

Laboratory Report

Diazepam Blocks Cerebral Metabolic and Circulatory Responses to Local Anesthetic-induced Seizures

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The effects of diazepam on canine cerebral metabolic and circulatory responses to lidocaine-induced seizures were examined. In four dogs, diazepam, 0.25 mg/kg, was given intravenously immediately after the onset of EEG seizures produced by infusion of lidocaine. Seizures were terminated within 0.8 ± 0.2 minutes and CMR_{O_2} and CBF decreased to 53 and 61 per cent of control, respectively. In another five dogs a single intravenous injection of 0.25 mg/kg diazepam decreased mean CMR_{O_2} and CBF to 84 and 85 per cent of control within 5 minutes, with return toward control over a 90-minute period. The results indicate that diazepam blocks the cerebral metabolic and circulatory responses to lidocaine-induced seizures. (Key words: Anesthetics, local: lidocaine; Anticonvulsants: diazepam; Complications: convulsions: diazepam; Brain: blood flow: diazepam; Brain: metabolism: diazepam.)

WE HAVE DESCRIBED the effects of non-seizure-inducing and seizure-inducing doses of lidocaine on canine cerebral metabolism and circulation.¹ We now examine the effects of diazepam on the cerebral metabolic and circulatory responses to lidocaine-induced seizures.

Materials and Methods

Nine fasted, unmedicated dogs weighing 12 to 26 kg were examined. Experimental methods used in the present study were the same as those described previously.¹ $P_{a_{O_2}}$ and $P_{a_{CO_2}}$ were maintained at 156 ± 8 mm Hg and 38 ± 2 mm Hg, respectively. Cerebral

epidural temperature and hemoglobin were maintained at 37 ± 0.3 C and 13 ± 0.9 g/dl, respectively.

Four dogs received an infusion of lidocaine intravenously at a rate of 3.6 ± 0.2 mg/kg/min until electroencephalographic (EEG) seizures were induced. Immediately after the onset of seizures, the lidocaine infusion was terminated and 0.25 mg/kg diazepam was administered intravenously over a 10-second period. Each dog was followed for 90 minutes after the onset of seizures. Another five dogs received a single intravenous injection of 0.25 mg/kg diazepam and were followed for 90 minutes. Statistical significance was tested by Student's t test, assuming $P < 0.05$ to be significant.

Results

With lidocaine infusion, mean cerebral metabolic rate for oxygen (CMR_{O_2}) decreased progressively to 77 per cent of control, and both cerebral blood flow (CBF) and mean arterial pressure (MAP) decreased before the onset of seizure (table 1). With diazepam, administered immediately after the onset of EEG seizure (seizure-inducing dose: 23.3 ± 3.1 mg/kg), seizure activity disappeared within 0.8 ± 0.2 minutes and mean CMR_{O_2} and CBF decreased further to 53 per cent and 61 per cent of control at 5 minutes, respectively, and thereafter returned toward control. MAP showed a transient but significant decrease at 2 minutes and returned toward control levels over the next 90 minutes. Cerebral metabolic rate for glucose ($CMR_{glucose}$) decreased significantly, paralleling the decrease in CMR_{O_2} , indicating that no significant change in oxygen-glucose index (OGI) had occurred.

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TABLE 1. Effects of Lidocaine and Subsequent Diazepam on Cerebral Metabolism and Circulation

Time (Min)	MAP (mm Hg)		CBF (ml/100 g/min)		CVR (mm Hg/ml/100 g/min)		CMR _{O₂} (ml/100 g/min)		OGI (Per Cent)		P _{aCO₂} (mm Hg)		P _{ssO₂} (mm Hg)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	98	7	61	4	1.6	0.1	6.0	0.2	87	2	36	2	33	3
Lidocaine 6 ± 0.7* (pre-seizure)	73	16	47*	4	1.5	0.2	4.7*	0.1	74	6	38	3	34	4
Diazepam														
2	61*	10	38*	3	1.6	0.2	3.5*	0.1	87	4	42	4	30	4
5	70	12	37*	1	1.9	0.3	3.2*	0.2	91	12	—	—	37	4
20	93	11	45	3	2.1	0.3	4.0*	0.2	109	17	40	5	35	6

* Significantly different from control ($P < 0.05$).

With 0.25 mg/kg diazepam alone, mean CMR_{O₂} decreased a maximum of 16 per cent at 2 to 5 minutes, with a concomitant decrease in CBF (15 per cent). These values returned toward control over a 90-minute period. No significant change in either MAP or cerebral vascular resistance (CVR) was observed. Mean OGI transiently decreased at 2 minutes (table 2), while CMR_{O₂} decreased significantly but CMR_{glucose} remained unchanged.

Discussion

Since Eidelberg² and his co-workers reported a lower incidence of cocaine-induced seizures in rats pretreated with benzodiazepine derivatives, several reports have pointed out that diazepam is an effective anticonvulsant agent in treatment of local anesthetic-induced seizures.^{3,4,5} Our previous study demonstrated increases in CMR_{O₂} and CBF to 112 per cent and 157 per cent of control, respectively, during lidocaine-induced seizures. In the present study,

CMR_{O₂} did not increase, but further decreased by a maximum of 47 per cent with a seizure-inducing dose of lidocaine and subsequent diazepam. This reduction in CMR_{O₂} was comparable to the amount of a maximum reduction of 30 per cent by lidocaine infusion before seizures observed in the previous study¹ and a maximum decrease of 16 per cent by diazepam. Thus, once the typical seizures were blocked, the additive effects of the two drugs on cerebral metabolic depression became apparent. Cerebral circulatory responses were also completely blocked by diazepam, indicating that the increase in CBF and the decrease in CVR during lidocaine-induced seizure were entirely the result of increased metabolic demands. After diazepam the decrease in CBF paralleled the decrease in CMR_{O₂} and did not threaten oxygen delivery, as judged by the unchanged OGI and sagittal sinus P_{O₂} (P_{ssO₂}).

The effects of diazepam on cerebral metabolism and circulation *in vivo* have not previously been reported. The present study

TABLE 2. Effects of Diazepam on Cerebral Metabolism and Circulation

Time (Min)	MAP (mm Hg)		CBF (ml/100 g/min)		CVR (mm Hg/ml/100 g/min)		CMR _{O₂} (ml/100 g/min)		OGI (Per Cent)		P _{aCO₂} (mm Hg)		P _{ssO₂} (mm Hg)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	110	9	60	2	1.9	0.2	6.3	0.4	96	4	41	2	34	2
2	98	11	51*	10	1.9	0.3	5.3*	0.1	77*	5	42	1	33	1
5	101	9	51*	2	2.0	0.3	5.3*	0.3	85	11	42	1	34	1
20	103	9	53*	2	2.0	0.3	5.5*	0.5	90	15	41	2	32	2

* Significantly different from control ($P < 0.05$).

has revealed that diazepam is a cerebral metabolic depressant. Although there has been no study concerning the effects of diazepam on the exchange rates of oxygen and glucose between blood and brain tissue, the most likely explanation for the transient but significant decrease in OGI 2 minutes after diazepam administration is an exchange rate of glucose which was slower than that of oxygen.

We conclude that diazepam is effective in blocking the EEG seizures, as well as in preventing the elevation of cerebral metabolism and circulatory changes, induced by lidocaine overdosage and that, in these circumstances, there exists a close relationship between cerebral metabolism and electrical activity.

References

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Endocrines

REGULATION OF ALDOSTERONE CONCENTRATION In normal man the renin-angiotensin system plays a major role in the regulation of aldosterone release. Experiments were performed to determine what factors regulate plasma aldosterone concentration in anephric patients and patients with transplanted kidneys. Peripheral renin activity, plasma aldosterone and serum potassium concentrations were measured with the patients in the supine and upright positions. Studies were performed in anephric patients on the first and third or fourth post-dialysis day. Studies in renal transplant recipients were performed during periods of high or low salt intake. Renin was essentially absent in anephric patients, and aldosterone concentrations did not change when they moved from the supine to the upright position. Significant elevations of serum potassium and aldosterone concentrations were found on the third or fourth day post-dialysis. Patients with functioning transplanted kidneys responded to a change from the supine to upright position with increases in peripheral renin activity and aldosterone concentrations, irrespective of sodium intake. Thus, the renin-angiotensin system is functional in patients with kidney transplants. Evidence that changes in potassium concentration rather than volume-related stimuli regulate aldosterone concentrations in anephric patients is provided. (Cooke, C.R., Ruiz-Maza, F., Kowarski, A. and others: *Regulation of Plasma Aldosterone Concentration in Anephric Man and Renal Transplant Recipients. Kidney Int* 3: 160, 1973.)