

Cerebral Circulatory and Metabolic Responses to Intravenously Administered Lorazepam

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Cerebral vascular and metabolic effects of lorazepam were evaluated in ten awake monkeys by use of a modification of the Kety-Schmidt technique. Five received ketamine, 10 mg/kg, im, five to eight hours prior to the study, but all animals were otherwise treated identically. Monkeys receiving ketamine had significantly greater ($P < 0.05$) cerebral blood flow (CBF) values before lorazepam was given (46 ± 1 ml/100 g/min) than did monkeys not receiving ketamine (41 ± 1 ml/100 g/min), but in all other respects, premedicated and unpremedicated animals did not differ. Lorazepam administration did not significantly alter systemic arterial blood pressure or blood-gas values. However, it did decrease CBF by 26 per cent and increase cerebral vascular resistance (CVR) by approximately 25 per cent ($P < 0.01$). The cerebral metabolic rate for glucose (CMR_g) decreased 42 per cent ($P < 0.05$). Following lorazepam administration, the cerebral metabolic rate for oxygen (CMR_{o₂}) decreased by 21–30 per cent. When combined CMR_{o₂} data for the two anesthetic groups are pooled, this decrease is significant ($P < 0.05$). This study indicates that sedative doses of lorazepam decrease cerebral blood flow and metabolism with minimal effects on blood pressure and blood-gas values. Lorazepam administration did not produce any change in cerebral metabolism indicative of brain hypoxia or ischemia. (Key words: Brain: blood flow; metabolism. Hypnotics: benzodiazepine, lorazepam.)

LORAZEPAM, a new benzodiazepine sedative, is similar in structure and action to diazepam. These agents differ in that lorazepam has greater potency,¹ better intramuscular absorption,² and possibly more profound amnesic properties.^{3,4} The most important distinction between the two drugs, however, is the prolonged action of lorazepam (hours),⁵ in marked contrast to the rapid termination of the diazepam effects when both drugs are intravenously administered.⁶

Diazepam has been found to decrease cerebral blood flow (CBF) and metabolism (CMR).⁷ It has been

used with apparent safety in patients with intracranial disease associated with intracranial hypertension.⁸ Because of its relationship to diazepam, lorazepam might also be a useful premedicant or induction agent for patients undergoing prolonged neurosurgical procedures. In order to provide basic cerebral hemodynamic and metabolic information, we studied the effects of intravenously administered lorazepam on CBF and CMR in awake subhuman primates.

Methods

Ten conditioned monkeys (*Macaca fascicularis*) of either sex weighing 3.5 to 5.0 kg were permitted access to water and deprived of food overnight. In five of the animals, ketamine, 10 mg/kg, was given intramuscularly as an induction agent, but all animals were otherwise treated identically. Anesthesia was induced with halothane and oxygen delivered into a cage and, thereafter, maintained by mask. After a tracheostomy was performed, inspired gases were adjusted to deliver halothane, 1–2 per cent, in nitrous oxide, 60 per cent, and oxygen. Temperature was monitored with a subcutaneously placed probe and servocontrolled to 37 C with a warming blanket.

A femoral vein and both femoral arteries were catheterized to permit blood sampling, drug administration, and pressure monitoring. A peripheral vein was cannulated for replacement of maintenance fluids. The animal was then turned to the prone position, and a sagittal sinus catheter (PE-90) was passed through a midline burr hole placed at the intraural line and advanced into the torcular to allow sampling of cerebral venous blood. To assure cannula patency, heparin, 100 units/kg, was given intravenously immediately before catheter insertion and

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Received from the Department of Anesthesia, Veteran's Administration Hospital, San Diego, and the University of California, San Diego, La Jolla, California 92093. Accepted for publication April 7, 1980. Supported in part by the Veteran's Administration Hospital and by Wyeth Laboratories. Presented at the annual meeting of the American Society of Anesthesiologists, San Francisco, October 1979.

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ABBREVIATIONS

BP	= systemic arterial blood pressure
CBF	= cerebral blood flow
CMR _g	= cerebral metabolic rate for glucose
CMR _{o₂}	= cerebral metabolic rate for oxygen
CVR	= cerebral vascular resistance
ICP	= intracranial pressure
Pa _{co₂}	= partial pressure of carbon dioxide in arterial blood
P _{ss_{o₂}}	= partial pressure of oxygen in sagittal sinus blood

supplemental doses of 50 units/kg were given every two hours. The electrocardiogram was recorded through two upper limb leads. All incisions were closed and infiltrated with bupivacaine, 0.5 per cent, containing epinephrine, 1:200,000, and halothane and nitrous oxide were discontinued. The monkey was secured in a restraining chair, placed in a radiation-shielded isolation chamber, and allowed to breathe room air. Pressure transducers were positioned at the midthoracic level and zeroed to atmospheric pressure. Mean pressures were obtained by electronic integration.

Cerebral blood flow was determined with a modification of the Kety-Schmidt technique using the trapezoid rule to calculate the area between the curves obtained from simultaneous sampling of arterial and sagittal sinus blood during desaturation of radioactive xenon (^{133}Xe).⁹ Twenty paired arterial and sagittal sinus blood samples for determination of ^{133}Xe concentration were obtained in 20- μl capillary pipets, sealed in micro test tubes, and counted in a gamma counter (Nuclear-Chicago®). The animals inhaled ^{133}Xe at a constant inspired concentration (40 μCi in 40 l air) for 30 min prior to desaturation. More than 95 per cent venous-arterial blood ^{133}Xe saturation was achieved prior to every flow determination. Oxygen was intermittently added to the closed rebreathing system to maintain an inspired concentration of about 21 per cent. During flow measurement, desaturation was followed for 30 min. The partition coefficients used in the calculations of CBF and corrected for hematocrit have been reported.¹⁰ At the end of the desaturation period twice the volume of blood lost (9 ml) due to sampling was replaced with physiologic saline solution.

Additional arterial and sagittal sinus blood samples were taken immediately prior to and 30 min after flow determinations began for analysis of blood-gas, pH, and glucose values. Arterial and venous blood oxygen contents were determined by the Klingenstein-Behar carbon monoxide method.¹¹ PaO_2 , PaCO_2 , and pH were measured with a Radiometer® Micro-Blood Gas Analyzer at 37 C and temperature-corrected according to the method of Severinghaus.¹² Glucose levels were determined by colorimetric enzymatic analysis with a Glucostat Kit® (Worthington Biochemical Company). From these data, cerebral metabolic rates for oxygen (CMR_{O_2}) and glucose (CMR_{G}) were calculated as the product of the arterial-sagittal sinus blood difference and CBF.

Control CBF and metabolic determinations were made at least two and a half hours after halothane had been discontinued, or five to eight hours after ketamine had been administered. All animals appeared fully alert within 30 min of discontinuation

of inhalational anesthesia and were given an additional two hours to allow for acclimation to the restraining chair before control determinations were made. Lorazepam, 4 mg/kg, was then given intravenously, and CBF and metabolic determinations were made in one hour. (This dosage and sedation time were obtained from preliminary studies in primates to determine the optimum intravenous dosage of lorazepam for sedation, as well as sedation time. Lorazepam dosage and flow measurement time are based on results of these early studies). In five additional animals, an equal volume of lorazepam solvent without active drug was administered in order to observe any sedative effect of the vehicle itself.

Statistically significant differences were established by use of the Student *t* test for paired or unpaired data. $P < 0.05$ was regarded as significant.

Results

Lorazepam administration resulted in noticeable sedation in all monkeys within minutes, and lasted throughout the duration of the study. Sleep was induced in eight animals, but they maintained intact corneal reflexes and were arousable with painful stimuli. One monkey remained awake, although calm, and another was totally unresponsive to all stimuli. Vehicle administration alone did not result in sedation in any animal. There was no change in physiologic variables after either ketamine or lorazepam administration (table 1). In no case did lorazepam administration result in a significant increase in PaCO_2 or decrease in blood pressure.

Prior to lorazepam administration, the group given ketamine had a slightly, but significantly, greater average CBF ($P < 0.05$) than did the halothane-induction animals (table 2). Cerebral metabolic rates for oxygen and glucose did not differ between the ketamine-halothane and halothane-only anesthetized groups during the pre-lorazepam control period. Following lorazepam administration, no significant difference existed among the cerebral hemodynamic and metabolic indices measured in the ketamine-halothane and halothane-only groups. Compared with the awake control state, lorazepam resulted in a significant ($P < 0.05$) 26 per cent decrease in CBF and a similar increase in CVR. The CMR_{O_2} declined by 21–30 per cent; however, only the halothane-ketamine group had values significantly different ($P < 0.05$) from control levels. When the CMR_{O_2} data for both anesthetic groups were pooled, a significant reduction ($P < 0.05$) in CMR_{O_2} occurred after lorazepam was given (Student *t* test for paired data). A significant reduction ($P < 0.05$) in mean CMR_{G} of about 42 per cent occurred. Despite the decrease in CBF, sagittal sinus blood oxygen tension

TABLE 1. Physiologic Conditions before and after Lorazepam Administration (Mean ± SEM)

	Temperature (C)	Mean Blood Pressure (torr)	pH _a	P _{aCO₂} (torr)	P _{aO₂} (torr)	P _{50O₂} (torr)	Arterial Blood Glucose (mg/dl)	Sagittal Sinus Blood Glucose (mg/dl)
Control Halothane (n = 5)	36.9 ± 0.1	110 ± 6	7.45 ± 0.02	34 ± 1	84 ± 4	27 ± 2	151 ± 24	137 ± 24
Halothane + ketamine (n = 5)	36.7 ± 0.6	114 ± 8	7.45 ± 0.02	34 ± 1	87 ± 3	29 ± 3	137 ± 18	124 ± 20
Lorazepam Halothane (n = 5)	36.8 ± 0.6	102 ± 8	7.48 ± 0.03	33 ± 1	87 ± 3	26 ± 1	120 ± 16	109 ± 19
Halothane + ketamine (n = 5)	36.3 ± 0.4	110 ± 9	7.43 ± 0.02	33 ± 1	90 ± 7	26 ± 2	179 ± 25	170 ± 26

TABLE 2. Cerebral Vascular and Metabolic Effects of Lorazepam Administration (Mean ± SEM)

	Cerebral Blood Flow (ml/100 g/min)	Cerebral Vascular Resistance (torr/ml/100 g/min)	Cerebral Metabolic Rate for Oxygen (ml/100 g/min)	Cerebral Metabolic Rate for Glucose (mg/100 g/min)	Oxygen Glucose Index
Control Halothane	41 ± 1	2.7 ± 0.1	2.7 ± 0.5	5.7 ± 0.5	0.7 ± 0.2
Halothane + ketamine	46† ± 1	2.5 ± 0.2	3.4 ± 0.4	5.6 ± 0.8	1.0 ± 0.2
Lorazepam Halothane	29* ± 2	3.5* ± 0.2	1.9 ± 0.2	3.4* ± 0.6	0.9 ± 0.2
Halothane + ketamine	35* ± 1	3.1* ± 0.2	2.7* ± 0.4	3.1* ± 0.5	0.9 ± 0.2

* Significant difference ($P < 0.05$) between groups pre- and post-lorazepam using Student *t* test for paired data.

† Significant difference ($P < 0.05$) between control groups with and without ketamine using Student *t* test for unpaired data.

remained unchanged, suggesting adequate oxygen delivery.

Discussion

In every animal, lorazepam reduced cerebral blood flow and metabolism. Less uniform influences of diazepam on cerebral metabolic indices have been reported. The CMR_{O₂} was either decreased or unchanged following diazepam administration.^{7,8,13} Maekawa *et al.* found no change in CMR_g after diazepam was given to dogs.⁷ The reasons for these discrepancies may be related to species differences, relative dose levels, and the relatively minor metabolic depressant effects of benzodiazepine drugs compared with drugs such as barbiturates. Droperidol also causes similar decreases in CBF without changing CMR_{O₂}.¹⁴ Strict coupling between cerebral metabolic and circulatory events is known to be modified or abolished by various anesthetic techniques.^{15,16} In summary, benzodiazepines reduce consciousness with cerebral hemodynamic and metabolic effects that are different from those of barbiturates, which cause dose-dependent parallel decreases in CBF and CMR.¹⁷

It is possible that prior administration of anesthetic agents may affect the response to lorazepam. It is known that ketamine increases CBF when measured immediately after intravenous administration.¹⁸ The duration of this effect is less certain, although hallucinations upon emergence can be prolonged. We, therefore, separated our animals into equal groups with and without prior ketamine injection, in order to define any possible long-term action of this agent given intramuscularly. Although those animals receiving ketamine had higher control CBF values, there was no direct correlation of CBF with time after administration of ketamine, *i.e.*, the CBF values were not greater five hours after ketamine than eight hours after ketamine. Nevertheless, the data suggest that ketamine (or emergence from ketamine) did result in a prolonged effect upon CBF, which is no longer apparent after lorazepam administration. Since many animal studies employ intramuscularly administered ketamine as an aid to induction, possibly prolonged cerebral effects must be taken into account in their interpretation. In the present study, however, except for the initial effect upon CBF alone, the anesthetic

technique was not critical and the effects of lorazepam were independent of the type of induction.

The dose of lorazepam necessary to produce sedation in our monkeys was much greater than amounts necessary for man. In studies involving healthy adults, 2–3 mg, im or iv, resulted in slight to moderate sedation, while doses to 10 mg increased central nervous system depression and produced stage I anesthesia lasting six to eight hours.¹ The half-life has been found to be approximately 12 hours.¹⁰ In a preliminary study using primates, we found that 4 mg/kg, iv, resulted in sedated animals arousable with painful stimulation and in a stable clinical state for hours. Smaller doses did not produce consistent sedation. This dose was, therefore, chosen to mimic the desired human response, and its physiologic effects were evaluated.

When doses this large are administered, significant amounts of vehicle are also delivered. Since lorazepam is practically insoluble in water, solutions are prepared in a base of propylene glycol and benzyl alcohol. Animal studies have shown that acute toxicity of lorazepam is due almost entirely to the vehicle, but the volumes needed are much greater than those used in this study.** Lack of observable vehicle effect in our monkeys was confirmed.

Agents that reduce CBF would be expected also to lower intracranial pressure (ICP). Preliminary studies by our group indicate this does occur after lorazepam administration in a cat model of intracranial hypertension.†† However, there are no data from studies that have examined effects of lorazepam in man with intracranial hypertension, and caution is required in extrapolating the potential ICP-decreasing action of lorazepam to patients. While Pa_{CO₂} values remained constant in our monkeys with tracheostomies, airway patency in premedicated patients cannot be assured if excessive sedation occurs. Hypercarbia resulting from airway obstruction could increase ICP in neurosurgical patients with poor intracranial compliance. In this regard, it may be safer to use lorazepam as an induction agent for anesthesia in neurosurgical patients with diminished levels of consciousness rather than as a premedicant. The combined effects of lorazepam and inhalational anesthetics upon CBF, CMR, and ICP have not been evaluated.

In summary, lorazepam, when used as a sedative in primates, decreases CBF and cerebral metabolism without significant blood pressure or arterial blood-gas changes. This occurs without signs of a change to anaerobic metabolism, and the effect appears similar

to that produced by diazepam. The prolonged action, better intramuscular absorption, and perhaps improved amnesic properties of lorazepam may be advantageous for certain neurosurgical patients.

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†† Unpublished data.