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# *The Detrimental Effect of Lidocaine on Cerebral Metabolism Measured in Dogs Anesthetized with Isoflurane*

*Leslie Newberg Milde, M.D.,* James H. Milde†*

**Previous studies in dogs have demonstrated that massive doses of intravenous lidocaine (160 mg·kg$^{-1}$) can inhibit cerebral oxygen metabolism to a greater degree when administered with pentobarbital than can pentobarbital alone. From these data, it was hypothesized that lidocaine decreases cerebral metabolism by two means: suppression of cortical electrical activity and stabilization of neuronal membranes, and it was suggested that lidocaine might provide protection for the ischemic brain. In an attempt to apply this property clinically, the effect of a lower, clinically tolerated dose of lidocaine (15 mg·kg$^{-1}$) on cerebral oxygen metabolism and cerebral blood flow was examined in dogs receiving deep isoflurane anesthesia. Once maximal metabolic suppression, as reflected by an isoelectric EEG, was achieved with isoflurane (3% end-expired), the administration of this dose of lidocaine had little effect on cerebral blood flow (CBF) and cerebral oxygen consumption ($CMRO_2$). The CBF was 94 ± 19 ml·min$^{-1}$·100 g$^{-1}$ during 3% isoflurane anesthesia, and was 102 ± 11 ml·min$^{-1}$·100 g$^{-1}$ with the addition of lidocaine. The $CMRO_2$ was 2.32 ± 0.23 ml·min$^{-1}$·100 g$^{-1}$ during isoflurane anesthesia, and was 2.18 ± 0.09 ml·min$^{-1}$·100 g$^{-1}$ following the administration of lidocaine. However, this dose of lidocaine did produce a derangement of cerebral metabolites. The cerebral concentration of ATP during 3% isoflurane anesthesia was 2.07 ± 0.04 μmol·g$^{-1}$ (cerebral ATP in normal unanesthetized dogs is 2.01 ± 0.01 μmol·g$^{-1}$). Cerebral ATP concentration was significantly reduced to 1.77 ± 0.05 μmol·g$^{-1}$ by lidocaine. The cerebral energy charge (EC) under 3% isoflurane was 0.904 ± 0.011. The administration of lidocaine significantly decreased the EC to 0.844 ± 0.002. From this study, it is concluded that, although a large but clinically tolerated dose of lidocaine did not produce additional metabolic suppression in the presence of maximal metabolic suppression produced by isoflurane, it may have a direct toxic effect on oxidative phosphorylation. Therefore, any measured decrease in cerebral metabolism produced by large doses of lidocaine may be due to a combination of factors, both "protective" and toxic, including suppression of electrical cortical activity, stabilization of membranes, and uncoupling of oxidative phosphorylation. (Key words: Anesthetics, local: lidocaine. Anesthetics, volatile: isoflurane. Brain: blood flow; electroencephalogram; metabolism; oxygen consumption. Metabolism: oxidative phosphorylation.)**

IT IS REPORTED that a massive dose of lidocaine (160 mg·kg$^{-1}$) given to dogs anesthetized with 1–1.5% halothane inhibits cortical electrical activity, which represents synaptic activity or interneuronal function, with a parallel decrease in cerebral oxygen metabolism ($CMRO_2$).[1] The magnitude of this effect is similar to that of several general anesthetics, including thiopental,[2] isoflurane,[3] and etomidate,[4] which have no effect on $CMRO_2$ in the absence of cortical electrical activity (indicated by an isoelectric EEG). However, if a maximal decrease in $CMRO_2$ is first achieved by pentobarbital through abolition of the cortical electrical activity, the administration of 160 mg·kg$^{-1}$ lidocaine then produces an additional 15% decrease in cerebral metabolism.[1] Other studies have revealed that lidocaine not only suppressed cortical electrical activity with a parallel decrease in $CMRO_2$,[5] but also suppressed ionic leaks across neuronal membranes, thereby reducing the energy requirements of those active transport processes which maintain normal ionic gradients across membranes.[6,7] Theoretically then, this ability of lidocaine to produce a greater decrease in cerebral metabolism than other general anesthetics might provide some cerebral protection during situations of cerebral ischemia.

However, massive doses of lidocaine produce such profound cardiac depression that cardiopulmonary bypass is necessary for support of the circulation, thus limiting any possible cerebral protection afforded by lidocaine to those patients on cardiopulmonary bypass. The purpose of the present study was to determine whether lower doses of lidocaine, which might be more clinically tolerated, could provide additional cerebral metabolic suppression to that of the general anesthetics. We studied the effect of a bolus dose of 15 mg·kg$^{-1}$ lidocaine on the cerebral and systemic hemodynamics and metabolism in dogs in which maximal metabolic suppression was achieved by isoflurane.

## Methods

Ten unmedicated, fasting mongrel dogs weighing 15–19 kg were anesthetized with 1.4% end-expired isoflurane in 30% oxygen and nitrogen for the surgical preparation. Inspired and end-expired respiratory and anesthetic gases were continuously monitored by mass spectrometry. Succinylcholine (40 mg) was given intravenously to facilitate endotracheal intubation. Ventilation was controlled with a Harvard pump® adjusted to maintain normocarbia. Cannulae were inserted into a femoral artery for pressure measurement and blood sampling and into a femoral vein for blood return collected during the direct measurement of cerebral blood flow. A peripheral intravenous catheter was placed for

* Associate Professor of Anesthesiology.
† Instructor in Anesthesiology.
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Address reprint requests to Dr. Milde: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

drug and fluid administration, isotonic saline infused at a rate of 75 ml·h$^{-1}$. A 5-French flow-directed pulmonary artery catheter was placed through the right internal jugular vein for measurement of mean pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP), blood sampling, and measurement of cardiac output by thermodilution. The electrocardiogram was recorded continuously from limb leads. Core temperature, measured by a thermistor in the pulmonary artery, and brain temperature, measured by a parietal epidural thermistor, were maintained near 37° C. Intracranial pressure (ICP) was monitored by an epidural fiberoptic device (LADD monitor) and a four-lead EEG was recorded continuously from electrodes (bifrontal and biparietal) cemented to the skull.

After heparinization (300–400 IU·kg$^{-1}$ intravenously), the sagittal sinus was exposed, isolated, and cannulated as previously described[8,9] for direct measurement of cerebral blood flow (CBF) by a square-wave electromagnetic flowmeter.‡ The cranium was closed rigidly by sealing the cranial openings with Surgicel® and Super Line® adhesive.

Arterial blood gases, sagittal sinus oxygen tension ($P_{ss}O_2$) and mixed venous oxygen tension ($P_vO_2$) were determined by electrodes. Blood oxygen contents were calculated from measurements of oxyhemoglobin concentration and oxygen tension.[10] $CMRO_2$ was calculated as the product of CBF and the arterial-sagittal sinus oxygen content difference, while whole body oxygen consumption ($\dot{V}O_2$) was calculated as the product of cardiac index (CI expressed as l·min$^{-1}$·m$^{-2}$) and the arterial-mixed venous oxygen content difference. Cerebral perfusion pressure was calculated as the difference between MAP (measured at head level) and ICP. The cerebral vascular resistance index (CVRI) was calculated as the quotient of cerebral perfusion pressure and CBF, and the systemic vascular resistance index (SVRI) was calculated as the quotient of MAP and cardiac index. Blood glucose and serum lactate were determined by standard enzymatic techniques.

Following surgical preparation, the isoflurane concentration was increased to produce burst suppression or isoelectricity on the EEG which previous studies have demonstrated is accompanied by maximal decrease in cerebral oxygen consumption.[3] The concentration of isoflurane necessary to achieve this was 3% end-expired or 2.1 MAC in the dog. Steady-state values for the cerebral and systemic hemodynamic and metabolic variables were then obtained over 30 min. Cerebral blood flow, CVRI, $CMRO_2$, ICP, and EEG were measured at 5-min intervals. Mean values were calculated from these six observations. Arterial and pulmonary pressures, blood gases, cardiac index, SVRI, $\dot{V}O_2$, blood glucose, and serum lactate were measured at 15-min intervals, and mean values were calculated from these two observations.

In six dogs, lidocaine (15 mg·kg$^{-1}$) was then injected, as a bolus, intravenously, and all hemodynamic and metabolic variables were measured at 5-min intervals for 20 min and mean values were calculated from these four observations.

At the end of the study, the dura overlying the cerebral hemispheres was excised and bilateral cerebral cortical biopsy specimens were taken[11] and prepared for analysis.[12] Tissue extracts were analyzed by enzymatic fluorometric techniques for phosphocreatine (PCr), ATP, ADP, AMP, glucose, lactate, and pyruvate.[13] The energy charge (EC) of the tissue was then calculated from the adenine nucleotides.[14]

Cerebral cortical biopsies were taken from the four dogs receiving isoflurane alone, referred to as the quality control isoflurane group, and from the six dogs which received 15 mg·kg$^{-1}$ lidocaine in addition to isoflurane.

Within-group comparisons of the effect of 3% isoflurane *versus* 3% isoflurane + 15 mg·kg$^{-1}$ lidocaine on systemic and cerebral metabolism and hemodynamics were analyzed in the test group by Student's *t* test for paired data. Comparison of the metabolic and hemodynamic data of the quality control isoflurane group with the test group receiving isoflurane followed by lidocaine were analyzed by Student's *t* test for unpaired data. Comparison of cerebral metabolic concentrations obtained at the end of the study was made between the quality control isoflurane group, the test isoflurane + lidocaine group, and a normal unanesthetized group[15] by Student's *t* test for unpaired data with a Bonferroni correction. Statistical significance was assumed if $P < 0.05$.

## Results

The data from the two groups of dogs, the quality control isoflurane group which received only isoflurane (3% end-expired) and the test group which received isoflurane (3% end-expired) to which was added 15 mg·kg$^{-1}$ lidocaine, are presented in tables 1–4. The effects of 3% end-expired isoflurane alone and with the addition of lidocaine on systemic hemodynamics are presented in table 1. There were no differences between the quality control group receiving isoflurane and the test group receiving isoflurane alone. However, the bolus of lidocaine produced the predicted cardiac depression as indicated by a significant decrease in cardiac index from 3.1 ± 0.3 to 2.0 ± 0.3 l·min$^{-1}$·m$^{-2}$ and a significant increase in both mean pulmonary ar-

‡ EP 300 API, Carolina Medical Electronics.

TABLE 1. Effect of Isoflurane and Lidocaine on Systemic Hemodynamics

| | Quality Control, Isoflurane (3%) n = 4 | Test: Isoflurane (3%) n = 6 | Test: Isoflurane (3%) + Lidocaine (15 mg·kg$^{-1}$) n = 6 |
|---|---|---|---|
| MAP (mmHg) | 92 ± 7 | 93 ± 3 | 109 ± 11 |
| Heart rate (beats/min) | 102 ± 8 | 110 ± 6 | 102 ± 3 |
| PAP (mmHg) | 20 ± 1 | 20 ± 1 | 29 ± 2* |
| PCWP (mmHg) | 10 ± 1 | 11 ± 1 | 21 ± 2* |
| C.I. (l·min$^{-1}$·m$^{-2}$) | 3.6 ± 0.7 | 3.1 ± 0.3 | 2.0 ± 0.3* |
| SVRI (mmHg·l$^{-1}$·min·m$^2$) | 28 ± 4 | 32 ± 3 | 57 ± 4* |
| $\dot{V}O_2$ (ml·min$^{-1}$·m$^{-2}$) | 152 ± 9 | 149 ± 10 | 152 ± 7 |

Mean ± S.E.
* Significantly different from 3% isoflurane values ($P < 0.05$).

tery pressure from 20 ± 1 to 29 ± 2 mmHg and pulmonary capillary wedge pressure from 11 to 21 mmHg. The sytemic vascular resistance also increased significantly from 32 to 57 mmHg·l$^{-1}$·min·m$^2$. This increase in afterload may have also contributed to the decreased cardiac index. However, despite the decreased cardiac function, the increase in systemic vascular resistance maintained mean arterial pressure at 90–110 mmHg. Heart rate and total body oxygen consumption were not affected by the addition of lidocaine.

The arterial blood values are presented in table 2. There were no differences among the blood gases or chemistries between the two isoflurane groups or with the addition of lidocaine.

The effects of isoflurane alone and isoflurane + lidocaine on cerebral hemodynamics and metabolism are presented in table 3. Despite the marked changes in systemic hemodynamics produced by the bolus of 15 mg·kg$^{-1}$ lidocaine (table 1), there were no changes in the cerebral blood flow (maintained above a mean of 90 ml·min$^{-1}$·100 g$^{-1}$), cerebral vascular resistance (maintained at 1.2–1.5 mmHg·ml$^{-1}$·min·100 g), or ICP (9 mmHg). Most importantly, this dose of lidocaine produced only an insignificant decrease in global cerebral metabolism which decreased from 2.32 ± 0.23 to 2.18 ± 0.09 ml·min$^{-1}$·100 g$^{-1}$.

TABLE 2. Effect of Isoflurane and Lidocaine on Arterial Blood Values

| | Quality Control, Isoflurane (3%) n = 4 | Test: Isoflurane (3%) n = 6 | Test: Isoflurane (3%) + Lidocaine (15 mg·kg$^{-1}$) n = 6 |
|---|---|---|---|
| $Pa_{O_2}$ (mmHg) | 206 ± 20 | 183 ± 16 | 182 ± 17 |
| $Pa_{CO_2}$ (mmHg) | 39 ± 0 | 39 ± 1 | 41 ± 1 |
| *p*H (units) | 7.33 ± 0.01 | 7.35 ± 0.00 | 7.32 ± 0.01 |
| Lactate (μmol·ml$^{-1}$) | 2.4 ± 0.3 | 1.9 ± 0.4 | 2.3 ± 0.4 |
| Glucose (mg·dl$^{-1}$) | 113 ± 13 | 90 ± 4 | 100 ± 6 |

Mean ± S.E.
No significant differences.

TABLE 3. Effect of Isoflurane and Lidocaine on Cerebral Hemodynamics and Metabolism

| | Quality Control, Isoflurane (3%) n = 4 | Test: Isoflurane (3%) n = 6 | Test: Isoflurane (3%) + Lidocaine (15 mg·kg$^{-1}$) n = 6 |
|---|---|---|---|
| CBF (ml·min$^{-1}$·100 g$^{-1}$) | 140 ± 30 | 94 ± 19 | 102 ± 11 |
| ICP (mmHg) | 10 ± 3 | 9 ± 2 | 9 ± 2 |
| CVRI (mmHg·ml$^{-1}$·min·100 g) | 0.5 ± 0.1 | 1.2 ± 0.3 | 1.5 ± 0.4 |
| $CMRO_2$ (ml·min$^{-1}$·100 g$^{-1}$) | 2.34 ± 0.25 | 2.32 ± 0.23 | 2.18 ± 0.09 |
| $P_{ss}O_2$ (mmHg) | 78 ± 8 | 64 ± 4 | 69 ± 5 |

Mean ± S.E.
No significant differences.

The cerebral metabolic concentrations obtained at the end of the study are presented in table 4. Also presented in table 4 are the normal values for cerebral metabolites in unanesthetized dogs for our laboratory.[15] There was no difference in cerebral metabolite concentrations between the quality control group receiving 3% isoflurane and the normal unanesthetized group. However, the large dose of lidocaine given to isoflurane anesthetized dogs produced a significant decrease in the cerebral energy stores. ATP concentration was significantly decreased from 2.07 ± 0.04 to 1.77 ± 0.05 μmol·g$^{-1}$; and the energy charge, which represents the energy balance of the cell between ATP regeneration and processes that consume ATP, was significantly decreased from 0.904 ± 0.011 to 0.844 ± 0.002. There was no change from normal in phosphocreatine, glucose, or lactate concentration in either the quality control isoflurane group or in the test isoflurane + lidocaine group.

TABLE 4. The Combined Effect of Isoflurane and Lidocaine on Cerebral Metabolism

| | Normal (15) n = 6 | Quality Control, Isoflurane (3%) n = 4 | Test: Isoflurane (3%) + Lidocaine (15 mg·kg$^{1}$) n = 6 |
|---|---|---|---|
| ATP (μmol·g$^{-1}$) | 2.01 ± 0.01 | 2.07 ± 0.04 | 1.77 ± 0.05* |
| Phosphocreatine (μmol·g$^{-1}$) | 2.99 ± 0.12 | 3.40 ± 0.12 | 3.08 ± 0.08 |
| Energy charge | 0.871 ± 0.001 | 0.904 ± 0.011 | 0.844 ± 0.002* |
| Glucose (μmol·g$^{-1}$) | 2.46 ± 0.18 | 3.64 ± 0.55 | 4.08 ± 0.25 |
| Lactate (μmol·g$^{-1}$) | 1.23 ± 0.04 | 1.27 ± 0.14 | 1.50 ± 0.06 |
| Lactate/pyruvate ratio | 11 ± 0 | 15 ± 1 | 12 ± 1 |

Mean ± S.E.
* Significantly different from normal and quality control 3% isoflurane values ($P < 0.05$ with Bonferroni correction).
Normal canine cerebral metabolites described in reference 15.

## Discussion

Lidocaine has long been administered as a supplement to inhalation anesthesia.[16] It has been shown to decrease the MAC of nitrous oxide, halothane,[17] and enflurane,[18] thereby acting as a general anesthetic. Lidocaine has a biphasic effect on cortical electrical activity and the cerebral metabolism necessary for that activity. In dogs, a low-dose single injection of lidocaine, 3 $mg \cdot kg^{-1}$, produces a 10% decrease in $CMRO_2$ which lasts approximately 5 min.[5] A moderate dose of lidocaine, 15 $mg \cdot kg^{-1}$, decreases cortical electrical activity as evidenced by changes in EEG activity, which is accompanied by a maximal decrease in $CMRO_2$ of 27%, which lasts approximately 20 min.[5] In cats, a 50-mg bolus of lidocaine (12.5–20 $mg \cdot kg^{-1}$), followed by a continuous infusion of lidocaine at a rate of approximately 1 $mg \cdot kg^{-1} \cdot min^{-1}$, produces burst suppression usually progressing to isoelectricity with time.[19] Higher doses of lidocaine, given as a continuous infusion at 3.8 $mg \cdot kg^{-1} \cdot min^{-1}$, first decrease $CMRO_2$ to 70% of control, and then increase $CMRO_2$ from 70% to 112% of control when seizures occur.[5] In that study, a mean dose of 26.8 $mg \cdot kg^{-1}$ lidocaine was necessary to induce seizures on EEG.[5] Massive doses of lidocaine, above the seizure threshold (160 $mg \cdot kg^{-1}$), abolish cortical electrical activity reflected by the production of an isoelectric EEG, and produce a maximal 35% decrease in $CMRO_2$ in dogs anesthetized with 1.4% halothane.[1] If suppression of electrical activity is first achieved in halothane-anesthetized dogs by the administration of 40 $mg \cdot kg^{-1}$ pentobarbital, then the administration of 160 $mg \cdot kg^{-1}$ lidocaine produces an additional decrease in cerebral metabolism; 15% more than that produced by either pentobarbital or lidocaine alone.[1] No explanation is given as to why the massive doses of lidocaine administered to pentobarbital-treated dogs produced an additional decrease in cerebral metabolism over that produced by lidocaine alone. However, an explanation as to why lidocaine plus pentobarbital produced an additional decrease in cerebral metabolism over that produced by pentobarbital alone was set forth.

Astrup *et al.* concluded that lidocaine decreases $CMRO_2$ by two mechanisms: suppression of cortical electrical activity and membrane stabilization.[1] Because of its ability to suppress this electrical activity, lidocaine resembles many of the general anesthetics.[2–4] In addition, lidocaine, by blocking sodium channels, thereby restricting sodium and potassium fluxes or leaks (its local anesthetic function), might decrease the work of the ion pumps and the attendant energy requirements necessary to maintain ion homeostasis.[1] Astrup *et al.* hypothesized that, in the normal brain, this might appear as a further reduction in oxygen metabolism. Their study seemed to support this. They observed additional metabolic inhibition following the administration of massive doses of lidocaine in animals in which cortical electrical activity was maximally suppressed by pentobarbital.

However, a nonspecific toxic effect on oxidative phosphorylation as has been observed with high dose halothane[20] might also explain the observed metabolic inhibition produced by lidocaine in this circumstance. The results of the present study make this the more likely explanation. Even with the lower dose of lidocaine (15 $mg \cdot kg^{-1}$), cerebral stores of ATP were significantly decreased to $1.77 \pm 0.05$ $\mu mol \cdot g^{1}$, and the energy charge was significantly decreased to $0.844 \pm 0.002$, reflecting a significantly decreased ATP concentration and a significantly increased AMP concentration. This denotes both consumption of ATP and a decrease in ATP regeneration. This occurred despite the fact that MAP remained normal ($109 \pm 11$ mmHg) and both a normal-high CBF ($91 \pm 19$ $ml \cdot min^{-1} \cdot 100\ g^{-1}$) and sagittal sinus oxygen tension ($69 \pm 5$ mmHg) indicated adequate oxygen supply.

An *in vitro* study also supports our conclusion that the observed decrease in cerebral metabolism produced by lidocaine may be partially due to a direct toxic effect on oxidative phosphorylation. In porcine brain mitochondria, lidocaine produced a dose-dependent inhibition of oxygen metabolism and a dose-dependent uncoupling of oxidative phosphorylation, indicated by the decreasing ratio of inorganic phosphate uptake into ATP to oxygen utilized.[21] This is due to a block of electron transport at the NADH dehydrogenase level.[21]

It had been originally suggested by Astrup *et al.* that lidocaine might provide protection for the ischemic brain because it provided additional metabolic suppression and reduced potassium efflux believed due to a membrane-stabilizing effect.[1,6] However, the demonstration of a direct toxic effect of lidocaine on oxidative phosphorylation make it an unlikely protective agent. In a feline model of severe cerebral ischemia, produced by 4–6 h of complete occlusion of the middle cerebral artery, lidocaine in doses sufficient to produce an isoelectric EEG (50 mg bolus followed by a continuous infusion of 50 $mg \cdot kg^{-1} \cdot h^{-1}$) failed to prevent the ischemic neuronal alterations in histopathology or histochemistry.[19]

In the present study, the cerebral concentration of phosphocreatine obtained under anesthesia with either 3% isoflurane or isoflurane + lidocaine remained normal because of decreased utilization due to suppression of cortical electrical activity and its attendant metabolic requirements by isoflurane and/or lidocaine. The cerebral glucose concentration under either anesthetic regimen increased because of the decreased glucose metabolism which parallels the decreased oxygen consumption.

Two technical aspects of the present study deserve comment. The dose of lidocaine chosen (15 $mg \cdot kg^{-1}$) was one which was known to provide burst suppression or electrical silence on EEG in dogs[5] and cats,[19] but one which would be clinically tolerated without the need for cardiopulmonary bypass which would have introduced additional variables. MAP was maintained within normal limits without therapeutic intervention, despite some changes in cardiac index and systemic vascular resistance. The stable systemic hemodynamics provided stable cerebral hemodynamics, so that the observed changes in cerebral metabolites could not be attributed to detrimental effects of cerebral blood flow or intracranial pressure. Cerebral hemodynamics and metabolism were followed for 20 min after the administration of lidocaine, because that is the length of time that 15 $mg \cdot kg^{-1}$ lidocaine has been shown to have an effect on $CMRO_2$.[5]

Secondly, isoflurane was chosen as the anesthetic to produce maximum metabolic suppression prior to the administration of lidocaine. Maximal metabolic suppression in the dog occurs when abolition of cortical electrical activity (isoelectric EEG) is produced by 3% isoflurane, and can be produced with little change in cerebral blood flow[3] and little cardiovascular change. This dose of isoflurane alone has no detrimental effects on cerebral metabolites.[3,22] This differs from the background anesthetic circumstance used by Astrup *et al.*[1] which consisted of 1–1.5% halothane, known to markedly increase cerebral blood flow and moderately decrease cerebral metabolism,[23] plus 40 $mg \cdot kg^{-1}$ pentobarbital, which decreases cerebral blood flow in parallel with the maximal metabolic suppression that barbituates can produce.[1,2]

It is concluded that, in dogs anesthetized with 3% isoflurane sufficient to produce an isoelectric EEG, the addition of a clinically tolerated dose of lidocaine (15 $mg \cdot Kg^{-1}$) has no effect on cerebral hemodynamics, but does alter the cerebral energy state. Furthermore, during anesthesia with 3% isoflurane, cerebral energy stores of high energy phosphates are sufficiently decreased with the administration of lidocaine to indicate a toxic effect on oxidative phosphorylation. High concentrations of lidocaine, in addition to decreasing cortical electical activity and stabilizing membranes, may impair cellular respiration and prevent ATP production.

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