

The Effects of Lidocaine on Canine Cerebral Metabolism and Circulation Related to the Electroencephalogram

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The effects of intravenously administered lidocaine on cerebral metabolism, circulation and EEG were studied in 16 dogs. Six dogs (Group I) received a single injection of 3 mg/kg lidocaine, which depressed CMRO₂ 10 per cent at 2 minutes, with return toward control within 5 minutes. Five dogs (Group II) received a single injection of 15 mg/kg, which depressed CMRO₂ 27 per cent at 2 minutes, with return toward control within 60 minutes. The changes in CMRO₂ paralleled changes in slow-wave activity of the EEG. Slower activity was accompanied by more significant decrease in CMRO₂. The other five dogs (Group III) received a constant infusion of lidocaine (3.8 ± 0.4 mg/kg/min) until EEG seizures were induced. The mean total dose of lidocaine needed to produce seizures was 26.8 ± 0.7 mg/kg, which depressed CMRO₂ 30 per cent before the onset of seizures. During the seizures, CMRO₂ increased to 112 per cent of control and CBF increased disproportionately more than the increase in CMRO₂. With the termination of seizures, CMRO₂ decreased again to pre-seizure level and returned toward control within 90 minutes. These results indicate that a non-seizure-producing dose of lidocaine depresses cerebral respiration, but the effect is reversed by a seizure-producing dose, i.e., that the effects of lidocaine on the brain show a dichotomy, which includes a metabolic component. (Key words: Anesthetics, local: lidocaine; Brain, metabolism: lidocaine; Brain, electroencephalogram: lidocaine; Metabolism, brain: lidocaine.)

ALTHOUGH LOCAL ANESTHETICS have been widely used as anticonvulsants,^{1,2} adjuncts in general anesthesia,^{3,4,5} analgesics,⁶ and antiarrhythmic drugs,^{7,8} little is known about the effects of local anesthetics on cerebral metabolism and circulation.

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Scheinberg *et al.*⁹ studied the cerebral metabolism and circulation following intravenous administration of procaine in man, and found no significant change in the cerebral metabolic rate for oxygen or circulatory functions except an increase in cerebral vascular resistance. Geddes *et al.*¹⁰ studied the effects of local anesthetics on oxygen consumption of the cortex of the rat brain *in vitro* and reported that lidocaine and other local anesthetics inhibit the potassium-stimulated respiration of the cortex in the presence of glucose.

A review of recent literature has failed to reveal any further report of the effects of lidocaine on cerebral metabolism and circulation. However, a curious dichotomy of the effects of local anesthetics on the brain has been extensively studied by neurophysiologic means^{11,12} and the differences of seizures produced by local anesthetics from those produced by other convulsants have been well documented.¹³ Accordingly, the present study was designed to examine the cerebral metabolic and circulatory responses elicited in dogs by 3 mg/kg, 15 mg/kg and electroencephalographic-seizure-producing doses of lidocaine and to relate those responses to the electroencephalogram (EEG).

Method

Sixteen fasted, unpremedicated dogs weighing 8 to 22 kg were anesthetized with halothane (1.0 to 1.5 per cent from a vaporizer calibrated by gas chromatography) in nitrogen (60 to 70 per cent) and oxygen. The trachea was intubated with a cuffed endotracheal tube with the aid of succinylcholine (30 mg), and thereafter 8 mg/kg/hour was given to maintain muscle paralysis. Ventilation was controlled with an animal respirator (ACOMA AR-300).

Tidal volume was approximately 15 ml/kg and respiratory frequency 16–20/min. These respiratory parameters were kept unchanged throughout the study. $Paco_2$ was maintained within the normal range during control measurements. Pao_2 was maintained at 161 ± 10 mm Hg by adjusting the inspired oxygen concentration.

Cannulas were placed in a femoral artery for blood sampling and pressure determination (strain gauge), in a femoral vein for reinfusion of blood, and in the other femoral vein for drug administration. Thereafter, the dogs were placed in a prone position.

The surgical preparation for direct measurement of cerebral blood flow (CBF) was originally described by Michenfelder *et al.*¹⁴ The percentage of the total brain weight drained by the cannula in the sagittal sinus was determined by injecting vinyl acetate at the completion of each experiment and was used to convert units of flow from ml/min to ml/100 g/min. Oxygen content of arterial or sagittal sinus blood was calculated from measurements of oxyhemoglobin (IL 182 CO-oximeter) and oxygen tension (IL 313 electrodes). pH and Pco_2 were measured with appropriate electrodes. The glucose content of blood was determined by an enzymatic method.¹⁵ The electroencephalogram was recorded using frontoparietal bipolar silver–silver chloride electrodes and was analyzed every 10 seconds with a frequency analyzer (Nihonkoden MAF-5) throughout the study. Analyzed values were expressed as percentages of the integrated voltage of δ (2–4 Hz), θ (4–8 Hz), α (8–13 Hz), β_1 (13–20 Hz) and β_2 (20–30 Hz) waves. To determine lidocaine concentrations in the blood and CSF, gas chromatographic analysis¹⁶ was used.

In the present study, prilocaine was used as an internal standard. Recovery rate was 98 per cent, and the coefficient of variance was 1.6 per cent. Cerebral metabolic rates for oxygen ($CMRO_2$) and glucose ($CMR_{glucose}$) were calculated as the products of CBF and arterial–sagittal sinus blood content differences [C(A-V)]. The oxygen–glucose index (OGI) was calculated as described by Cohen *et al.*¹⁷ Cerebral vascular resistance (CVR) was calculated as the ratio of mean arterial pressure (MAP) to CBF.

After completion of the surgical preparation, inspired halothane was maintained at 0.2 per cent for the remainder of the study so that any possible effects of residual halothane on $CMRO_2$, CBF and the EEG could be kept constant throughout the study. Control measurements were obtained over a 30-minute period, and mean values were calculated from five to eight consecutive determinations of CBF and C(A-V) O_2 and three determinations of C(A-V) $_{glucose}$. Following control determinations, the dogs were divided into three groups, according to the lidocaine doses administered. Six dogs (Group I) received 3 mg/kg of lidocaine over 10 sec and were followed for 20 minutes. Five dogs (Group II) received 15 mg/kg over 30 sec and were followed for 60 minutes. The other five dogs (Group III) received lidocaine infusion at a constant rate (3.8 ± 0.4 mg/kg/min) until EEG seizures were induced, and were followed for 150 minutes from the start of infusion. Infusion was discontinued as soon as the seizure pattern appeared in the EEG. In each dog in this group, a 19-gauge needle was placed in the cisterna magna to obtain cerebrospinal fluid (CSF) samples for the determination of the lidocaine concentration. Brain temperature was monitored by a parietal epidural thermistor and maintained at 37 ± 0.4 C by external means. Hemoglobin levels were maintained above 12.0 g/dl. No evidence of extracerebral contamination of blood or other cerebral vascular anomalies was found at autopsy. Statistical significance was tested by Student's *t* test for paired data; $P < 0.05$ was considered significant.

Results

The effects of 3 mg/kg of lidocaine (Group I) on cerebral metabolism, circulation, and EEG are summarized in table 1 and figure 1. Lidocaine, 3 mg/kg, produced a significant decrease in $CMRO_2$, which returned toward control within 5 minutes. Mean $CMRO_2$ decreased a maximum of 10 per cent at 2 minutes. Increases in the integrated voltage of the slow-wave activities at 3 to 16 minutes were statistically significant. The lidocaine concentrations of arterial and sagittal-sinus blood equilibrated at 2 minutes (4 μ g/ml),

TABLE 1. Effects of Lidocaine on Cerebral Metabolism and Circulation, Group I, 3 mg/kg

Time (Min)	MAP (mm Hg)		CBF (ml/100 g/Min)		CVR (mm Hg/ml/100 g/Min)		CMRO ₂ (ml/100 g/Min)		OGI (Per Cent)		Paco ₂ (mm Hg)		P ₅₀ O ₂ (mm Hg)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	102	10	70	9	1.56	0.24	6.1	0.5	83	7	42.1	1.6	30.8	4.2
1	110	11	71	9	1.68	0.26	5.9	0.4	72	8	40.9	3.2	33.2	3.8
2	107	9	70	10	1.66	0.24	5.5*	0.4	—	—	—	—	33.7	4.1
5	105	8	79	10	1.46	0.22	5.6	0.4	86	7	39.5	1.2	37.2	3.6
20	94	9	70	10	1.46	0.19	6.0	0.4	81	7	41.2	1.6	31.2	4.6

* Significantly different from control, $P < 0.05$.

TABLE 2. Effects of Lidocaine on Cerebral Metabolism and Circulation, Group II, 15 mg/kg

Time (Min)	MAP (mm Hg)		CBF (ml/100 g/Min)		CVR (mm Hg/ml/100 g/Min)		CMRO ₂ (ml/100 g/Min)		OGI (Per Cent)		Paco ₂ (mm Hg)		P ₅₀ O ₂ (mm Hg)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	122	9	64	3	1.89	0.08	5.6	0.4	93	3	38.1	1.3	32.8	2.2
1	79*	15	49*	3	1.59	0.22	4.5*	0.3	84	4	—	—	28.6	2.2
2	90*	13	55	6	1.61	0.10	4.0*	0.3	—	—	—	—	35.3	3.1
5	105	10	68	5	1.55	0.10	4.1*	0.3	91	11	46.7*	1.8	41.5*	2.2
12	118	9	82	6	1.58	0.10	4.3*	0.4	75	14	47.0*	2.4	44.6*	2.1
20	119	8	77	4	1.56	0.16	4.6*	0.3	85	6	47.1*	2.1	38.3	1.1
60	122	1	67	2	1.82	0.06	5.4	0.4	92	14	46.3*	1.9	31.5	2.2

* Significantly different from control, $P < 0.05$.

TABLE 3. Effects of Lidocaine on Cerebral Metabolism and Circulation, Group III, Lidocaine Infusion

Time (Min)	MAP (mm Hg)		CBF (ml/100 g/Min)		CVR (mm Hg/ml/100 g/Min)		CMRO ₂ (ml/100 g/Min)		OGI (Per Cent)		Paco ₂ (mm Hg)		P ₅₀ O ₂ (mm Hg)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	106	13	54	2	1.94	0.21	6.0	0.3	87	3	33.7	1.4	29.5	1.3
2	105	14	54	2	1.95	0.23	5.7*	0.3	86	7	—	—	31.9	1.7
7 ± 0.6†	73	17	40*	4	1.78	0.27	4.2*	0.3	89	10	37.2	1.8	28.8	3.5
10 ± 0.8†	73*	14	85	20	0.91*	0.11	6.7	0.4	81	6	41.5*	2.4	34.9	3.4
16	91	14	53	4	1.78	0.30	4.6*	0.3	79	7	—	—	38.6	4.4
20	99	14	49	3	2.09	0.41	4.3*	0.1	91	8	42.7*	2.2	37.9	2.8
60	105	14	53	3	1.83	0.33	5.2*	0.2	82	8	—	—	30.6	2.4
120	98	14	51	4	1.95	0.37	5.7	0.3	82	5	36.6	1.9	31.6	2.8

* Significantly different from control, $P < 0.05$.

† Values at 7 ± 0.6 and 10 ± 0.8 minutes represent before and during the seizure period, respectively.

when the EEG started to show predominant slow-wave activity (δ and θ waves). Changes in MAP, CBF, CVR and blood-gas values were all statistically insignificant.

The effects of 15 mg/kg of lidocaine (Group II) are summarized in table 2 and figure 2. Mean CMRO₂ decreased a maximum of 27 per

cent at 2 minutes and thereafter returned toward control within 60 minutes. Slow-wave activity (δ wave) predominated immediately after the injection, with concomitant decreases in fast-wave activities (β_1 and β_2 waves). These EEG changes were statistically significant and thereafter gradually returned toward control

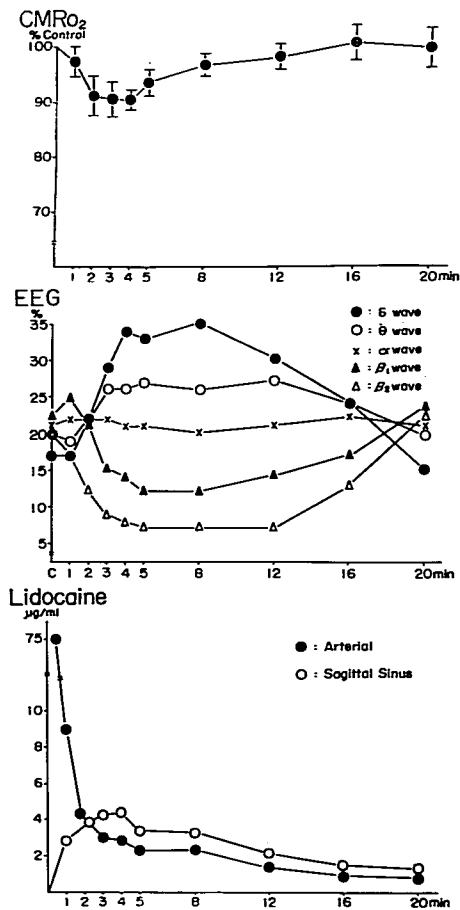


FIG. 1. Effects of lidocaine, 3 mg/kg, on CMRO₂ (mean \pm SE) and EEG (mean) related to blood lidocaine concentration (mean). Reductions in CMRO₂ 2, 3, 4, and 5 minutes after injection were significant ($P < 0.05$).

over a 45–60-minute period. The lidocaine concentrations of arterial and sagittal-sinus blood equilibrated at 2 minutes (21 μ g/ml). No significant change was observed in MAP, CBF, or CVR except a decrease in CBF at 1 minute and a decrease in MAP at 1 to 2 minutes. In this

group, Paco₂ increased significantly after administration of lidocaine (table 2).

With a constant rate of infusion (Group III), 26.8 \pm 0.7 mg/kg were necessary to induce EEG seizures. Results are summarized in table 3 and figure 3. Mean CMRO₂ significantly

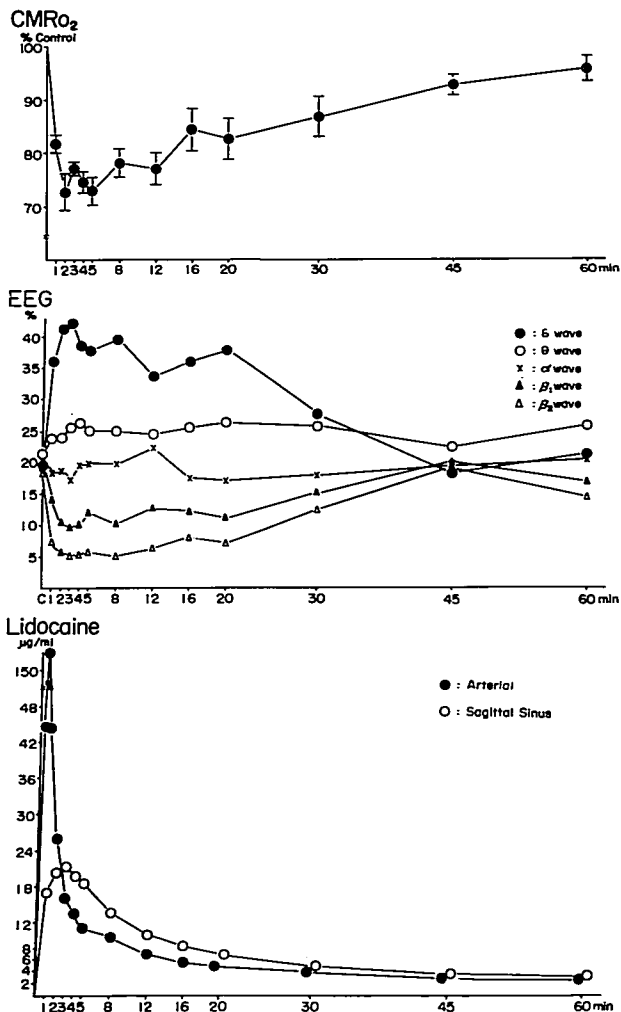


FIG. 2. Effects of lidocaine, 15 mg/kg, on CMRO₂ (mean ± SE) and EEG (mean) related to blood lidocaine concentration (mean). Reductions in CMRO₂ from 1 through 45 minutes after injection were significant ($P < 0.05$).

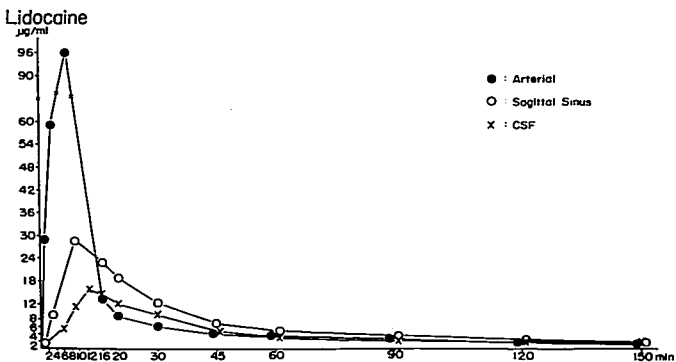
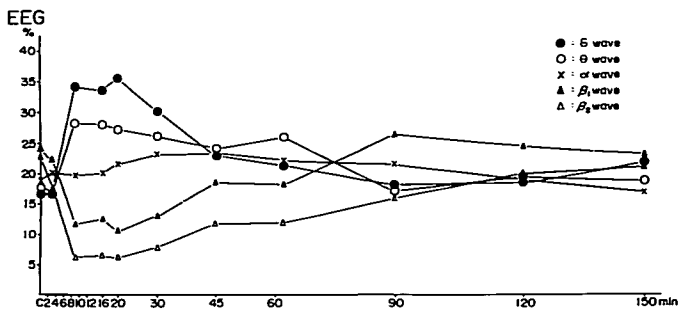
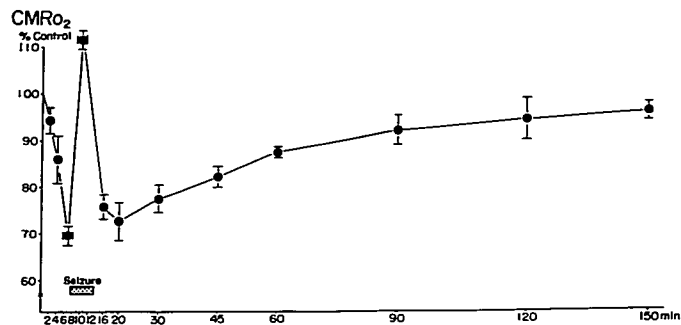


FIG. 3. Effects of infusion of lidocaine, 26.8 ± 0.7 mg/kg, on CMRO₂ (mean \pm SE) and EEG (mean) related to blood and CSF lidocaine concentrations.

decreased throughout the 60-minute period after the start of infusion, except during seizures, when $CMRO_2$ increased to 112 ± 6 per cent of control. Although this increase in $CMRO_2$ from control was not statistically significant, individual $CMRO_2$'s ranged from 107 to 126 per cent of control in four of the five dogs. In the remaining dog, $CMRO_2$ increased from 69 per cent (pre-seizure) to 92 per cent (during seizure) of control. The actual increase in mean $CMRO_2$ in five dogs from the pre-seizure value was 42 per cent, which was statistically significant. The durations of typical seizures, characterized by bursts of high-voltage spike waves, varied among dogs but averaged 6.3 ± 1.9 minutes. For 2 to 3 minutes before and after typical seizures, spike-and-d waves were occasionally observed. Figure 4 illustrates the EEG changes and corresponding $CMRO_2$ values in one dog of this group. The arterial blood lidocaine level gradually increased, reached a peak at 7 minutes ($96 \mu\text{g/ml}$), corresponding to the time of termination of infusion, and thereafter declined rapidly. Sagittal-sinus blood lidocaine levels increased more slowly than the arterial blood levels and reached a peak ($29 \mu\text{g/ml}$) at 9 minutes. Lidocaine in CSF showed a much slower increase, reaching a peak at 13 minutes ($16 \mu\text{g/ml}$). Thereafter, all these levels declined in a similar fashion. Immediately before the seizures, CBF decreased significantly from 54 to 40 ml/100 g/min with a concomitant decrease in MAP. During seizures, MAP remained at the pre-seizure level and CBF increased from 40 (pre-seizure) to 85 ml/100 g/min with a concomitant decrease in CVR from 1.78 to 0.91 mm Hg/ml/100 g/min. All other circulatory and metabolic changes were statistically insignificant. $Paco_2$ increased significantly from 33.7 ± 1.4 mm Hg of control to 41.5 ± 2.4 mm Hg during seizures and to 42.7 ± 2.2 mm Hg at 20 minutes (table 3).

There was no significant change in OGI in any group.

Discussion

Most local anesthetic effects are believed to be dose-related, but a dichotomy of these effects on the brain is well documented.¹⁸ At low blood levels, lidocaine and procaine are

potent anticonvulsants,^{1,2} whereas at high levels they act as convulsants.^{11,12,13} Our results showed that both 3 mg/kg and 15 mg/kg of lidocaine act as a cerebral metabolic depressant, as indicated by significant reductions in $CMRO_2$. Larger doses of lidocaine (26.8 ± 0.6 mg/kg) given at a constant infusion rate caused a maximum of 30 per cent reduction in $CMRO_2$ before the onset of seizures. Once the seizures were induced, $CMRO_2$ strikingly increased, indicating that the cerebral effects of lidocaine are not proportional to dose.

In man, Scheinberg *et al.*⁹ found no significant change in $CMRO_2$ with procaine. The discrepancy between their results and ours is probably accounted for by the smaller doses (750 mg over 15 to 20 minutes, in adults) used in their study, although differences in methodology, species, and drugs administered may also be responsible. In the study by Geddes *et al.*,¹⁰ lidocaine (5 mM/l) reduced oxygen consumption of potassium-stimulated brain slices to 85 per cent of control, but the lidocaine concentration was incomparably higher than ours. The present study indicates that 3 mg/kg lidocaine, which is close to the dose used clinically, produces a significant reduction in $CMRO_2$. The constant infusion provided an opportunity to detect metabolic involvement in a dichotomy of the effects of lidocaine on the brain.

The EEG changes are compatible with those reported by other investigators.^{19,20} EEG frequency analysis used in this study may be inappropriate to detect paroxysmal activity, because steady EEG patterns for a 10-second period are mandatory for accurate frequency analysis. However, as shown in figures 1, 2 and 3, frequency analysis was a useful tool to demonstrate the relationship between the EEG pattern and $CMRO_2$ or blood lidocaine concentration. In Group III, typical high-voltage sharp-wave bursts followed by a short period of postictal silence were accompanied by an increase in $CMRO_2$ (fig. 4: 10 min), whereas mean $CMRO_2$ remained decreased during periods characterized on the EEG by polyspikes and wave activity considered to be of a convulsive pattern (fig. 4: 12 min).

Cerebral circulatory changes in Group I were slight and insignificant, whereas in Group II there was a transient but significant

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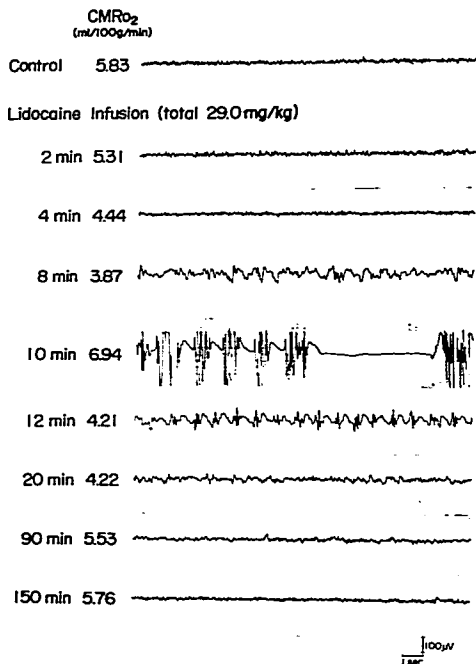


FIG. 4. Representative EEG correlating values of CMRO₂ with infusion of lidocaine (29 mg/kg).

decrease in MAP at 1 to 2 minutes, probably resulting from a direct myocardial depressant effect of lidocaine. A significant decrease in CBF during this period suggests insufficient autoregulation of cerebral vessels for the rapid change in MAP. The increase in CBF observed 5 minutes after lidocaine in Group II was accompanied by an increase in PaCO₂, which causes cerebral vasodilatation. In Group III, there was also a temporal disturbance of autoregulation immediately before the onset of seizures. Assuming that each 1-mm Hg increase in PaCO₂ causes a 2.4 per cent increase in CBF,²¹ the CBF increase in Group II during 5 to 60 minutes is entirely accounted for by the increase in PaCO₂. However, in Group III an increase in CBF during seizures due to an increase in PaCO₂ (8 mm Hg) would be 10 ml/100 g/min. Therefore, the remainder of the CBF increase (21 ml/100 g/min) would be due

to lidocaine. From the present study it is concluded that lidocaine has no significant effect on CBF except during seizures. No possible explanation for the increase in PaCO₂ which occurred in this study is available at present.

Since the increases in CMRO₂ and CBF during seizures were 112 and 157 per cent of control, respectively, CBF was sufficient for the cerebral oxygen demands. This was also evidenced by the absence of any significant change in OGI. The increases in CMRO₂ and CBF during seizures are compatible with those reported by Plum *et al.*,²² who studied cerebral metabolism and circulation during pentylenetetrazol-induced seizures. However, they reported that much of the increase of CBF during pentylenetetrazol-induced seizures was a passive response to the elevated blood pressure. Our results clearly indicate

that an increase in CBF during seizures is not the result of an increase in MAP.

As shown in figures 1 and 2, maximum reductions in $CMRO_2$ occurred at approximately 2 minutes, when arterial blood and sagittal-sinus blood lidocaine concentrations equilibrated. With infusion, the time difference between the appearance of peak lidocaine levels in the arterial blood, sagittal sinus blood, and CSF was approximately 6 minutes. Thereafter, lidocaine in CSF gradually declined, but remained between the arterial and sagittal-sinus blood levels. These results indicate a negligible blood-brain barrier for this drug, as suggested by Usubiaga *et al.*²³ for procaine.

Although long-term observation was impossible in this study, it is noteworthy that the metabolic, circulatory, and EEG changes induced by seizure-producing doses of lidocaine reverted to baseline values completely. Mark *et al.*¹⁹ found no adverse neurologic or behavioral effect in dogs followed for more than a week after procaine-induced seizures.

A clinical interpretation of this study indicates that an oxygen supply sufficient to meet the increased cerebral oxygen demand during lidocaine-induced seizures is provided by an increase in CBF. However, it should be added that cerebral damage may still be possible in those patients who have underlying cerebrovascular or myocardial disease.

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