses sufficient to suppress or flatten the EEG, lidocaine hydrochloride did not reduce the extent or severity of ischemic neuronal injury. Reducing the duration of ischemia from six to four hours did not result in a favorable modification of ischemic alterations in either the treated or the control group. There was good agreement between the results of histochemical (TTC) and histological methods of assessment.

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Time-Related Asymmetric Changes of Brain Microvessel β-Adrenergic Receptors in the Two Hemispheres After Carotid Occlusion

MARIA SANDRA MAGNONI, PH.D., LUDOVICO FRATTOLA, M.D.,* GIULIO PASINETTI, PH.D., STEFANO GOVONI, PH.D., FIORENZO BATTAINI, PH.D., AND MARCO TRABUCCHI, M.D.†

SUMMARY. The effect of short term and long term ischemia induced by right carotid occlusion was studied on β-adrenergic receptor function in rat cerebral microvessels. The results show a different time-related dependency of the two hemispheres to ischemia, with a pronounced and more persistent decrease in the number of capillary β-receptors in the left side of the brain. The data suggest the existence of asymmetries in the control of brain microvasculature which may mediate the different time-course of β-receptor changes in response to ischemia.

Stroke Vol 17, No 5, September-October 1986

NEUROTRANSMITTER CONTENT and metabolism appear to be altered in various cerebral areas after temporary or permanent ischemia.1-11 The altered pattern of neuronal activity may influence brain capillary function. In fact, increasing evidence suggests that microcirculation in the brain is under neuronal control and that β-adrenergic receptors in cerebral capillaries may play an important role in the regulation of microvessel function.12-17

Recent studies demonstrated a different responsiveness of the microvasculature of the two hemispheres to ischemia. In fact, 48 h occlusion of the right carotid artery in the rat and in the gerbil induces a reduction in the number of β-receptors in brain capillaries of both hemispheres; notably, the reduction in the contralateral hemisphere is more marked than in the ipsilateral one, suggesting a different sensitivity of the microvasculature of the two sides of the brain to ischemia.18,19 To further investigate the responsiveness of the microvasculature of the two hemispheres to ischemia and the changes of its regulatory mechanisms, the natural evolution of the phenomenon was studied by measuring the effect of right carotid ligature on β-adrenergic receptors in brain capillaries at early (2 to 38 h) and late times (96 h and 14 days) after the occlusion.
An evaluation of the effect of lidocaine in experimental focal cerebral ischemia.
M T Shokunbi, A W Gelb, S J Peerless, M Mervart and P Floyd

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