Anesthesiology
56:172–176, 1982

Cerebral Metabolic, Vascular and Protective Effects of Midazolam Maleate

Comparison to Diazepam

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The effects of midazolam maleate and diazepam on cerebral metabolism and circulation were examined for each drug in six dogs maintained on N_2O 70 per cent and halothane < 0.1 per cent. Midazolam maleate at 0.2 mg/kg and diazepam at 0.3 mg/kg (the ED 100 per cent for induction of anesthesia for each drug in humans) did not decrease metabolic rate for oxygen (CMR_{O_2}) but did decrease cerebral blood flow (CBF) to about 55 per cent of control. Additional drug administrations (2.0, 5.0, and 10.0 mg/kg midazolam maleate, and 3.0 and 7.5 mg/kg diazepam) resulted in dose-related decreases in CMR_{O_2} to a maximum of 55 per cent of control after 10.0 mg/kg midazolam maleate. Concomitant with the initial decreases in CMR_{O_2}, there was a change in the EEG as reflected by a decrease in frequency and an increase in amplitude. This EEG change suggests that 2.0 mg/kg midazolam maleate and 3.0 mg/kg diazepam represent a comparable canine anesthetic dose. Each additional dose of midazolam maleate decreased CBF to a greater extent than did the added doses of diazepam. Brain biopsies taken at the end of the midazolam maleate studies revealed a normal cerebral energy state (phosphocreatine, ATP, ADP, and AMP) and normal glucose, lactate, and pyruvate concentrations. In a hypoxic mouse model ($F_{I_{O_2}} = 0.05$), midazolam maleate provided greater protection from hypoxia (2.8 × control survival time) than diazepam (1.6 × control survival time). By comparison barbiturates in this model provide a survival time which is 4.0 × control. (Key words: Anesthetics, intravenous: benzodiazepines, midazolam maleate, diazepam. Brain: metabolism; oxygen consumption; hypoxia; blood flow; electroencephalography.)

MIDAZOLAM MALEATE‡ is a new water-soluble benzodiazepine being evaluated for use as an induction agent in anesthesia. When given intravenously, this drug has a shorter duration of action and produces less pain and thrombophlebitis than diazepam.[1,2] Studies have shown midazolam maleate to be a safe and effective induction agent.[1–5] Hemodynamic stability has been reported in both clinical trials[1–5] and canine studies.[6] In this study, cerebral effects of midazolam maleate and diazepam were evaluated. Results are compared to the reported cerebral effects of the benzodiazepines, diazepam,[7,8] and lorazepam,[9] and to the cerebral effects of barbiturates.[10] When it was found that midazolam produced a larger decrease in the cerebral metabolic rate for oxygen (CMR_{O_2}) than diazepam in the dog, the study was extended to evaluate the possibility that midazolam maleate would provide greater cerebral protection from hypoxia than diazepam using a mouse model.

Methods

CANINE CEREBRAL STUDIES

Twelve unmedicated, fasting mongrel dogs weighing 16–20 kg were studied. Anesthesia was induced with halothane (1 per cent) and nitrous oxide (60–70 per cent) in oxygen. Succinylcholine (30 mg) was given to facilitate endotracheal intubation and thereafter continuously infused (100 mg/h) to maintain muscle paralysis. Ventilation with a minute volume sufficient to maintain a Pa_{CO_2} of 40 ± 1 mmHg (mean ± SEM) was controlled with a Harvard® pump. Pa_{O_2} was maintained at 158 ± 3 mmHg by adjusting inspired oxygen concentration. TRIS Buffer [Tris (hydroxymethyl) amino methane] was administered as needed to keep the buffer base (BB^+) at 40 ± 1 mEq/l. A cannula was inserted in the left femoral vein for fluid and drug administration. A femoral artery was cannulated for blood sampling and continuous monitoring of mean arterial pressure (MAP) obtained from the cyclic arterial pressure by means of resistance-capacitance filtering. Each animal was positioned prone and the posterior sagittal sinus cannulated as described previously[11] for direct cerebral blood flow (CBF) measurement and cerebral venous blood sampling. CBF was measured intermittently by timed collection. Brain temperature was monitored by a parietal epidural thermistor probe and maintained at 36.9 ± 0.0° C with heat lamps. The electroencephalographic activity (EEG) was monitored with bifrontoparietal electrodes. The CMR_{O_2} was determined as the product of CBF and the arterial-cerebral venous (sagittal sinus) blood oxygen content difference. Blood oxygen contents were determined from measurements of oxygen tension (IL 313 at 37° C), and oxyhemoglobin concentrations (IL 282 CO-Oximeter)

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Received from the Department of Anesthesiology, Mayo Medical School and Mayo Clinic, Rochester, Minnesota. Accepted for publication June 4, 1981. Supported in part by a Research Grant from Hoffman-LaRoche, Inc., Nutley, New Jersey, and Research Grant NS-7507 from the National Institute of Health, Public Health Service.

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‡ Dobralam®: Midazolam maleate-RO21-3081, as base equivalent dissolved in water, manufactured by Hoffman-LaRoche Inc., Nutley, New Jersey 07110. Each ml contains 3.5 mg midazolam maleate, 4 mg tartaric acid, 0.1 mg disodium edetate, 7.0 mg sodium chloride, 0.01 ml benzyl alcohol and NaOH–10 per cent in sufficient quantity to bring the *p*H to 3.3 ± 0.1.

0003-3022/82/0300/0172 $00.75

using 1.39 ml/g as the oxygen carrying capacity of hemoglobin. Cerebral vascular resistance (CVR)was calculated as the ratio of MAP and CBF.

At the completion of the surgical procedure halothane was discontinued. When end-expired halothane was <0.1 per cent and after stable CMR_{O_2} measurements were established, midazolam maleate was given to six dogs in sequential intravenous doses of 0.2, 2.0, 5.0, and 10.0 mg/kg and diazepam was given to another six dogs in doses of 0.3, 3.0, and 7.5 mg/kg with a dosing interval of 39 ± 1 min (mean ± SEM) for each. All doses were given as a bolus over 30 s. A fourth dose of diazepam (15 mg/kg) was omitted to allow time for evaluation of the effects of N_2O in the background anesthetic. Studies were limited to 2.5 hours after initial drug administration in accord with a previous study validating the stability of this canine preparation.[12] In three of the dogs given diazepam, N_2O was replaced by N_2 with the initial dose of diazepam and was reintroduced after the final dose of diazepam. In the other three dogs given diazepam, N_2O was replaced with N_2 after the last dose of diazepam.

Responses of cerebral and systemic variables were determined at 5, 15, and 30 min after each drug dose and at 10 and 25 min following the terminal alterations in either inspired N_2O and N_2. Reported values for CBF and CMR_{O_2} are the mean of three determinations. Cerebral and systemic values at each of the cumulative drug doses were compared to control values using Student's *t* test for paired data.

At the conclusion of the study brain biopsies were taken in the midazolam maleate treated dogs by a suction technique that deposits a 200–400 mg sample into liquid nitrogen in less than one second.[13] The preparation of the biopsy samples for analysis was done in a refrigerated chamber at −25° C.[14] Tissue extracts were analyzed by enzymatic fluorometric techniques for ATP, ADP, AMP, and phosphocreatine (PCr), glucose, lactate, and pyruvate.[15] The sum of the adenine nucleotides (ΣAd = [ATP] + [ADP] + [AMP]) was determined.[16] The energy state of the tissues was expressed as the energy charge potential of the adenine nucleotide pool (ECP = [ATP] + 0.5 [ATP]/ΣAd). Using Student's *t* test for unpaired data, the biopsy results from the midazolam maleate treated dogs were compared to biopsy data from seven barbiturate anesthetized dogs from a previous study.[17]

Mouse Protection Studies

Four hundred and fifteen adult male albino mice§ weighing 33 ± 4 g (mean ± SD) were given free access to food pellets and tap water. The mice received intraperitoneal doses of midazolam maleate from 0.2–90 mg/kg, diazepam from 0.3–30 mg/kg, or an equal volume of 0.9 per cent sodium chloride (controls). The volume of intraperitoneal injection was 10 ml/kg except for doses of midazolam maleate larger than 30 mg/kg. Volumes as high as 36 ml/kg were necessary because of the low concentration of midazolam maleate in the drug preparation from the manufacturer. The larger intraperitoneal volumes injected did not alter control survival time. Lack of exploratory behavior, ataxia, or anesthesia (loss of righting reflex for more than 30 s) at each dose was noted. The median anesthetic dose of midazolam maleate in the mouse (AD_{50}) was calculated by the method of Litchfield and Wilcoxon.[18]

Twenty min after injection, mice were placed individually in one of five gas tight flow-through chambers, which were supplied with room air, for temperature equilibration (ambient temperature 35° C). Thirty min after injection the mice were exposed to 5 per cent oxygen in nitrogen as described previously.[19] Survival time, defined as the time from initiation of hypoxic gas delivery to cessation of respiration, was recorded for each animal. Sixteen animals were studied at each drug dose. For each group of five animals, one or two control animals were rotated among chambers. Survival data were analyzed using an analysis of variance. Where variance was confirmed, individual doses were compared to controls using Student's *t* test for unpaired samples. Differences were considered significant at a *P* value of less than 0.05. An additional 16 experimental animals injected with 60 mg/kg midazolam maleate and 9 control animals were exposed to 8 min of hypoxia and then returned to room air.

Results

Canine Cerebral and Systemic Studies

After diazepam administration, differences in CMR_{O_2} and CBF resulting from variations in either N_2 or N_2O in the inspired gases were insignificant and, therefore, data for the diazepam dogs were pooled. CMR_{O_2} did not change following the first dose of either midazolam maleate (0.2 mg/kg) or diazepam (0.3 mg/kg) (table 1). Subsequently progressive decreases in CMR_{O_2} were seen after all remaining doses (2.0, 5.0, and 10.0 mg/kg midazolam maleate; 3.0 and 7.5 mg/kg diazepam). The lowest CMR_{O_2} attained was 55 per cent of control after 10.0 mg/kg midazolam maleate. Concomitant with the initial decreases in CMR_{O_2} there was a change in the EEG as reflected by a decrease in frequency and an increase in amplitude.

Midazolam maleate and diazepam reduced CBF at all doses studied as compared to control (table 1). The first dose of midazolam maleate (0.2 mg/kg) and the first dose of diazepam (0.3 mg/kg) resulted in similar de-

§ Sprague Dawley, Madison, Wisconsin.

TABLE 1. Cerebral Metabolic and Vascular Effects of Diazepam and Midazolam Maleate

Incremental Dose Administered mg/kg		Time After Dose (Min)	CMR_{O_2} · ml · min^{-1} · 100 g^{-1}		CBF ml · min^{-1} · 100 g^{-1}		CVR (mmHg)/ (ml · min^{-1} · 100 g^{-1})		MAP (mmHg)	
			Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam	Diazepam	Midazolam
Control			5.50 ± 0.30†	5.29 ± 0.31†	119 ± 13	104 ± 8	1.21 ± 0.11	1.25 ± 0.13	138 ± 7	126 ± 7
Diazepam	Midazolam									
0.3	0.2	5	5.48 ± 0.29	4.74 ± 0.44	66 ± 7*	61 ± 3*	1.33 ± 0.14	1.47 ± 0.14	86 ± 10*	89 ± 9*
		30	5.42 ± 0.25	5.59 ± 0.50	59 ± 5*	55 ± 3*	1.74 ± 0.18	1.65 ± 0.10*	102 ± 11	90 ± 4*
3.0	2.0	5	4.46 ± 0.26*	4.08 ± 0.21*	55 ± 5*	37 ± 1*	1.30 ± 0.13	1.97 ± 0.09*	71 ± 10*	72 ± 6*
		30	4.37 ± 0.29*	4.00 ± 0.11*	49 ± 6*	37 ± 0*	1.69 ± 0.11	2.03 ± 0.10*	80 ± 8*	74 ± 4*
7.5	5.0	5	3.93 ± 0.30*	3.44 ± 0.11*	61 ± 8*	34 ± 1*	1.25 ± 0.13	2.67 ± 0.15*	73 ± 9*	90 ± 5*
		30	4.00 ± 0.20*	3.62 ± 0.16*	46 ± 4*	31 ± 1*	1.71 ± 0.13	2.35 ± 0.22*	79 ± 8*	73 ± 5*
—	10.0	5	—	2.90 ± 0.11*	—	32 ± 2*	—	2.88 ± 0.20*	—	91 ± 4*
		30	—	3.27 ± 0.09*	—	30 ± 2*	—	2.89 ± 0.39*	—	84 ± 7*

* Significantly different from control (Paired t, $P < 0.05$). † Mean ± SE for six dogs.

creases in CBF (104 ± 8 to 61 ± 3 ml · min^{-1} · 100 g^{-1} and 119 ± 13 to 66 ± 7 ml · min^{-1} · 100 g^{-1}, respectively). Larger doses of midazolam maleate (2.0 and 5.0 mg/kg) decreased CBF to a greater extent than comparable doses of diazepam (3.0 and 7.5 mg/kg). The final dose of 10 mg/kg midazolam maleate did not further decrease CBF.

A decrease in MAP was seen following all doses of diazepam and midazolam maleate as compared to control (table 1). In the dogs given midazolam maleate there were no alterations in the cerebral energy state as compared to dogs anesthetized with barbiturates.[17] Both the cerebral ECP and lactate levels were normal (table 2).

Mouse Survival Studies

The mean survival times of control mice in the midazolam maleate and diazepam studies were 4.1 ± 0.1 min (N = 90) and 3.9 ± 0.1 min (N = 54), respectively. Both midazolam maleate (beginning at 2.0 mg/kg) and diazepam (beginning at 1.5 mg/kg) significantly prolonged survival time (fig. 1). Midazolam maleate treated mice had a maximal survival time of 11.6 ± 1.1 (N = 16) min at a dose of 75 mg/kg, while diazepam treated mice had a maximal survival time of 6.2 ± 0.4 (N = 16) min at 15 mg/kg.

At the doses of midazolam maleate and diazepam where protection from hypoxia became significant the mice no longer exhibited exploratory behavior. The dose of midazolam maleate providing the longest survival time (75 mg/kg) exceeded the AD^{50} for midazolam maleate (63 mg/kg). Mice at the maximally protective dose of diazepam (15 mg/kg) were not anesthetized (loss of righting reflex) but were ataxic and had no exploratory behavior. At 30 mg/kg diazepam anesthesia was induced in six of 16 mice, but no protection was seen.

Thirteen of the 16 mice injected with 60 mg/kg midazolam maleate survived 8 min of hypoxia and were returned to room air. Twenty-four hours later the 13 surviving mice appeared normal. The nine control mice were all dead after 5 min of hypoxia.

Discussion

Cerebral effects of the benzodiazepines lorazepam and diazepam have been reported previously. In *macaca fascicullaris*, intravenous lorazepam (4.0 mg/kg), which induced sleep from which 8 of 10 monkeys could be aroused, was found to decrease mean CMR_{O_2} to 70–79 per cent of control.[9] Carlsson *et al.* studying the rat in the presence of 70 per cent nitrous oxide, found that diazepam in sedative and anesthetic doses (0.75 and 7.5 mg/kg) decreased CMR_{O_2} to about 60 per cent of control while no change in CMR_{O_2} was seen in the absence of N_2O.[8] Maekawa *et al.*,[7] using the same canine model as this laboratory, reported a transient decrease in CMR_{O_2} to 84 per cent of control with 0.25 mg/kg di-

TABLE 2. Cerebral Tissue Metabolic Effects of Midazolam Maleate

Metabolic Variable	Cerebral Biopsy Values (Mean ± SEM for Six Dogs)	
	Control (Barbiturate Anesthesia)*	Midazolam Maleate
ATP, μmol/g	2.14 ± 0.10	1.97 ± 0.05
ADP, μmol/g	0.30 ± 0.01	0.27 ± .02
AMP, μmol/g	0.06 ± 0.01	0.04 ± .01
ΣAd, μmol/g	2.50 ± 0.09	2.28 ± 0.25
ECP	0.92 ± 0.01	0.92 ± 0.02
P-creatine, μmol/g	3.04 ± 0.17	2.58 ± 0.11
Glucose, μmol/g	2.21 ± 0.18	1.93 ± 0.39
Lactate, μmol/g	1.04 ± 0.14	1.52 ± 0.18
Pyruvate, μmol/g	0.06 ± 0.01	0.06 ± 0.01

* Data from previous study.[19]

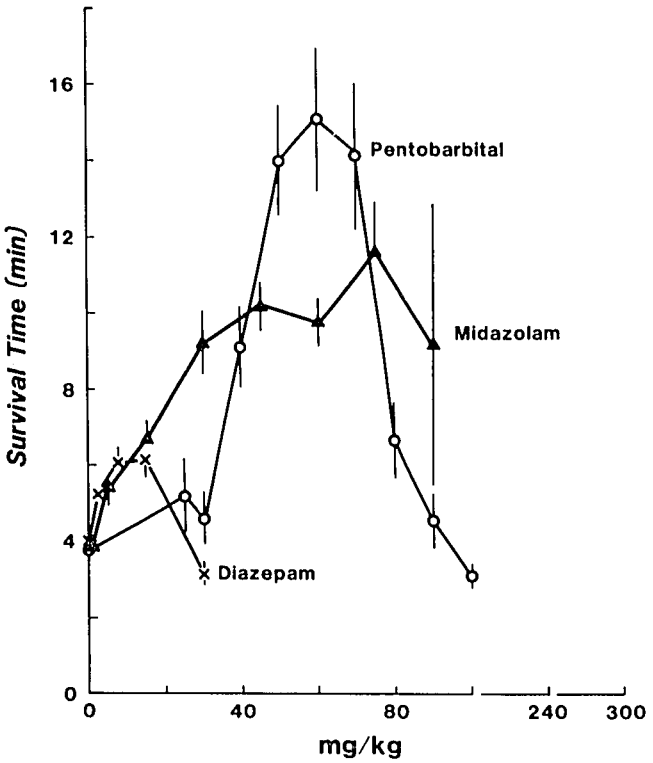

FIG. 1. Mean survival time ± SEM for mice exposed to 5 per cent oxygen after injection of various doses of diazepam, midazolam maleate and pentobarbital.[23]

azepam. We saw a transient statistically insignificant decrease in CMR_{O_2} to 90 per cent of control after 0.2 mg/kg midazolam maleate and no decrease in CMR_{O_2} after 0.3 mg/kg diazepam. (These doses are the ED 100 per cent for induction of anesthesia in humans.[2]) Maekawa *et al.* in their study of diazepam used a background anesthetic of 0.2 per cent halothane. We used less than 0.1 per cent halothane and 60–70 per cent nitrous oxide to provide added analgesia for the experimental animals, and to duplicate the clinical setting in which midazolam maleate would be used commonly. Nitrous oxide, which moderately increases CMR_{O_2} in this model,[20,21] may blunt drug-induced decreases in CMR_{O_2}. However, in contrast to results in rats reported by Carlsson,[8] no large differences in CMR_{O_2} were seen between our animals given diazepam with and without a background of N_2O. Larger doses of midazolam maleate (2, 5, and 10 mg/kg) and diazepam (3.0, 7.5 mg/kg) resulted in dose-related decreases in CMR_{O_2}. Concomitant with the initial decreases in CMR_{O_2} there was a change in the EEG to a sleep pattern suggesting that 2.0 mg/kg midazolam maleate and 3.0 mg/kg diazepam represent a comparable canine anesthetic dose. The lowest CMR_{O_2} was 2.9 ml · min^{-1} · 100 g^{-1} (55 per cent of control) after 10 mg/kg midazolam maleate. Since our animals remained hemodynamically stable, it is probable that even larger doses of midazolam maleate would be tolerated with decreases in CMR_{O_2} possibly approaching those seen with barbiturates (to 2.22 ± 1.1 ml · min^{-1} · 100 g^{-1}).[10]

Our observation that both midazolam maleate and diazepam decrease CBF is in agreement with earlier studies done with diazepam,[7,8] and lorzepam.[9] After 4.0 mg/kg lorazepam, Rockoff *et al.*[9] saw a decrease in CBF to 72 per cent of control as well as an increase in CVR in monkeys without nitrous oxide. Diazepam in rats with 70 per cent nitrous oxide causes a decrease in CBF to 45–55 per cent of control after doses of 0.75 and 7.5 mg/kg.[8] In dogs, after 0.25 mg/kg diazepam in the absence of N_2O, Maekawa *et al.*[7] saw a decrease in CBF from 60 to 51 ml · min^{-1} · 100 g^{-1}. After 0.2 mg/kg midazolam maleate or 0.3 mg/kg diazepam, we saw a comparable CBF with a decrease from control of 104 to 55 ml · min^{-1} · 100 g^{-1} for midazolam maleate, and 119 to 59 ml · min^{-1} · 100 g^{-1} after diazepam. Our control values for CBF are higher than the values of Maekawa *et al.* because of the nitrous oxide in the background anesthetic.[21] Consistent reductions in CBF were not seen after further doses of diazepam. Subsequent administrations of midazolam maleate, however, resulted in increased CVR and a dose-related decrease in CBF to 31 ml · min^{-1} · 100 g^{-1} after 5.0 mg/kg. Following large doses of barbiturates, CBF may be as low as 18 ± 2 ml · min^{-1} · 100 g^{-1}[22] compared to a maximally decreased CBF with midazolam maleate of 30 ± 2 ml · min^{-1} · 100 g^{-1}. This appeared to be the maximal decrease in CBF obtainable with midazolam maleate in this model as the final dose of 10 mg/kg caused no further decrease in CBF.

In the mouse study midazolam maleate provided greater protection from hypoxia (2.8 × control survival time) than diazepam (1.6 × control survival time). By comparison pentobarbital in an earlier study from this laboratory prolonged survival time to 4.0 × control.[23] The dose-response curves (fig. 1) show that protection from hypoxia is gained with less midazolam maleate and diazepam than pentobarbital. At the lowest protective doses of midazolam maleate and diazepam, mice show a lack of exploratory behavior, demonstrating a coupling between functional effects and protection. Similar to our finding in the dog, midazolam maleate may decrease CMR_{O_2} to a greater extent than diazepam in the mouse, and therefore provide greater protection from hypoxia.

Reasons for the decrease in survival time seen at the highest doses of midazolam maleate, diazepam, and pentobarbital are probably because of cardiorespiratory depression caused by these drugs. This cardiorespiratory depression could only be countered by appropriate support measures. The fact that the 13 mice whose survival time was prolonged with midazolam maleate had no neurologic deficits 24 hours after the hypoxic insult es-

tablishes the correlation between the prolongation of the time to cessation of respiration and ultimate brain survival.

In summary, midazolam maleate in sufficient dosage produces a profound depression of canine CMR_{O_2} without severe hemodynamic depression or alteration in the cerebral energy state. In the hypoxic mouse model it produces a degree of protection which approaches that seen with barbiturates. Accordingly, midazolam maleate or a similar longer acting benzodiazepine may provide an alternative to the barbiturates for use in cerebral protection research.

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