

THE EFFECT OF LIDOCAIN ON CEREBRAL BIOELECTRIC ACTIVITY AND ULTRASTRUCTURE IN FOCAL ISCHAEMIA

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SUMMARY:

In this study, we evaluated whether Lidocain would reduce ischaemic brain damage and restore bioelectric activity in cats subjected to permanent unilateral occlusion of the middle cerebral artery.

In the Lidocain treated group there was a statistically significant improvement in the latencies and amplitudes of somatosensory evoked potentials. The treated group showed also a more limited infarct area on the coronal brain sections. Light and electron microscope examination revealed that the histopathological infarct process was delayed in the treated group.

KEY WORDS:

Focal brain ischaemia, Cerebral infarction, Lidocain, Somatosensory evoked potentials

INTRODUCTION :

One of the most important factors, affecting mortality and morbidity in cranial surgical procedures is cerebral ischaemia. Since there is no widely accepted method in the treatment of this condition, several agents have been used to prevent the consequences of this entity (1,16,18).

Most scientists agree that protection of the brain from the harmful effects of ischaemia is a multifactorial, complicated problem that will not be solved by the discovery of a single pharmacological agent. At the same time, most acknowledge that injury by ischaemia can be altered favourably in certain circumstances by a variety of drugs, with many different modes of action. Previous experimental investigations of focal cerebral ischaemia have demonstrated the biphasic nature of ischaemic injury (1). The primary phase is thought to be reversible with preservation of tissue viability, if the ischaemia is relieved (2,14,21). The secondary phase is characterized by tissue necrosis and, therefore,

is irreversible (17,18). The first step of this secondary phase is destruction of the membrane leak of sodium and potassium and prevention, or reduction of metabolic disturbances associated with ischaemia (3,12,13,23).

The present study was undertaken to evaluate whether lidocain a membrane stabilizing agent, would reduce ischaemic brain damage and restore bioelectric activity in cats subjected to permanent unilateral occlusion of the middle cerebral artery.

MATERIALS and METHODS

Twelve cats of either sex, weighing an average of 3.1 kg were anaesthetized with intramuscular injection of ketamine hydrochloride (30 mg/kg). Intravenous and femoral arterial catheters were placed for continuously monitoring the blood pressure and for administration of drugs. One million units of penicillin G were administered intramuscularly and the cats were placed in a stereotaxic apparatus (David Kopf Instruments.).

Gross Type E 2 platinum-iridium needle electrodes were used for somatosensory evoked potential (SEP) measurements. Paired stimulating electrodes were placed over the right distal median nerve proximal to the transverse carpal ligament. The left side of the scalp was incised and retracted to allow placement of small recording needle electrodes into the left capsula interna. The reference electrode was placed at the chin. Somatosensory evoked responses were obtained by applying a stimulus (2.5 mVolts) to the right median nerve and recording from the cortical electrode. The responses were amplified by a differential preamplifier and displayed by an oscilloscope (Tektronix). The evoked potentials resulting from 256 to 512 median nerve stimulations were averaged by a model signal averager. At the end the SEP's were plotted on an X-Y recorder. After obtaining a satisfactory set of baseline signals, the right proximal MCA was exposed using a modified retroorbital microsurgical technique (22). In all cats, the MCA was occluded proximal to the take-off of the lenticulostriate arteries.

Twelve cats were equally divided into two groups. Six animals in Group 1 were treated with Lidocain, 20 mg/kg given as an intravenous bolus 30 minutes after MCA occlusion in a volume of 20 ml/kg. In the following two hours they received an intravenous infusion of 16 mg/kg Lidocain at a rate of 2 ml/kg/hour.

Group 2 cats received an intravenous infusion of 0.9 % saline solution, 20 ml/kg during the first 30 minutes of occlusion. After drug administration, saline solution was infused intravenously at a rate of 2 ml/kg/hour in all cats for the remainder of the experimental period.

All cats underwent SEP recordings at one hour and 24 hours postocclusion. The time from stimulus to two major reproducible positive voltage deflections (P1 and P2) and the major negative voltage deflection (MN) were recorded and used to compare the interpeak latencies. The amplitude of the cortical potential between the positive deflection P2 and the major negative deflection MN was the second criterion for comparing both groups. Covariance analysis was used to demonstrate the statistical significance between both groups.

Ten days after occlusion, the brains of the cats were removed and immersed in 10 % formaldehyde for 21 days. Coronal sections were obtained at the level of the mid-suprasylvian and ecto-sylvian gyrus. The infarct area was measured by planimetry of tracings from projected photographic slides of those sections and measurements were confirmed on histological slides from the same three sections. The areas of infarction were reported as a percentages of the total coronal section. The t-test was used to determine the statistical significance of differences in the average infarct areas in the two groups. In both groups light and electron microscopic study were also done to find the stage of the infarction. In the electron microscope study the structure of mitochondria, disaggregation of polysomes, distention of endoplasmic reticulum, dispersion of organelles and cellular fragmentation were compared.

RESULTS

Prior to MCA occlusion, there was no significant difference between the two groups in the interpeak latencies or in the P2-MN interpeak amplitude. The first positive deflection (P1) occurred 4.54 ± 0.04 msec and the second (P2) 7.84 ± 0.06 msec after the stimulus. The negative deflection (MN) was recorded at 10.75 ± 0.09 msec. The peak-to-peak amplitude of the major positive-negative voltage complex (P2-MN) was 5.30 ± 0.44 μ V.

One hour after left MCA occlusion all cats demonstrated slowing of the interpeak latency on the left hemisphere recordings (Table: 1). P1 latency increased to 4.88 ± 0.6 msec in the first group and to 4.98 ± 0.9 msec in the second ($p > 0.1$). P2 latency showed the most marked slowing. The interpeak latency increased from 7.76 ± 0.10 msec to 14.00 ± 1.3 msec in the first group ($p < 0.005$) and from 7.84 ± 0.06 msec to 14.60 ± 0.2 msec in the second group ($p < 0.005$). The most occlusion MN latency increased to 18.20 ± 0.2 msec in the first group ($p > 0.005$). There was a significant decrease to 2.22 ± 0.4 μ V of the pre-occlusion P2-MN amplitude ($p < 0.0001$) in the first and to 1.99 ± 0.3 μ V in second group ($p < 0.0001$). There was no significant difference between interpeak latencies and the P2-MN interpeak amplitude in both groups one hour after MCA occlusion (Table: 2).

Table I : The average P1, P2 and MN latencies of Groups I and II

	Before clipping	Right after clipping	24 hours after clipping
1. Group			
P1	4.58±0.09 msec	4.88±0.6 msec	4.8±0.9 msec
P2	7.76±0.10 msec	14.00±0.3 msec	9.4±0.4 msec
MN	10.60±0.18 msec	18.20±0.2 msec	13.7±0.9 msec
2. Group			
P1	4.54±0.04 msec	4.98±0.9 msec	7.4±1.0 msec
P2	7.84±0.06 msec	14.60±0.2 msec	17.7±1.8 msec
MN	10.75±0.09 msec	20.80±0.8 msec	21.8±2.1 msec

Table II : The average P2-MN voltage amplitude of both groups

	Before clipping	Right after clipping	24 hours after clipping
1. Group	5.28±0.70µV	2.22±0.4µV	3.92±0.3µV
2. Group	5.30±0.44µV	1.99±0.3µV	1.33±0.2µV

In the first group, at 24 hours after MCA occlusion, the interpeak latency showed evidence of improvement. The P1 component was 4.8 ± 0.9 msec, but P2 component decreased to 9.4 ± 0.4 msec from 14.0 ± 0.3 msec, ($p < 0.005$), and MN component was decreased to 13.7 ± 0.9 msec, ($p < 0.01$). The peak-to-peak amplitude of the left hemisphere P2-MN component, also measured after 24 hours, showed a significant increase to $3.92\pm 0.3\mu V$ (Fig:1). In the control group after 24 hours there was continued slowing of the interpeak latencies. The latencies of P1 component increased to 7.4 ± 1.0 msec ($p < 0.005$), P2 component increased to 17.7 ± 1.8 msec (< 0.05), and the MN component to 21.8 ± 2.1 msec (> 0.1). The P2-MN amplitude remained depressed at $1.33\pm 0.2\mu V$ level (Fig: 2). This was only 25 % of the pre-occlusion amplitude.

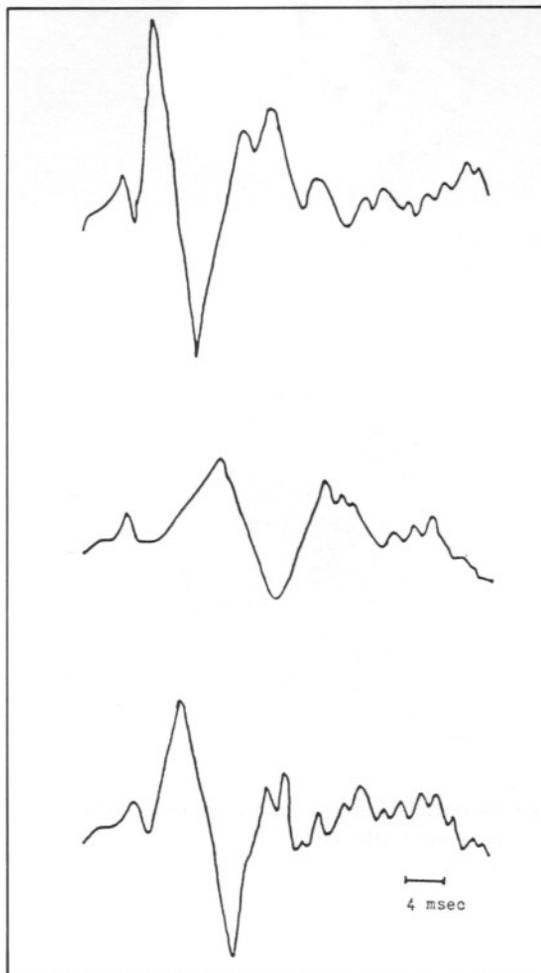


Fig 1 : SEP's in Group I: Before, right after and 24 hours after clippings

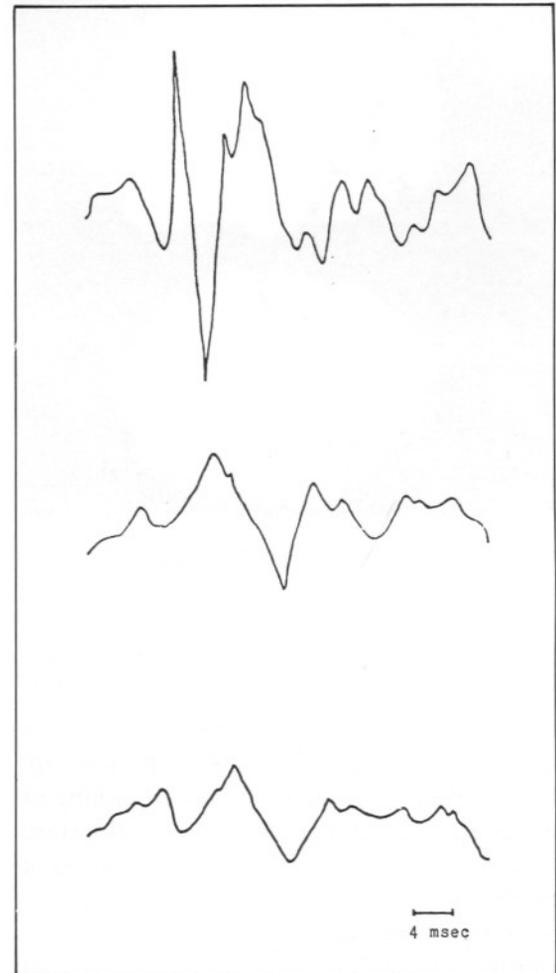


Fig 2 : SEP's in Group II: Before, right after and 24 hours after clipping.

The infarct size increased progressively from anterior to posterior. In Group 1 it was $44.0 \pm 1.1\%$ in the midsuprasylvian gyrus and $52.2 \pm 1.1\%$ in the ectosylvian gyrus (Fig : 3). In Group 2 the average area of infarction was $56.6 \pm 1.7\%$ in the first section and $60.8 \pm 1.7\%$ in the second (Fig: 4). There was a significant difference in infarct size in all the sections $p(<0.0001$ and $<0.005)$.

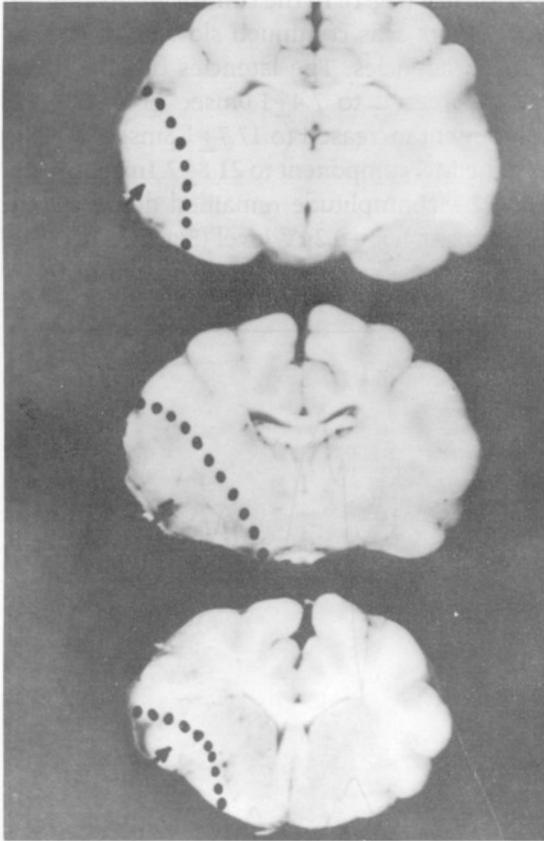


Fig 3 : Limited infarct area in lidocain group.

Light microscope examination of the Lidocain group revealed inactive necrotic areas, clear leucodiapedesis and infiltration of leucocytes without any capillary proliferation. This appearance was interpreted as the beginning of the second step of infarction (Fig : 5). Contrary to Group 1 the control group show no areas of necrosis. The whole necrotic tissue was cleaned and there was diffuse vascular proliferation which is a typical sign of the end of the second step of infarction (Fig : 6).

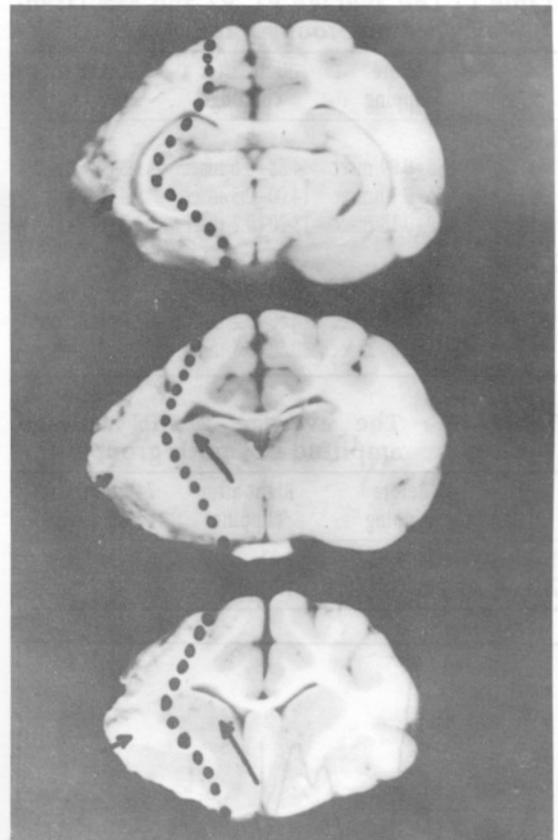


Fig 4 : Infarct area with secondary ventricular dilatation in control group.

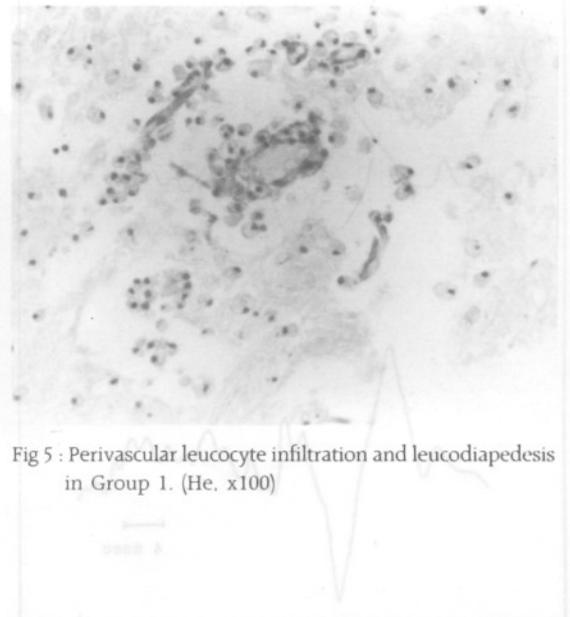


Fig 5 : Perivascular leucocyte infiltration and leucodiapedesis in Group 1. (He. x100)

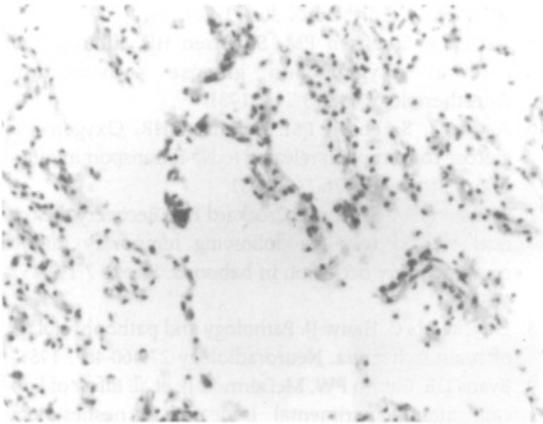


Fig 6 : The whole necrotic tissue is cleaned in the control group. (HE. x100)

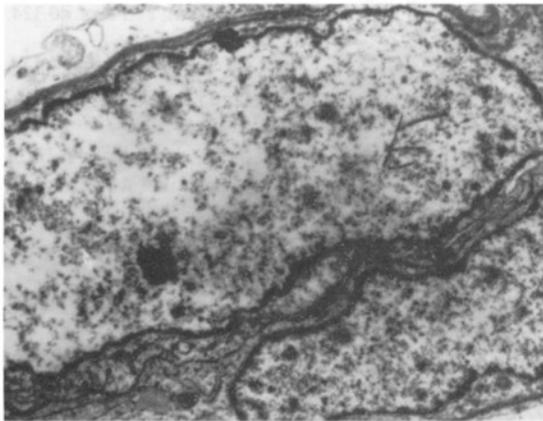


Fig 7 : Preserved endothelium including the basal lamina. (x10300)

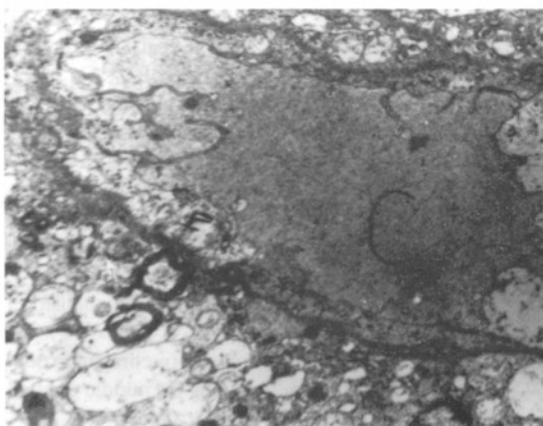


Fig 8 : Severe perivascular aedema in control group. (x10300)

DISCUSSION

Despite extensive research with global focal ischaemia model, adequate treatment for oc-

clusive stroke has not yet been found. Ideally treatment of acute focal ischaemia should be directed toward protecting cerebral tissue during the primary reversible phase thereby preventing or retarding transition into the secondary phase (1,8,14), because it is clear that areas of brain with cell death and tissue loss cannot be expected to recover function. The potential for collateral flow in focal ischaemia may facilitate possible reversal of neuronal damage after extended periods of ischaemia; therefore the pathophysiological features and treatment differ from those of global ischaemia (9). Various agents have been shown to have a beneficial effect in acute cerebral ischaemia when administered at an early stage.

The natural history and utility of SEP's during experimental cerebral ischaemia and infarction in cats have been well characterized by Meyer et al (19). Changes in the interpeak latencies with experimental stroke correlate with the size and location of the infarction. Especially, loss of P2-MN amplitude appears to be a sensitive measure of the onset of ischaemia. The pre-occlusion interpeak latencies measured in our animals corresponded to these described by others.

Lidocain inhibits electrocortical activity, with a consequent decrease in oxygen and glucose consumption, which means suppression of synaptic transmission and inhibition of metabolism in normal tissue. This action has been described by Astrup (1,4) as a "barbiturate-like effect". Secondly, lidocain has a specific membrane sealing or stabilizing effect that restricts the movement of sodium and potassium across the membrane and thus reduces the metabolic demand of the active transport systems for these ions. Numerous experimental and clinical studies have been performed to evaluate to use of lidocain for the treatment of cerebral ischaemia (3,4,5,6,7,10,11,15,20,23), but the results were inconsistent because different animal models, techniques, drug dosages and schedules and routes of administration were used.

Gedes and Quantel (15) were the first, to demonstrate that lidocain can decrease oxygen consumption in rat cortex. Wagman (23) used

lidocain to depress cortical activity in rats and cats. It is significant that so far Evans and Kobrine (10,11) have only demonstrated protection of cerebral function when lidocain is given prior to acute cerebral ischaemia induced by air embolism, and they suggest that lidocain may be a useful agent for reducing intracranial hypertension associated with ischaemic or traumatic injuries to the brain. Astrup (3,4,5) used lidocain to demonstrate these effects in much higher doses than would be acceptable clinically. But other studies demonstrated that even at low doses, lidocain has both these effects (7).

We used clinically compatible dosages. All these studies were based on histopathological and blood flow studies. However evoked potential changes that occur following lidocain application in experimental stroke produced by MCA occlusion in cats have not been described. This is the first study to correlate the bioelectric activity of the brain and histological changes caused by lidocain treatment of focal cerebral ischemia. Our results demonstrate that lidocain can ameliorate postischaemic brain injury if given immediately after occlusion of the MCA. It preserved significantly the SEP latencies near to the preischaemic levels and the percentage of post-occlusion infarction was significantly reduced. Further experimental, especially clinical, studies should be done in the hope that lidocaine will find wide acceptance in clinical use.

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