

Effects of Delayed Administration of Low-dose Lidocaine on Transient Focal Cerebral Ischemia in Rats

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Background: The authors' previous study demonstrated that a clinical antiarrhythmic dose of lidocaine, when given before ischemia, is neuroprotective in a rat model of transient focal cerebral ischemia. In this study, the authors investigated whether the administration of this dose of lidocaine, when delayed until 45 min after the onset of ischemia, also reduces ischemic brain injury.

Methods: Lidocaine was administered as an intravenous bolus (1.5 mg/kg) followed by an intravenous infusion ($2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) for 165 min, beginning 45 min after the onset of a 90-min period of transient focal cerebral ischemia. Control animals were given the same volume of saline. Focal cerebral ischemia was induced by occluding the right middle cerebral artery using an intraluminal suture. Neurologic outcome and body weight loss were quantified 7 days later. The brain was fixed 7 days after ischemia and brain sections were stained with hematoxylin and eosin for assessment of infarct size and the number of intact neurons. In separate experiments, local cerebral blood flow and the electroencephalogram were measured during ischemia and 180 min into the reperfusion period. Infarct size was assessed after 24 h.

Results: Infarct size, at either 24 h or 7 days after ischemia, was not significantly reduced in the lidocaine group. However, the number of intact neurons was significantly increased in both the ischemic penumbra and core of the lidocaine group 7 days after ischemia, compared with the vehicle group. Rats treated with lidocaine demonstrated better neurologic outcome and less weight loss ($P < 0.05$). Lidocaine treatment had no significant influence on local cerebral blood flow and electroencephalogram during ischemia and reperfusion.

Conclusions: Administration of a clinical antiarrhythmic dose of lidocaine, beginning 45 min after the onset of ischemia, reduces ischemic brain injury after transient focal cerebral ischemia in the rat. This indicates that delayed administration of neuroprotective agents may reduce brain damage resulting from ischemia.

THERE are a number of *in vitro* and *in vivo* investigations suggesting that lidocaine can reduce ischemic cerebral injury.¹⁻¹³ Our recent study demonstrated that a clinical antiarrhythmic dose of lidocaine is neuroprotective in a rat model of transient focal cerebral ischemia.¹⁴ However, all of these studies involved administration of lidocaine before the onset of ischemia. In the clinical

setting, therapeutic procedures are frequently started after the onset of cerebral ischemia.

Experimental and clinical studies have shown that focal cerebral ischemia produces a densely ischemic core and an ischemic penumbra with a moderate reduction of blood flow.^{15,16} Recent evidence suggests that ischemic brain injury after focal ischemia progresses slowly within the ischemic region, especially the ischemic penumbra.¹⁷⁻²⁰ The infarct develops over a period of many hours. Although there would seem to be little hope of rescuing cells in the ischemic core, delayed therapeutic interventions may still protect neurons in the penumbra. A few studies have shown that several agents are neuroprotective in the rat model of transient focal cerebral ischemia even if administration is delayed.²¹⁻²³ Therefore, in the current experiment, we investigated whether administration of a clinical antiarrhythmic dose of lidocaine 45 min after the onset of ischemia reduces brain injury following transient focal cerebral ischemia in rats. In addition, we examined the effect of this dose of lidocaine on local cerebral blood flow (LCBF) using a laser Doppler flowmeter.

Material and Methods

Animals and Surgical Preparation

This study was approved by the Institutional Animal Care and Use Committee of the State University of New York Downstate Medical Center. Male Wistar rats (weight, 280-340 g) were allowed access to food and water before surgery. Anesthesia was induced with a gas mixture of isoflurane (3%), oxygen (40%), and nitrogen (remainder); the animals were then orally intubated and mechanically ventilated with 2-2.2% isoflurane in the same gas mixture. The end-tidal carbon dioxide, inspiratory oxygen, and inspiratory isoflurane concentrations were monitored continuously using an airway gas monitor (DATEX Intrumentarium Co., Helsinki, Finland), and ventilation was adjusted to maintain normocapnia. Temperature probes were inserted into the rectum and the left-side temporalis muscle of each animal. Rectal and pericranial temperatures were kept constant at $38.0 \pm 0.2^\circ\text{C}$ by surface heating or cooling using a temperature-controlled heating pad (Harvard Apparatus Ltd., Edenbridge, Kent, United Kingdom) and a temperature controller (Physitemp, Clifton, NJ) throughout the surgical procedure. The tail artery and right femoral vein were cannulated for monitoring of arterial blood pressure, periodic blood sampling for arterial gases, pH, blood glucose concentration, and hematocrit (10 min

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Received from the Departments of Anesthesiology and Physiology and Pharmacology, State University of New York Downstate Medical Center, Brooklyn, New York. Submitted for publication April 15, 2002. Accepted for publication July 30, 2002. Supported by the National Institute of General Medical Sciences, Bethesda, Maryland, and Brooklyn Anesthesia Research, P.C., Brooklyn, New York. Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 13-17, 2001.

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before ischemia, at 45 min of ischemia, and 60 min after the end of ischemia) and for drug administration. Animals were prepared for middle cerebral artery (MCA) occlusion according to the method of Koizumi *et al.*²⁴ An incision was made in the midline of the neck, the right-side carotid bifurcation was exposed, and the external carotid artery and the internal carotid artery were dissected. After completion of the surgical preparation, the isoflurane concentration was reduced to 1.7%.

Transient Focal Ischemia and Drug Administration

After a 30-min period of physiologic stabilization, the right-side common carotid artery and the external carotid artery were ligated, and the blood flow of the internal carotid artery was transiently interrupted. An arterial incision was made on the carotid bifurcation near the internal carotid artery, and a 19-mm length of silicone-coated 4-0 nylon suture was inserted into the lumen of the internal carotid artery until it blocked the origin of the MCA. At 45 min after the onset of ischemia, animals were randomly allocated to either the vehicle group ($n = 15$) or the lidocaine group ($n = 14$). The number of successful MCA occlusions was 11 for each group. Two animals from the vehicle group and one from the lidocaine group had a subarachnoid hemorrhage due to vessel perforation. Two animals from each group had no neurologic disturbance 30 min after recovery from anesthesia, presumably due to unsuccessful MCA occlusion. All seven of these animals were excluded from the study. In the lidocaine group, a 1.5-mg/kg (1 mg/ml in saline) bolus dose of lidocaine was administered intravenously over a period of 2 min beginning 45 min after the onset of ischemia. Thereafter, a continuous infusion of lidocaine was initiated at a rate of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and continued until 120 min after the end of ischemia. A previous study demonstrated that the plasma lidocaine concentration with the same dosage regimen was $1.2 \pm 0.4 \text{ } \mu\text{g/ml}$ at 75 min after the beginning of lidocaine administration.¹⁴ In the vehicle group, the animals were given the same volume of saline. After 90 min of ischemia, reperfusion was accomplished by withdrawal of the intraluminal suture, and the neck incision was closed. At 180 min of reperfusion, the temperature probes and the catheters were removed, the trachea was extubated, and the animal was allowed to survive for 7 days. The animal's body weight was measured before the experiment and 7 days after ischemia.

Quantification of Ischemic Cerebral Damage

A neurologic examination was done at 30 min and 7 days after recovery from anesthesia. This was performed by an observer who was blinded to the experimental groups. A standard scoring scale was used: 0, normal; 1, fails to extend the left forepaw; 2, circles to the left; 3, falls to the left; and 4, does not walk spontaneously or exhibits a consciousness disturbance.²⁵ Rats

that exhibited convulsions, that sustained consciousness disturbances, or that were without neurologic deficits 30 min after recovery from anesthesia were excluded from the study.

Seven days after ischemia, the animals were anesthetized with 3% isoflurane and perfused transcardially with saline, followed by a 10% buffered formalin solution for the fixation of tissues. The brain was removed and post-fixed in a 10% formalin solution for 4 to 5 days at 4°C. Each brain was cut into seven 2-mm-thick coronal blocks using a rat brain matrix. The blocks were cryoprotected with a series of 20, 25, and 30% sucrose solutions in phosphate buffer solution at 4°C, embedded in molds with embedding compound (Sakura Finetek U.S.A., Inc., Torrance, CA) and dry ice, and stored at -70°C until sectioned. A thin coronal section (16 μm), 1 mm from the anterior surface of each coronal block, was cut on a cryostat. The sections were dried and stained with hematoxylin and eosin. Video images of individual sections were obtained with a charge-coupled device camera (Pixera Corp., Los Gatos, CA) equipped with a macro lens. Brain areas were traced and measured with an image analysis system (NIH Image 1.60; National Institutes of Health, Bethesda, MD). The volume of infarction was calculated as the integrated product of the cross-sectioned area for the sections and the distance between sections.

For quantitation of neuronal damage, intact neurons were counted in an area of 0.22 mm^2 on hematoxylin-and-eosin-stained sections (from the third coronal block) at $\times 250$ magnification using a light microscope. The ischemic penumbra and the ischemic core were chosen for cell counting. In accordance with previous studies on the measurement of local cerebral blood flow in this focal ischemia model,^{15,26} the primary somatosensory cortex was defined as the ischemic penumbra, and the secondary somatosensory cortex was defined as the ischemic core. Both regions were delineated on each slice by referring to a rat brain atlas.²⁷ The counting was performed by an observer who was blinded to the experimental groups.

Local Cerebral Blood Flow Measurement and Electroencephalography

In a separate experiment, 14 animals were used to determine the effect of lidocaine on cerebral blood flow and the electroencephalogram. These rats were prepared as described earlier, except that a laser Doppler probe (Probe 407-1; Perimed, Jarfalla, Sweden) and a monopolar electroencephalographic electrode (a stainless steel screw) were placed on the right side of the skull. The skull was exposed, and a small area of the skull overlying the right parietal cortex was thinned. The laser Doppler probe was firmly fixed on the skull (2 mm posterior and 5 mm lateral to the bregma). LCBF was continuously recorded throughout the experiments. The electro-

Table 1. Physiological Variables in the Experimental Groups

	24-h Experiment		7-day Experiment	
	Vehicle	Lidocaine	Vehicle	Lidocaine
Number	7	7	11	11
10 min before the onset of ischemia				
MABP (mmHg)	95 ± 6	93 ± 11	87 ± 5	85 ± 6
Arterial pH	7.44 ± 0.02	7.45 ± 0.02	7.43 ± 0.02	7.42 ± 0.04
Pao ₂ (mmHg)	137 ± 17	146 ± 20	148 ± 19	134 ± 25
Paco ₂ (mmHg)	43 ± 3	41 ± 4	42 ± 2	43 ± 2
Glucose (mg/dl)	187 ± 21	198 ± 30	182 ± 23	169 ± 23
45 min after the onset of ischemia				
MABP (mmHg)	103 ± 8 *	101 ± 11 [†]	105 ± 7*	108 ± 7*
Arterial pH	7.44 ± 0.03	7.45 ± 0.04	7.43 ± 0.04	7.43 ± 0.02
Pao ₂ (mmHg)	142 ± 23	158 ± 8	158 ± 18	150 ± 18
Paco ₂ (mmHg)	44 ± 4	42 ± 4	41 ± 3	42 ± 2
Glucose (mg/dl)	185 ± 16	199 ± 26	186 ± 22	175 ± 19
60 min after the end of ischemia				
MABP (mmHg)	90 ± 3	96 ± 7	92 ± 8	94 ± 4
Arterial pH	7.44 ± 0.01	7.44 ± 0.01	7.42 ± 0.02	7.42 ± 0.01
Pao ₂ (mmHg)	131 ± 23	154 ± 16	158 ± 9	152 ± 15
Paco ₂ (mmHg)	43 ± 3	42 ± 3	42 ± 2	43 ± 2
Glucose (mg/dl)	189 ± 17	189 ± 25	188 ± 14	175 ± 22

Data are mean ± SD. † $P < 0.05$, * $P < 0.01$ (paired Student *t* test) versus 10 min before the onset of ischemia.

MABP = mean arterial blood pressure; Pao₂ = arterial oxygen tension; Paco₂ = arterial carbon dioxide tension.

encephalographic electrode was attached to the right skull (4 mm lateral and 0 mm posterior to the bregma), and the reference electrode was placed under the skin of the neck. Electroencephalographic activity was continuously recorded with a Macintosh type of computer using a Maclab Bio Amp and a Maclab/4e analog-to-digital converter (AD Instruments Pty Ltd., Castle Hill, Australia). The bandpass was set at 0.5–30 Hz, and changes in electroencephalographic amplitude were quantified using spectral analysis. Both LCBF and electroencephalographic data were reported as percent of the baseline before ischemia. The animals were randomly assigned to the vehicle or lidocaine group ($n = 7$ for each), and the dosage regimen for lidocaine administration was the same as described before. The animal was allowed to recover from anesthesia 180 min after the end of ischemia; 24 h later, the brain was fixed and removed. The third of seven coronal blocks was processed for measuring infarct size as described above. This block was chosen since it has a maximal lesion area that is well correlated with total infarct volume.^{21,28} To correct for the effect of brain edema, infarct areas were adjusted by the ratio of the areas of both cerebral hemispheres (left over right). Cell counting was not performed on these sections because 24 h after the onset of an ischemic event is too short a time to evaluate cellular ischemic neuronal injury accurately.¹⁷

Statistical Analysis

All values, except for neurologic scores, are presented as mean ± SD. Infarct size, body weight, number of intact neurons, and physiologic variables were analyzed

with the unpaired Student *t* test. LCBF and electroencephalographic data were analyzed with two-way analysis of variance followed by Bonferroni posttests. LCBF and electroencephalographic data for each time point were further analyzed with the more sensitive unpaired Student *t* test. Neurologic scores are reported as the median (quartile deviation). Neurologic scores were compared by the use of the two-tailed Mann-Whitney U test. A value of $P < 0.05$ was considered significant.

Results

Mean arterial blood pressure, arterial oxygen tension, arterial carbon dioxide tension, arterial pH, blood glucose concentration, and hematocrit did not differ significantly between the vehicle and lidocaine groups for the 7-day and the 24-h experiments. During the period of ischemia, there was a slight increase in mean arterial blood pressure in all groups. Moderate hyperglycemia was also noted in all groups, but there were no differences between the vehicle and lidocaine groups (table 1).

Middle cerebral artery occlusion induced an immediate reduction of LCBF to approximately 20% of baseline (fig. 1). Throughout the 90-min ischemic period, LCBF remained at 20–35% of baseline. Following withdrawal of the intraluminal suture, LCBF gradually recovered, but it did not return completely to baseline. Delayed hypoperfusion persisted until the end of the 180-min post-ischemic observation period. There were no significant differences between the vehicle and lidocaine groups at any time point during ischemia and reperfusion, even when the more sensitive Student *t* test was used.

Table 2. Infarct Areas at 24 h after Ischemia (mm²)

	Total Infarct Area	Cortical Infarct Area	Subcortical Infarct Area
Vehicle (n = 7)	22.5 ± 6.7	12.3 ± 5.3	9.2 ± 4.2
Lidocaine (n = 7)	17.6 ± 8.6	9.1 ± 7.0	8.6 ± 2.1

Values are mean ± SD. Infarct area was measured using hematoxylin and eosin stained sections from the third coronal block of brain tissue.

increased in both the ischemic penumbra and the ischemic core of the lidocaine group compared with the vehicle group.

Discussion

This study demonstrates that a clinical antiarrhythmic dose of lidocaine, when administered 45 min after the onset of a 90-min period of transient focal cerebral ischemia, is effective in reducing ischemic cerebral injury. Although the size of the infarct was not significantly reduced in the lidocaine-treated rats, there was an increase in the number of surviving neurons in both the ischemic penumbra and the ischemic core, an improvement of neurologic outcome, and an increase of post-ischemic body weight. This dose of lidocaine did not significantly alter cerebral blood flow during ischemia and reperfusion.

The measurement of infarct size is a standard method for evaluating the extent of cerebral damage after focal cerebral ischemia. However, there may not be a precise 1:1 correspondence between infarct size and the amount of cell death.¹⁷ Infarct measurement is based on differences in staining between the infarct and the non-infarct areas. Identification of the infarct requires a certain percentage of the cells in that region to die. In the periinfarct area, there is some cell death but no infarct; even in the infarct area there are surviving neurons, especially at early stages of ischemia.²⁰ Thus, we mea-

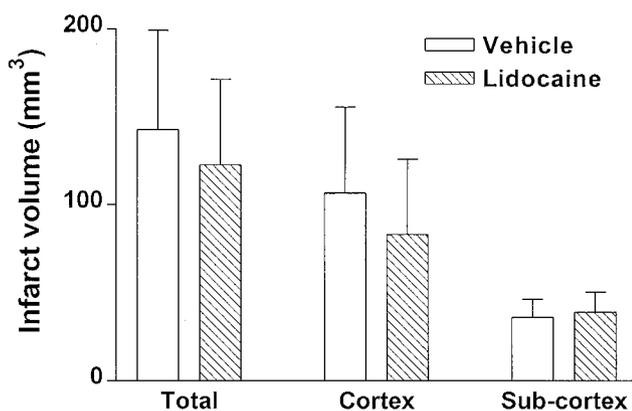


Fig. 5. Total, cortical, and subcortical volumes of infarct 7 days after ischemia. Infarct volume (mm³) was measured in brain sections stained with hematoxylin and eosin. Data are presented as mean ± SD.

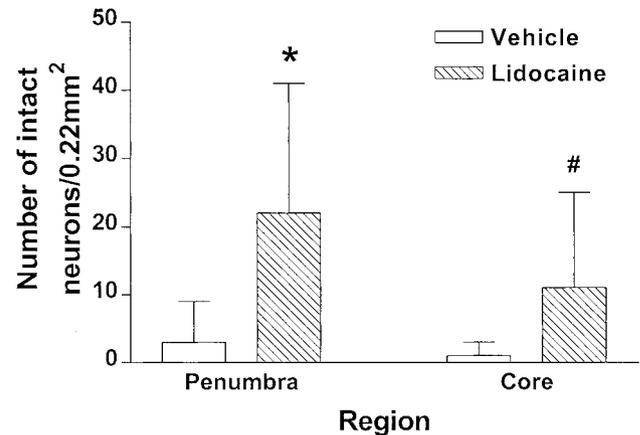


Fig. 6. The number of intact neurons in the ischemic penumbra and the ischemic core 7 days after ischemia. Intact neurons were counted in an area of 0.22 mm² on hematoxylin and eosin stained sections at ×250 magnification using a light microscope. The histologist was blinded to the treatment. The primary somatosensory cortex was defined as the ischemic penumbra and the secondary somatosensory cortex as the ischemic core. Values are mean ± SD. **P* < 0.01, #*P* < 0.05 versus the vehicle group.

sured both the infarct size and the number of intact neurons as an index of ischemic cerebral damage. We found no significant differences in infarct size at 24 h and 7 days after ischemia between the lidocaine and vehicle groups; however, the number of intact neurons at 7 days after ischemia was significantly increased in both the ischemic penumbra and the ischemic core of the lidocaine group compared with the vehicle group.

The precise mechanism by which lidocaine reduced the cerebral damage after transient focal cerebral ischemia is unknown. Recent experimental and clinical studies indicate that focal cerebral ischemia produces a densely ischemic core and an ischemic penumbra.^{15,16} Neuronal necrosis after MCA occlusion progresses from the core of densest ischemia toward the penumbral region of less dense ischemia, the latter is thought to contain potentially salvageable neurons.^{17,18} The onset of irreversible damage in the penumbra may occur after several hours and perhaps even days after ischemia. Most therapeutic attempts have been directed toward increasing the survival of salvageable neurons in the penumbra. Although the pathophysiology of the penumbral ischemic damage is not completely understood, repetitive depolarizations due to glutamate efflux and/or the release of potassium from the deteriorating ischemic core have been suggested to play an important role.^{17,18,29-32} In addition, oxidative metabolism of glucose and ATP generation may be impaired as a result of a reduction of blood flow in the penumbra.³³⁻³⁵ Repetitive depolarizations are especially harmful to the energetically stressed cells in the penumbra. Lidocaine may reduce ischemic cell damage by attenuating ATP depletion, reducing repetitive depolarizations, blocking Na influx, and/or inhibiting the release of glutamate.^{1,2,4,12,13,36}

Li *et al.*³⁷ reported that there were some intact neurons in the ischemic core 46 h after 2 h of MCA occlusion. This suggests that delayed therapeutic interventions might be effective in rescuing neurons in this region. We found significantly more intact neurons in the ischemic core of the lidocaine group compared with the vehicle group. This indicates that delayed administration of lidocaine can rescue neurons in the ischemic core. Although there would be little lidocaine available to the ischemic core during the period of MCA occlusion, lidocaine can enter this region after the onset of reperfusion. Thus, in this region, lidocaine administration may protect those neurons that are damaged but not dead from secondary damage.

The current study found that lidocaine-treated rats had better neurologic outcome and less body weight loss 7 days after ischemia, despite the absence of significant reduction of infarct size. Histochemistry of the ischemic cerebral damage is the conventional end point for evaluating the efficacy of neuroprotective therapies. However, the most important clinical end point is a functional one, because the goal of clinical therapies is not only to reduce infarct size, but also to improve function.

The neurologic scoring system used in the current study is mainly designed to test sensorimotor function.^{38,39} Sensorimotor dysfunction is commonly noted in the rat subjected to transient MCA occlusion. The mechanism of motor dysfunction after transient MCA occlusion is unclear. Bolay *et al.*⁴⁰ has demonstrated that motor dysfunction after transient MCA occlusion is due to a persistent synaptic transmission failure within the motor cortex. Thus, impairment of sensorimotor function may reflect changes in synaptic electrophysiologic function and may not necessarily reflect changes in infarct size. It is well known that extensive connections exist between motor cortex and sensory cortex and between the cortex and the subcortex.⁴¹⁻⁴³ These structures are involved in the processing and integration of sensorimotor information.^{44,45} The preservation of more neurons in the primary somatosensory cortex with lidocaine may be one of the factors in the improvement of neurologic function. It has been reported that abnormal glucose metabolism after MCA occlusion occurred not only in the MCA territory area but also in the "unaffected area," such as the substantia nigra, pars reticularis, and superior colliculus.⁴⁶ Lidocaine has multiple pharmacologic effects that are potentially neuroprotective, such as decelerating ischemic transmembrane ion shifts,¹ inhibiting anoxic depolarization,¹³ reducing the release of excitatory amino acids,^{2,12,36} scavenging oxygen free radicals,⁴⁷ and reducing intracranial pressure.⁴⁸ It may also reduce swelling by blocking Na influx.¹ Thus, lidocaine may mitigate impairment of those brain regions distant from the area of infarction and allow the animal to compensate for lost function using other brain areas.

This may have partially contributed to improvement of neurologic outcome observed in the lidocaine-treated rats.

In the current study, we measured LCBF using a laser Doppler flowmeter and did not find a significant effect of lidocaine on LCBF. Thus, the neuroprotective effect of lidocaine observed in this study appears to be not a result of an intras ischemic blood flow improvement. Using a rather high concentration of lidocaine (≈ 10 times higher than the concentration used in the current study), Shokunbi *et al.*⁸ found that lidocaine can increase the blood flow in the ischemic areas. It is possible that the effect of lidocaine on cerebral blood flow is dose dependent, and a clinical antiarrhythmic dose of lidocaine may not have a significant effect on cerebral blood flow. The laser Doppler probe in this study was placed near the secondary somatosensory region, which is the core of the infarct. Our measurements only reflect LCBF changes in the core of the infarct. We cannot rule out improvements in cerebral blood flow that might have occurred in the ischemic penumbra.

The data in the current study suggest a promising therapeutic use for lidocaine in cerebral ischemia. A recent clinical study has shown that lidocaine is neuroprotective in patients undergoing cardiac operations.⁴⁹ A major practical advantage is that this dose of lidocaine has little systemic toxicity and can be administered very shortly after the onset of ischemia. Our previous study demonstrated that this dose of lidocaine reduces infarct size when given before ischemia.¹⁴ Although infarct size was not significantly reduced by delayed administration of lidocaine in the current study, the number of intact neurons in both the penumbra and core was increased and neurologic outcome improved. The difference in the efficacy of neuroprotection between preadministration and delayed administration of lidocaine may reflect the fact that some neurons in both the penumbral and core areas became irreversibly damaged before lidocaine administration was started.

It should be noted that in the current study, the animals were killed at 7 days after ischemia. Several studies have shown that ischemic brain injury after focal ischemia progresses slowly and the maturation of the lesion may take longer than 1 week.⁵⁰⁻⁵² We cannot exclude the possibility that administration of lidocaine may have simply delayed the progression of ischemic brain injury and the observed difference in the number of intact neurons and the neurologic outcome might not differ between treated and untreated groups after a longer survival period. However, delaying the progression of ischemic brain injury is important because this may provide a therapeutic window for other interventions.

In conclusion, we have demonstrated that administration of a clinical antiarrhythmic dose of lidocaine, beginning 45 min after the onset of transient focal cerebral ischemia, reduces ischemic cerebral damage and improves neurologic and physiologic outcomes. The neu-

roprotective effect of lidocaine observed in this experiment appears not to be due to an improvement of the intraschemic blood flow.

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