

The Effects of Diazepam on Cerebral Blood Flow and Oxygen Consumption in Rats and its Synergistic Interaction with Nitrous Oxide

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The effects of diazepam on cerebral blood flow (CBF) and cerebral oxygen uptake (CMR_{O_2}) was studied using a 133 Xenon modification of the Kety-Schmidt (1948) technique in paralyzed, artificially ventilated rats with and without simultaneous administration of 70 per cent nitrous oxide. Diazepam was given iv in doses that induced light to heavy sedation or general anesthesia. When given with 70 per cent nitrous oxide, diazepam in sedative and anesthetic doses lowered CBF and CMR_{O_2} to about 60 per cent of control. In the absence of nitrous oxide all doses of diazepam caused moderate (20–30 per cent) decreases in CBF, but CMR_{O_2} remained unchanged or was only slightly lowered. It is concluded that diazepam interacts with nitrous oxide to produce a reduction in CMR_{O_2} similar to that seen in barbiturate anesthesia, but that alone the drug produces sedation and anesthesia without a comparable decrease in CMR_{O_2} . (Key words: Hypnotics, benzodiazepines, diazepam; Anesthetics, gases, nitrous oxide; Brain, blood flow; Brain, oxygen consumption; Interactions (drug), diazepam and nitrous oxide.)

THE BENZODIAZEPINES are compounds that have anti-anxiety, anticonvulsant, muscle relaxant, and hypnotic properties. Although benzodiazepines have been in clinical use for more than a decade, there is little information about their effects on cerebral blood flow (CBF)

and cerebral metabolic rate for oxygen (CMR_{O_2}). In a recent article¹ it was reported that when 0.25 mg · kg⁻¹ diazepam was given to dogs exposed to 0.2 per cent halothane CMR_{O_2} decreased transiently by at most 17 per cent of control.

The present experiments were designed to obtain quantitative data about CMR_{O_2} and CBF following diazepam administration, and, since anesthetic doses of diazepam are frequently combined with nitrous oxide, to measure possible interactions between N₂O and diazepam.

Methods

All experiments were performed on male Wistar rats weighing 350–395 g. The animals had free access to tap water and commercial rat pellets (San-Bolagen, Malmö, Sweden) until operation.

STUDIES OF BEHAVIOR

The diazepam used in the CMR_{O_2} and CBF experiments was given to unanesthetized, spontaneously breathing rats, and their behavior was studied. Using halothane anesthesia, a catheter was placed in a tail vein. After the operation the rat was allowed to recover for at least two hours before diazepam was administered. The following time-dosage protocol was employed: an intravenous infusion of 0.75, 1.5, 2.25, 3.75 or 7.5 mg · kg⁻¹ diazepam was given during the first minute followed by twice the initial dose per hour. Thus, for example, when 0.75 mg · kg⁻¹ was given initially, the subsequent infusion was 1.5 mg · kg⁻¹ · hr⁻¹. The protocol produced a constant level of sedation or anesthesia for an hour. The animals were observed for an hour and the level of sedation or anesthesia was judged on the basis of spontaneous activity, respiration (frequency), and reflex patterns

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Received from the Brain Research Laboratory, E-blocket, and the Department of Anaesthesia, University Hospital, S-221 85, Lund, Sweden. Accepted for publication March 25, 1976. Supported by a grant from the Swedish Medical Research Council (Project No. 14X-263) and by USPHS grant No. RO 1 NS07838-07 from the NIH.

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TABLE 1. Observations in Rats, Diazepam Given Intravenously in Increasing Doses (See Text)

Initial Dose of Diazepam (mg · kg ⁻¹)	Degree of Wakefulness	Motor Activity	Spontaneous Respiration	Reaction to Stimuli; Reflexes
0.75	Light sedation	Resting in a natural prone position	Normal	Normal reactions to sound and pain stimuli; normal ciliary and corneal reflexes
1.5	Moderate sedation	Lying in lateral position with normal righting reflex	Normal	Almost normal reactions to sound and pain stimuli; normal ciliary and corneal reflexes
2.25	Moderate to marked sedation	Lying in lateral position, depressed righting reflex	Normal	Weak reaction to sound, slow reaction to pain; no ciliary reflex; normal corneal reflex
3.75	Strong sedation	Lying in lateral position, weak and slow righting reflex	Normal	No reaction to sound, weak reaction to pain; weak corneal reflex
7.5	Anesthesia	No righting reflex	Normal	No reaction to sound, pain or corneal stimulation

(righting reflex, ciliary and corneal reflexes), as well as reactions to stimuli (clapping of hands, touch and pinching of tail). Some rats in each group also had a catheter in a tail artery, for measurement of arterial blood gases.

STUDIES OF CMR_{O₂} AND CBF

The animals were anesthetized with 2–3 per cent halothane, delivered via a Dräger vaporizer to a jar. When unresponsive to stimuli, they were tracheotomized and immobilized with tubocurarine chloride (0.5 mg · kg⁻¹, iv). Halothane was then discontinued and the animals ventilated with 70 per cent N₂O in O₂ so as to obtain PaCO₂ values of 35–40 torr. Both femoral arteries were cannulated for blood pressure recording via a pressure transducer (Elema, Sweden) and sampling of arterial blood. Both femoral veins were cannulated for administration of diazepam and infusion of donor blood during CBF and CMR_{O₂} determinations. The skull was prepared with a skin incision permitting exposure of the distal part of the superior sagittal sinus by a dental drill. Rectal temperature was maintained at approximately 37 C by means of a heating bulb.

Fifteen minutes after the operative procedure had been finished, arterial blood gases were measured. When they were normal, the initial dose of diazepam was administered (see above) and continuous infusion started. As the

diazepam infusion was started, N₂O was replaced with N₂ in the same concentration. Thirty minutes later, CBF and CMR_{O₂} were determined. In two groups diazepam was given in (initial) doses of 0.75 and 7.5 mg · kg⁻¹, respectively, but N₂O and O₂ (70:30) were continued.

CBF was determined with a modification of the Kety–Schmidt² technique described by Norberg and Siesjö,³ using ¹³³Xenon as a tracer. Fifteen minutes before the start of CBF measurements a small amount of the tracer (about 10 μCi per animal) was added to the inspired gas to saturate the brain. At the end of the saturation period blood samples (about 40 μl) were taken from artery and superior sagittal sinus for measurement of oxygen content (C_{O₂}), arteriovenous oxygen difference [C(a–v)_{O₂}], and ¹³³Xenon activity, following which administration of ¹³³Xenon was discontinued. During the ensuing desaturation arterial and cerebral venous blood samples were taken repeatedly for 15 minutes for measurement of radioactivity. CBF was calculated from the desaturation curves, using the trapezoid rule.² Three minutes after the start of CBF measurement, another C(a–v)_{O₂} was determined. If this C(a–v)_{O₂} differed by more than 10 per cent from the former value, the experiment was discarded. CMR_{O₂} was calculated as the product of the CBF values and the second C(a–v)_{O₂}.

Arterial blood P_{O₂}, P_{CO₂} and pH were measured at 37 C using microelectrodes, with appropriate corrections for body temperature. Arterial and venous C_{O₂}'s were measured according to the method of Fabel and Lübbers.^{4,5}

Statistical significances of the differences were calculated by means of Student's *t* test.

Results

EFFECTS ON BEHAVIOR AND PHYSIOLOGIC VARIABLES

The smallest dose (0.75 mg · kg⁻¹ initially) of diazepam produced light sedation (table 1), but reactions to stimuli were normal (see Methods). With initial doses of 1.5–3.75 mg · kg⁻¹, it was possible to distinguish moderate from strong sedation, with observable differences in muscle tone and reactions to sound, pain,

and reflex stimuli. With the largest dose (7.5 mg · kg⁻¹ initially) complete anesthesia was obtained, with total loss of consciousness and loss of reflexes. The drug did not affect spontaneous respiration, even when increasing doses led to general anesthesia. Respiration was checked by counting the rate, but in those animals in which blood gases were measured, Pa_{O₂}'s ranged from 86 to 98 torr and Pa_{CO₂} from 33.3 to 41.3 torr.

Table 2 shows the physiologic data obtained in rats used for CBF and CMR_{O₂} studies. Using animals anesthetized with nitrous oxide (70 per cent) as controls, there was no significant change in mean arterial blood pressure with increasing doses of diazepam except in the group receiving 7.5 mg · kg⁻¹ diazepam without N₂O, although there was a slight reduction in blood pressure during the initial injection of the drug. The decrease never exceeded

TABLE 2. Physiologic Data in Rats Given Diazepam with or without 70 Per Cent N₂O (n = Number of Animals; Means ± SEM)

Group	n	Mean Arterial Blood Pressure (torr)	Temperature (C)	Pa _{O₂} (torr)	Pa _{CO₂} (torr)	pH	C _{A_{O₂}} (ml · 100 ml ⁻¹)
Control N ₂ O/O ₂	5	152 ± 7	36.9 ± 0.2	133 ± 4	36.4 ± 0.8	7.380 ± 0.007	23.90 ± 0.48
Diazepam, 0.75 mg · kg ⁻¹ N ₂ /O ₂	6	149 ± 2	37.9 ± 0.2	127 ± 5	38.8 ± 0.8	7.400 ± 0.008	22.68 ± 0.47
N ₂ O/O ₂	6	147 ± 4	36.8 ± 0.2	138 ± 6	36.1 ± 0.5	7.390 ± 0.012	22.79 ± 0.64
Diazepam, 1.5 mg · kg ⁻¹ N ₂ /O ₂	4	163 ± 9	36.7 ± 0.2	137 ± 5	35.3 ± 0.5	7.410 ± 0.010	24.05 ± 0.72
Diazepam, 2.25 mg · kg ⁻¹ N ₂ /O ₂	3	157 ± 5	36.8 ± 0.1	127 ± 8	35.8 ± 0.8	7.397 ± 0.001	23.16 ± 0.24
Diazepam, 3.75 mg · kg ⁻¹ N ₂ /O ₂	6	146 ± 5	37.1 ± 0.3	124 ± 11	37.2 ± 0.8	7.360 ± 0.010	22.85 ± 0.68
Diazepam, 7.5 mg · kg ⁻¹ N ₂ /O ₂	5	123† ± 4	36.9 ± 0.2	121* ± 3	39.7 ± 1.4	7.349 ± 0.012	22.58 ± 0.36
N ₂ O/O ₂	6	156 ± 4	36.8 ± 0.2	128 ± 13	37.3 ± 0.8	7.252† ± 0.026	21.26* ± 0.79

* *P* < 0.05 compared with control group.

† *P* < 0.01 compared with control group.

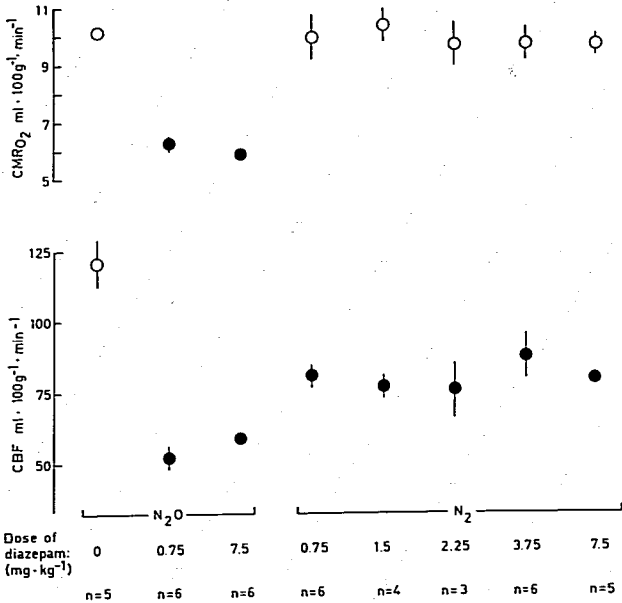


FIG. 1. Cerebral metabolic rate for oxygen (CMR_{O_2}) and cerebral blood flow (CBF) measured in animals anesthetized with nitrous oxide (control) or given diazepam with and without nitrous oxide. Values are means and vertical bars indicate \pm SEM, in some groups smaller than the symbol. Solid symbols indicate significance ($P < 0.05$). n = number of animals.

25 torr and lasted less than 5 minutes. Temperatures remained approximately 37 C in all groups. $P_{a_{O_2}}$ was somewhat lower in the group given 7.5 mg · kg⁻¹ diazepam without N₂O, but was still above 120 torr. There was no significant difference in arterial P_{CO_2} . However, in the group given 7.5 mg · kg⁻¹ diazepam in combination with N₂O, non-respiratory acidosis occurred. Its cause is unknown. Arterial oxygen content did not change significantly in any group except the group given 7.5 mg · kg⁻¹ in combination with N₂O. Since this decrease corresponds to a reduction in hemoglobin concentration from about 17 to 15 g · 100 ml⁻¹, it had no influence on the present conclusions.

EFFECTS ON CMR_{O_2} AND CBF

The effects of diazepam (0.75 and 7.5 mg · kg⁻¹ initially) on CMR_{O_2} and CBF in ani-

mals exposed to 70 per cent N₂O and 30 per cent O₂ are illustrated in the left part of figure 1. With both doses there were reductions in CMR_{O_2} to about 60 per cent of control and in CBF to 45–55 per cent of control. The reduction in CBF was unrelated to changes in blood pressure or arterial P_{CO_2} 's and the decrease in CMR_{O_2} occurred at constant body temperature (see table 2). The control animals were anesthetized with 70 per cent N₂O and 30 per cent O₂.

The right part of figure 1 shows values for CMR_{O_2} and CBF in rats that received diazepam in the absence of nitrous oxide. Although CBF was reduced in most animals following administration of diazepam, there was no, or only a very slight, depression of CMR_{O_2} . The data also demonstrate that CMR_{O_2} showed no variation with the dose of diazepam, although effects

on behavior varied from light sedation to anesthesia (see above).

Discussion

The present results can be summarized as follows. First, when either a sedative ($0.75 \text{ mg} \cdot \text{kg}^{-1}$) or an anesthetic ($7.5 \text{ mg} \cdot \text{kg}^{-1}$) dose of diazepam was used in combination with nitrous oxide, CBF and CMR_{O_2} were reduced to about 60 per cent of control (70 per cent N_2O). Second, in the absence of nitrous oxide, diazepam in doses of 0.75 – $7.5 \text{ mg} \cdot \text{kg}^{-1}$ reduced CBF but had minimal effects on CMR_{O_2} . It is concluded that diazepam induces sedation and anesthesia without a comparable reduction in cerebral oxygen uptake, but that it interacts with nitrous oxide to produce a depression of metabolic rate comparable to that observed during barbiturate anesthesia. The moderate effect of diazepam alone is similar to that found in dogs by Sari *et al.*,¹ although these investigators found the decrease in CMR_{O_2} to be significant following $0.25 \text{ mg} \cdot \text{kg}^{-1}$. There appears to be no previous report on an interaction between diazepam and nitrous oxide. To evaluate the quantitative effect of diazepam on CMR_{O_2} , we discuss below the method used for measuring CBF and CMR_{O_2} , as well as available information about CMR_{O_2} in unanesthetized animals.

The present method for evaluating CBF (and CMR_{O_2}), based on the Fick principle,² is associated with neither slow equilibration of tissue regions with tracer nor extracerebral contamination of venous blood.^{3,6} The results should, therefore, be quantitative. However, in all animal studies there is the problem of obtaining a proper control group. In many studies the effects of anesthetic, analgesic, or sedative drugs have been evaluated in the presence of background anesthesia, *e.g.*, nitrous oxide. As the present results demonstrate, this procedure has the drawback that drug interaction may occur. In order to clarify this, we discuss below the influence of nitrous oxide on CMR_{O_2} and CBF and attempt to deduce the values that apply to the unanesthetized state.

Although it is usually concluded that 70 per cent N_2O has only a small influence on CMR_{O_2} , the actual results obtained in man range from no significant effect⁷ to reduction by about 25 per cent.^{8,9} In dogs, 70 per cent N_2O

has been found to increase CMR_{O_2} by 11 per cent.¹⁰ In man, simultaneous awake controls have not been studied and, in the dog, control animals were given spinal anesthesia and had their cervical sympathetic and vagus nerves cut. Results from this laboratory have consistently shown that CMR_{O_2} in Wistar rats exposed to 70 per cent N_2O in O_2 is close to $10 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.^{2,11–13} We recently compared CMR_{O_2} and CBF in the rat during administration of 70 per cent N_2O to values obtained in paralyzed but unanesthetized animals, to which local anesthesia was given to minimize pain.^{12,14} Five and 30 minutes after withdrawal of nitrous oxide, CMR_{O_2} increased to 14.8 and 18.9 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, respectively, with comparable increases in CBF. Although non-confirmative results have been reported,¹⁵ one previous study¹⁵ indicated that administration of epinephrine increases CMR_{O_2} . We reported that adrenalectomy or administration of a β -adrenergic blocker (propranolol) prevents the increase in CMR_{O_2} in immobilized, unanesthetized rats.^{12,15} Apparently, withdrawal of nitrous oxide in ventilated animals leads to a stress-induced increase in CMR_{O_2} that is mediated by catecholamines.

Two observations demonstrate that 70 per cent N_2O alone has little, if any, effect on CMR_{O_2} in the rat. First, in adrenalectomized animals, or in animals pretreated with propranolol, ventilation with 70 per cent N_2 –30 per cent O_2 or 70 per cent N_2O –30 per cent O_2 was associated with CMR_{O_2} values of 11 and $10 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, respectively.¹¹ Second, previous results from this laboratory have shown that animals ventilated with 70 per cent N_2 –30 per cent O_2 and given fentanyl citrate for analgesia have a CMR_{O_2} close to $11 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.¹⁶ We conclude that if 70 per cent N_2O reduces CMR_{O_2} , the effect does not exceed 10 per cent. Tentatively, CMR_{O_2} in the absence of anesthesia is close to $11 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ in rats.

Table 3 lists CBF and CMR_{O_2} values obtained in unanesthetized, adrenalectomized rats (figures taken from Carlsson *et al.*¹³), in rats anesthetized with 70 per cent N_2O , and in animals from the present groups given diazepam in various doses with and without simultaneous nitrous oxide anesthesia. The rats receiving 1.5 or 2.25 $\text{mg} \cdot \text{kg}^{-1}$ diazepam, representing

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TABLE 3. Arteriovenous Difference for Oxygen ($C(a-v)_{O_2}$), Cerebral Blood Flow (CBF), and Cerebral Metabolic Rate for Oxygen (CMR_{O_2}) in Unanesthetized, Adrenalectomized Rats and Rats Given Nitrous Oxide or Diazepam (Means \pm SEM)

Group	n	$C(a-v)_{O_2}$ (ml·100ml ⁻¹)	CMR_{O_2} (ml·100 g ⁻¹ ·min ⁻¹)	
			CBF	CMR_{O_2}
Unanesthetized and adrenalectomized	6	9.95 \pm 0.66	114 \pm 5	11.2 \pm 0.6
70 per cent N ₂ O	5	8.54 \pm 0.38	121 \pm 8	10.1 \pm 0.2
Diazepam, 0.75 mg·kg ⁻¹ , + 70 per cent N ₂ O	6	12.07† \pm 0.29	52† \pm 4	6.2† \pm 0.3
Diazepam, 7.5 mg·kg ⁻¹ , + 70 per cent N ₂ O	6	9.96 \pm 0.52	59† \pm 2	5.8† \pm 0.2
Diazepam, 0.75 mg·kg ⁻¹	6	12.37† \pm 0.61	81† \pm 4	9.9 \pm 0.8
Diazepam, 1.5–2.25 mg·kg ⁻¹	7	13.11† \pm 0.32	78† \pm 4	10.0 \pm 0.5
Diazepam, 3.75 mg·kg ⁻¹	6	11.17 \pm 0.75	88* \pm 8	9.6 \pm 0.6
Diazepam, 7.5 mg·kg ⁻¹	5	12.31* \pm 0.30	78† \pm 2	9.6 \pm 0.4

* $P < 0.05$ compared with unanesthetized, adrenalectomized animals.¹³

† $P < 0.01$.

‡ $P < 0.001$.

moderate to marked sedation, were pooled (see Results). In animals given diazepam plus nitrous oxide, both CMR_{O_2} and CBF were reduced to about 55 per cent of control compared with unanesthetized, adrenalectomized animals. There was no difference in CMR_{O_2} or CBF between the two doses of diazepam given in combination with nitrous oxide, even though the doses differed by a factor of ten. None of the groups of animals receiving diazepam in the absence of nitrous oxide had a CMR_{O_2} that differed significantly from that obtained with 70 per cent N₂O, nor was there any significant difference when the diazepam groups were compared with the unanesthetized group. CMR_{O_2} did not vary with the dose of diazepam administered and, when the total material is considered, it is obvious that any reduction of CMR_{O_2} by diazepam did not exceed 10 per cent. However, the data strongly suggest that diazepam reduced CBF, since CBF values obtained with all doses of diazepam were lower than those measured during nitrous oxide anesthesia, or in unanesthetized, adrenalectomized animals.

The cause of this reduction in blood flow is unknown.

The present results allow two major conclusions. First, there is interaction between diazepam and nitrous oxide and, when administered in combination, these compounds reduce CMR_{O_2} to values encountered during surgical anesthesia with barbiturates (for data obtained in rats, see Nilsson and Siejö¹⁶). The results cast some doubt on the validity of previous studies in which the influences of anesthetic, analgesic, or sedative drugs have been examined during administration of nitrous oxide. Second, the results present an exception to the general rule that there is a parallelism between reduction in level of consciousness and lowering of CMR_{O_2} .^{17,18} In this respect diazepam gives results similar to those obtained using anesthesia with ketamine,^{19,20} cyclopropane, and ether (for references see Smith and Wollman²¹).

The authors are grateful to Gunilla Gidö for skilful technical assistance.

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Airway Management

TRACHEAL OBSTRUCTION AND THE LASER A 38-year-old woman had severe tracheal obstruction secondary to tumor. The authors report the use of a surgical laser following induction of general anesthesia and insertion of an 8 mm x 40 cm ventilating bronchoscope. The tumor was partially vaporized and partially carbonized by the laser. At the termination of the operation respiratory difficulty was completely relieved. The authors conclude that this technique may be

useful for the palliation of inoperable tumors producing significant tracheal obstruction. (Laforet EG, Berger RL, Vaughan CW: *Carcinoma obstructing the trachea: Treatment by laser radiation*. *N Engl J Med* 294: 941-943, 1976.) ABSTRACTER'S COMMENT: I regret that the authors did not comment at all upon the anesthetic technique used in this extremely difficult case of airway management.

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