Continuous Lidocaine Infusion and Focal Feline Cerebral Ischemia

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We measured somatosensory evoked potentials, infarct size, and cerebral blood flow in 20 cats subjected to occlusion of the middle cerebral artery for 3 hours, followed by an equal period of reperfusion. The cats were randomized into a treatment group that received a continuous infusion of 2 mg/kg lidocaine hydrochloride or a control group that received an equivalent volume of normal saline. All 10 treated cats retained measurable evoked potentials throughout the experiment. In five control cats, evoked potentials disappeared completely at some point during the occlusion (difference between groups significant at \( p < 0.001 \)). Mean amplitude of the major cortical wave in the nine treated cats with cerebral infarcts was higher than that of the nine corresponding controls (\( p < 0.05 \)). Lidocaine reduced the mean \( \pm \) SEM size of the infarcts from 30.1 \( \pm \) 6.0% in the control group to 14.7 \( \pm \) 4.9% in the treated group (\( p < 0.05 \)). As blood flow was reduced in the infarct and peri-infarct zones in the control but not the treated cats, our results suggest that the beneficial effects of lidocaine may be due to preservation of blood flow in the ischemic zone. (Stroke 1990;21:107-111)

Work from this laboratory\(^1\) did not bear out the expectation from other in vivo studies\(^2,3\) that very high doses of lidocaine protect the brain during experimental cerebral ischemia. At high doses lidocaine produces hypotension, which may further impair cerebral perfusion in stroke\(^4\); high-dose lidocaine has also been shown to act as a metabolic poison.\(^4\) However, other in vivo studies\(^5,6\) suggest that certain features of cerebral ischemia are ameliorated by clinically relevant (i.e., lower) doses of lidocaine, particularly if the ischemia is transient and not severe.

Despite this lack of uniformity of opinion, investigation of the role of lidocaine in focal cerebral ischemia retains importance and interest. Lidocaine is already in clinical use and enjoys a reputation for safety;\(^7\) it has an adjunctive role in neuroanesthesia since it has been shown to reduce the increases in intracranial pressure associated with endotracheal intubation.\(^8\) If found experimentally to exert a salutary effect in temporary focal cerebral ischemia, lidocaine would be potentially useful in clinical situations in which ischemia is anticipated. We report on the influence of a continuous infusion of clinically relevant doses of lidocaine on the consequences of temporary focal cerebral ischemia assessed by measuring somatosensory evoked potentials (SSEPs), cerebral blood flow (CBF), and infarct size.

Materials and Methods

Twenty cats weighing 2.5–4.0 kg underwent transorbital occlusion of the left middle cerebral artery (MCA). Anesthesia was induced with 30 mg/kg i.p. ketamine hydrochloride and 0.1 mg/kg i.p. atropine sulfate. The cats were mechanically ventilated to maintain Paco\(_2\) at 30–35 mm Hg, and anesthesia was maintained with 0.5–1.5% halothane in an air/oxygen mixture (FI\(_O_2\) of 0.4) titrated to keep blood pressure at approximately 120/70 mm Hg. The cats were placed on a thermal blanket, and a rectal probe was inserted. The femoral artery and vein were cannulated. A left anterolateral thoracotomy was performed, the left atrium was cannulated, and the chest was closed in layers. Pulse, systemic blood pressure, left atrial pressure, core temperature, and end-tidal CO\(_2\) were continuously monitored.

The left MCA was transorbitally exposed as previously described.\(^9\) Ten cats randomized into the treatment group were pretreated with lidocaine hydrochloride. A 5-mg/kg bolus dose was injected intravenously over 3–5 minutes; the bolus dose was immediately followed by a 3 mg/kg infusion for 25 minutes. The MCA was then occluded at its origin.
with a microtourniquet or a Sugita temporary aneurysm clip. The lidocaine infusion was continued until the end of the experiment at a rate of 2 mg/kg/hr. Serum lidocaine levels were measured by fluorescent polarization immunoassay half an hour after the bolus dose and hourly thereafter. The clip was removed 3 hours after application, and vessel patency was confirmed by inspection under the microscope. The remaining 10 cats, which served as controls, had their MCAs exposed, occluded, and reopened as above but received an equivalent volume of normal saline.

For SSEP monitoring, a pair of subcutaneous stimulating electrodes were placed over each median nerve. A pair of Ag/AgCl cup electrodes were placed over the coronal sutures 1 cm lateral to the midline and connected to a common frontonasal lead. Each median nerve was stimulated with a square-wave pulse of 2 mA current (sufficient to produce ipsilateral forepaw twitching before muscle paralysis) and 0.2 msec duration at a rate of 4.5 pulses/sec, and SSEPs were recorded over the contralateral hemisphere. The stimuli were generated by, and the SSEPs were recorded on, a Nicolet Compact 4 averager (Madison, Wisconsin), which averaged 256 responses and displayed the result. At each recording epoch, two sets of responses were obtained from each hemisphere. SSEP was recorded after MCA exposure, but before lidocaine/saline infusion (baseline); immediately before MCA occlusion; 15, 30, 60, 90, 120, 150, and 180 minutes after MCA occlusion; and 15, 30, 60, 90, 120, 150, and 180 minutes after reopening of the MCA. The amplitude of the major cortical wave was measured from the trough of the major positive deflection to the peak of the major negative deflection. Each measurement was expressed as a percentage of the corresponding baseline SSEP.

To measure CBF 15 minutes before MCA occlusion (baseline), 120 minutes after MCA occlusion, and 15 and 120 minutes after reopening of the MCA, a 5-mm-thick coronal slice was obtained at the level of the optic chiasm. The slice was incubated in 50 ml of a 2% solution of 2,3,5-triphenyl-2H-tetrazolium chloride (TTC) at 37° C for 30 minutes. Both sides of the incubated slices were photographed. In the presence of functional pyridine nucleotide-linked enzyme systems, TTC turns bright red. The areas not stained red were regarded as infarcted and were mapped and expressed as percentages of the total cross-sectional area of the slice. The size of the infarct in each slice was determined by averaging the areas of pallor on the two surfaces of the slice. We and others have found this to provide a reasonable correlation with other techniques of assessing infarct size (References 10 and 11 and C. Hampf, A.W. Gelb, S.J. Peerless, and T. Shokunbi, unpublished observations).

To calculate CBF, full-thickness tissue samples were obtained from the brain in the zone of infarction and its periphery as delineated by TTC staining. The size and location of these areas differed from cat to cat, necessitating tissue samples that were correspondingly variable; this may have contributed to the interanimal variation in CBF. Mirror-image samples were obtained from the right hemisphere. These and the blood samples were analyzed in a five-channel Gamma well counter (Model 1282001, LKB Computagamma Counter, Gaithersburg, Maryland). CBF was calculated using standard techniques.

For statistical analysis, we used the $\chi^2$ test to compare number of cats with a given attribute, analysis of variance to compare SSEP amplitude and CBF, and the two-tailed $t$ test or the Mann-Whitney test to compare other variables between the groups. All results are reported as mean±SEM.

### Results

Pulse, systemic blood pressure, blood gases, and core temperature were maintained within the normal ranges throughout the experiment (Table 1). However, pre-occlusion pH was significantly lower in the control group. Mean serum lidocaine level in the treated group was below the threshold (21 μmol/l) for cardiovascular toxicity and epileptogenesis.

One cat in each group sustained no infarct at all. In the remaining cats, mean infarct sizes were 14.7±4.9% and 30.1±6.0% ($p<0.05$) for the treated and control groups, respectively.
Before MCA occlusion, mean amplitudes of the major SSEP cortical wave in the two hemispheres were similar in both groups. In the treated group, mean amplitude after 30 minutes of lidocaine infusion did not differ significantly from baseline.

Except for one in the control group, all cats suffered a reduction in SSEP amplitude in the left hemisphere within 15 minutes after MCA occlusion; the one control cat enjoyed an initial increase in SSEP amplitude but subsequently succumbed to the effect of ischemia. The amplitude decrement persisted until the end of the occlusion in 18 cats; one control and one treated cat recovered their SSEP amplitude before clip release. A measurable SSEP was always observed in the left hemisphere of all 10 treated cats, whereas the SSEP completely disappeared in five of the 10 control cats at some point during MCA occlusion (p<0.001). Furthermore, SSEP amplitude in the left hemisphere of six of the nine treated cats without recovery remained at ≥50% of baseline during MCA occlusion, while it did so in only two of the nine control cats without recovery (p<0.05). During reperfusion, two more control cats improved to SSEP amplitudes in the left hemisphere of >50% of baseline.

Among the 18 cats with cerebral infarcts, mean SSEP amplitude in the left hemisphere was higher in the treated than in the control group (Figure 1). After 180 minutes of reperfusion, recovery of SSEP amplitude in the left hemisphere was incomplete in both groups (70.1±10% and 45.1±11% of baseline in the treated and control groups, respectively).

Four cats (two from each group) were excluded from statistical analysis of CBF because a complete set of measurements was unobtainable due to technical reasons. In the control group, mean CBFs in the core and periphery of the infarct after 120 minutes of occlusion were significantly (p<0.05) lower than baseline and significantly (p<0.05) lower than those in the treated group (Table 2). In the treated group, core and periphery CBFs after 120 minutes of occlusion were not different from baseline. There was no significant difference between groups in CBF at other times.

To ascertain the effect of lidocaine infusion on CBF, baseline measurements were compared between groups. Mean baseline CBF in the right hemisphere in the treated group did not differ significantly from that in the controls. However, in the treated group there was a significant difference in baseline CBF between hemispheres (Table 2); baseline CBF in the core of the infarct was significantly lower than that in the corresponding area of the right hemisphere. In the control group, there was no difference between hemispheres in baseline CBF.

### Discussion

In a previous study from our laboratory, in which only a single bolus injection of lidocaine was used, we found a transient preservation of the SSEP and no reduction in infarct size. A single intravenous dose of lidocaine results in an initially high plasma concentration, which decays rapidly because of extensive first-pass hepatic metabolism and rapid distribution to all areas of the body.

### Table 2. Hemispheric Cerebral Blood Flow in Cats Subjected to Temporary Middle Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th>Time</th>
<th>Core of infarct</th>
<th>Periphery of infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Control</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>26.99±5.3*</td>
<td>35.49±5.4</td>
</tr>
<tr>
<td>Right</td>
<td>48.61±10.7</td>
<td>47.46±8.4</td>
</tr>
<tr>
<td>After 120 minutes of occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>31.56±10.5†</td>
<td>12.26±3.0†</td>
</tr>
<tr>
<td>After 15 minutes of reperfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>38.79±9.8</td>
<td>50.06±17.5</td>
</tr>
<tr>
<td>After 120 minutes of reperfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>56.18±12.1</td>
<td>67.50±24.8</td>
</tr>
</tbody>
</table>

Data are mean±SEM ml/100 g/min, n=8 for each group.

* p<0.05 different from right by two-tailed t test.
† p<0.05 different from control by two-tailed t test.
‡ p<0.05 different from baseline by analysis of variance.
tissues. It appeared reasonable to hypothesize that a stable plasma level would prolong lidocaine's protection of ischemic cerebral tissue, particularly if the MCA occlusion is brief and the vessel is reopened. The results of our present study validate this hypothesis.

It is apposite to note that the SSEP was always present in treated cats and that even when cerebral infarction had supervened, the SSEP amplitude was better preserved in them than in the control cats. We previously showed a transient preservation of the SSEP by a single bolus injection of lidocaine. In another study in which the ischemic insult was milder and transient, the decrease in SSEP amplitude was attenuated and its recovery was assisted by a similar dose of lidocaine. Thus, three studies have shown lidocaine to have a beneficial effect on SSEP. It is conceivable that ischemia results in mainly inhibitory influences on the SSEP that are removed by lidocaine with a resultant sparing of the SSEP, which has little to do with ultimate tissue survival. The reduction in infarct size in our present study and the previously demonstrated correlations between SSEP and CBF and neuronal injury make this proposed mechanism unlikely. It therefore appears that a continuous infusion of lidocaine enhances SSEP preservation during temporary MCA occlusion and increases the likelihood that the area of cerebral infarction will be small.

The effect of lidocaine on CBF and vascular resistance appears to be dose-dependent. Observations in rats have revealed that high lidocaine concentrations in the plasma were associated with a reduction in CBF and an increase in cerebral vascular resistance, whereas these parameters were unaltered at low lidocaine concentrations. We have shown that baseline CBF was not significantly altered by lidocaine infusion alone. This result extends the previous observations in conscious rats and suggests that in anesthetized, nonischemic cats, low-dose lidocaine does not reduce CBF.

The data obtained from CBF measurements indicate a relative preservation of blood flow in the ischemic zones of lidocaine-treated cats. This leads us to suggest that the benefits of a continuous infusion of lidocaine may be partly or completely attributable to better perfusion of ischemic tissue in treated animals. This may be due to a specific vasodilatory action on the intact microcirculation adjacent to the infarct. Other explanations for the protective effect of lidocaine include prevention of intracranial pressure elevation, reduction of cerebral metabolic rate, stabilization of membranes, and prevention of sodium influx with a concomitant reduction in energy expenditure. However, the importance of the vascular effect is emphasized by the fact that lidocaine is not beneficial in global ischemia, a condition in which no potential for collateral circulation exists and other sodium channel blockers that do not enhance CBF in focal ischemia are not beneficial.

Ipsilateral hemispheric CBF appeared not to be reduced by MCA occlusion in the treated cats, perhaps because it was already diminished (as indicated by a significant interhemispheric difference before clip application). It is unlikely that this reduction in baseline CBF is due to lidocaine alone since it was not observed in the contralateral hemisphere in the same cats. It seems that operative manipulation before clip application is the crucial risk. The lower pH in the control group may have served to offset this reactive vasoconstriction, thus making the interhemispheric difference in baseline CBF less apparent. However, lidocaine has been shown to constrict before it dilates the peripheral arterial vessels. Perhaps this vasoconstriction is augmented in traumatized vessels.

In conclusion, we have demonstrated that a continuous infusion of low-dose lidocaine enhanced residual CBF in temporary focal cerebral ischemia in cats and resulted in preservation of the SSEP and in smaller cerebral infarcts.

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References


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