Cardiovascular Responses to Diazepam and Midazolam Maleate in the Dog

David J. Jones, Ph.D.,* Linda C. Stehling, M.D.,† Howard L. Zauder, M.D., Ph.D.‡

Previous clinical studies establishing the efficacy of midazolam maleate (RO 21-3981), a new water-soluble benzodiazepine for induction of anesthesia, have not critically evaluated the effects of this agent on the cardiovascular system. The present study compares the cardiovascular effects of midazolam maleate and diazepam in conscious dogs. Systemic arterial, pulmonary arterial and central venous pressures, cardiac output, LV_{max} dP/dt, heart rate and regional coronary blood flow were measured 3 min following intravenous administration of diazepam (0.5, 1.0, and 2.5 mg/kg) or midazolam maleate (0.25, 1.0, and 10.0 mg/kg). Midazolam maleate increased heart rate 10–20 per cent with all three doses and decreased mean arterial blood pressure approximately 10–20 per cent at 1.0 and 10 mg/kg. Cardiac output was increased 10–12 per cent with all three doses of midazolam maleate, and LV_{max} dP/dt was decreased 13–16 per cent at the two higher doses. Diazepam at all three doses did not alter heart rate or mean arterial blood pressure. Diazepam, 1.0 and 2.5 mg/kg, produced significant (17 per cent) decreases in LV_{max} dP/dt, and 2.5 mg/kg produced a significant (10 per cent) increase in cardiac output. Neither drug in any dosage altered regional coronary blood flow, systemic or coronary vascular resistance, stroke volume, or stroke work. Maximum alterations in cardiovascular variables occurred with doses of midazolam maleate that are 10–15 times the recommended clinical induction dosage. It is concluded that in concentrations necessary for induction of anesthesia midazolam maleate has minimal effects on cardiovascular function. (Key words: Heart: blood flow, myocardial; cardiac output; contractility. Hypnotics, benzodiazepines: diazepam; midazolam maleate. Induction: anesthesia.)

THE UTILIZATION OF DIAZEPAM as an intravenous agent for induction of anesthesia is limited by pain or injection and a significant incidence of thrombophlebitis at the injection site.[1,2] The incidence of pain on injection has been reported to be as high as 67 per cent,[2] and that of thrombophlebitis, 3.5 per cent.[1] A recent study by Graham et al.[3] indicates that both diazepam and the propylene glycol–alcohol vehicle needed for solubilization may cause these effects. Alternative vehicles that do not employ an organic solvent base

have been used with a moderate decrease in the incidence of irritation at the injection site.[2,4]

Unlike diazepam, midazolam maleate (RO 21-3981) is water-soluble, which should minimize irritation at the injection site as well as provide enhanced compatibility with other intravenous solutions. Moreover, neuropharmacologic studies in animals indicate that midazolam maleate is approximately threefold more potent than diazepam, with approximately a third the toxicity.§ While the efficacy of midazolam maleate as an agent for induction of anesthesia has been established in both laboratory and clinical studies,[5,6] a critical evaluation of the effects of this agent on the circulatory system in lacking. We have compared the effects of midazolam maleate and diazepam on the cardiovascular system in conscious, chronically instrumented dogs.

Methods and Materials

In 20 heartworm-free, well-nourished and well-hydrated mongrel dogs (16–31 kg) sterile thoracotomies were performed during halothane anesthesia. Following exposure of the heart, a stab incision was made in the left ventricle near the apex and a calibrated solid-state pressure transducer (P-18; Konigsberg Instruments) implanted. A 15-gauge polyvinyl catheter was placed in the left atrial appendage and an 18-gauge polyvinyl catheter in the aorta. In addition, in all of the dogs given midazolam maleate and four animals given diazepam, an electromagnetic flow probe was placed around the root of the ascending aorta for continuous measurement of cardiac output. The catheters and wires were brought outside the skin at the back of the neck.

Central venous, pulmonary arterial, and pulmonary capillary wedge pressures and cardiac output were measured via a triple-lumen Swan-Ganz thermo-dilution catheter (Instrumentation Laboratories) placed via the right external jugular vein. The animals were allowed to recover for two to ten days, during which conditioning to reclining in a hammock was carried out. Following the surgical procedure the animals were treated prophylactically with two injections of procaine penicillin G, 600,000 units. During the recovery period, the health of the animals was

* Assistant Professor of Anesthesiology, University of Texas Health Science Center, San Antonio.

† Associate Professor of Anesthesiology and Pediatrics, State University of New York, Upstate Medical Center, Syracuse, New York.

‡ Professor and Chairman of Anesthesiology, Professor of Pharmacology, State University of New York, Upstate Medical Center, Syracuse, New York.

§ Runser RH, Hoffmann–La Roche Inc., Nutley, New Jersey: Personal communication.

monitored by examination of hematocrits and body temperatures. All animals could exercise normally, and electrocardiographic abnormalities were not present.

A Zepeda® SWFI electromagnetic flowmeter was used for measuring cardiac output from the electromagnetic flow-probe signal. The flow probes were calibrated *in vitro* before implantation. *In-vivo* calibration of the aortic flow probes was made by comparing the cardiac output values obtained with those obtained by the thermodilution technique (Instrumentation Laboratories, Model 601 Thermodilution Cardiac Output Computer). The calibrations agreed to within 7 per cent. Systemic pressure values were measured through Statham strain gauges (P23Db) zeroed to the midline of the sternum. Electrocardiograms were obtained from subcutaneous needle electrodes placed along the sternum. All signals were inscribed on a Beckman Dynagraph recorder. Arterial blood-gas and pH values were measured using an Instrumentation Laboratories Model 213 blood-gas analyzer.

Coronary blood flow was measured according to the techniques of Buckberg *et al.*,[7] using 15 ± 5-μm carbonized microspheres labeled with ^{125}I, ^{141}Ce, ^{85}Sr, or ^{46}Sc. Microspheres (3M Company) were obtained as 1 mCi of nuclide in 10 ml dextran, 10 per cent, and Tween 80, 0.05 per cent. The stock solution was diluted in sterile saline solution with one drop of Tween 80, so that each milliliter, the volume injected, contained 800,000 microspheres. Individual or serial injections of this quantity of microspheres did not result in any change in heart rate or blood pressure.

Total counts represented by the 1 ml of microspheres to be injected were measured by counting the radioactivities of five weighed 10-μl samples of the labeled microspheres from the injection syringe. By weighing the syringe volumes to be injected and multiplying by the average counts/mg of spheres from the 10-μl samples, one could accurately determine total counts injected. This procedure avoided the inefficiency of the gamma counter at levels greater than 2×10^5 counts/min.

Before each injection, microspheres were thoroughly mixed by alternate agitation for 5 min in an ultrasonic bath and a vortex agitator. The syringe volume of the microsphere mixture was then injected into the left atrium over a 15-sec interval via the previously implanted catheter and flushed in with 10 ml of warm isotonic saline solution. Cardiac output by thermodilution was measured in duplicate immediately prior to and immediately following the microsphere injection.

Each dog was killed by an overdose of thiopental sodium and the heart was removed. The ventricles were separated from atria, vessels and fat, and dissected into left and right ventricles and septum. These regions were then weighed and a representative section approximating the middle third of each area was cut into uniform-weight samples of 1–2 g. The tissue samples were subsequently weighed and counted in a Packard AutoGamma multichannel gamma counter. Computer-assisted average flow to each region was calculated using the following formula:

$$\text{Flow (ml/min/g tissue)} = \frac{\text{cardiac output (ml/min)}}{\text{total counts injected (counts/min)}} \times \frac{\text{(counts/min)}}{\text{tissue weight (g)}}$$

All tissue counts were simultaneously corrected for overlapping counts of the accompanying isotopes by this same computer algorithm.

Measurements of all variables were made prior to and 3 min following the termination of administration of control vehicle or drug. All vehicle or drug administrations were made through a percutaneous 16-gauge polyethylene catheter placed in a cephalic vein at the time of the study. Administrations were given over a 15-sec period, followed by a 10-ml sterile saline flush. Midazolam maleate was administered in doses of 0.25, 1.0, and 10 mg/kg at 45-min intervals. Diazepam was administered in doses of 0.5, 1.0, and 2.5 mg/kg at similar 45-min intervals. The sequences in which dosages of drugs were administered were randomized. Malic acid vehicle (0.1 mM) and diazepam vehicle were administered in volumes of 0.25 ml/kg at the

start of each animal study. These did not alter any cardiovascular variable, compared with pre-vehicle-administration values.

Conventional formulas were used for calculation of stroke volume, stroke work, and systemic vascular resistance. An estimate of coronary vascular resistance was calculated by dividing the product of mean arterial and right atrial pressures by average coronary blood flow.

To determine the significance of observed changes, intragroup comparisons of the four sets of measurements were made employing the Student t test for paired samples.

Results

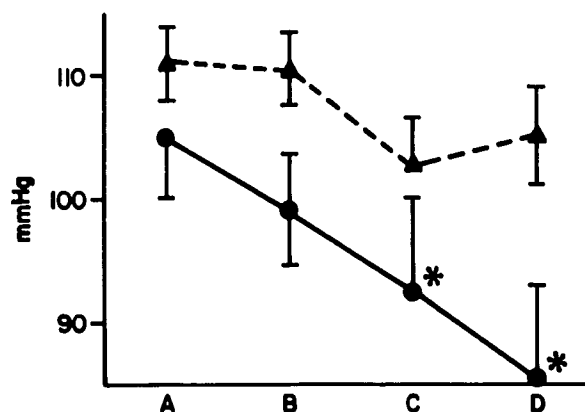Relatively minor changes in cardiovascular variables were found with midazolam maleate and diazepam

Fig. 1. Effects of diazepam (*triangles*) midazolam maleate (●) on mean arterial pressure (torr ± SEM). *A*, diazepam or midazolam maleate vehicle (0.25 ml/kg); *B*, diazepam, 0.5 mg/kg; midazolam maleate, 0.25 mg/kg; *C*, diazepam, 1.0 mg/kg; midazolam maleate, 1.0 mg/kg; *D*, diazepam, 2.5 mg/kg; midazolam maleate, 10.0 mg/kg. *P < 0.05 vs. vehicle control; **P < 0.005 vs. vehicle control.
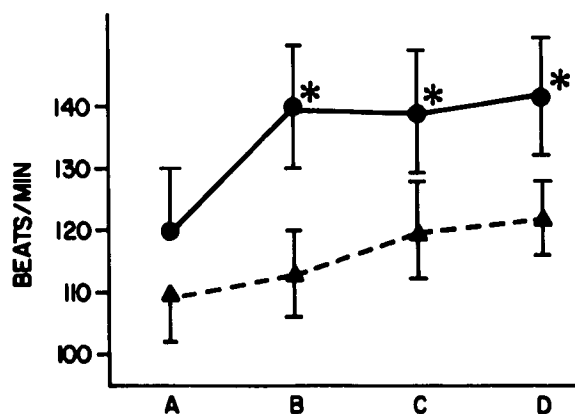
with a significant decrease in systemic vascular resistance (fig. 4). With both midazolam maleate and diazepam, the increase in cardiac output at the higher dosages occurred in spite of a significant decrease in contractility, as represented by decreases in LV_{max} dP/dt (fig. 5). Stroke volume and stroke work were unaffected by either drug or dosage (table 1). Also unchanged within groups were arterial blood-gas and pH values, as well as central venous, pulmonary arterial and pulmonary capillary wedge pressures (data not shown).

Coronary blood flow was not altered significantly in any of the three areas by any dose of midazolam maleate or diazepam (table 1). An insignificant increase in flow was evident with the highest dose of midazolam maleate, and this increase, combined with a decreased arterial pressure, was reflected in a decrease in calculated coronary vascular resistance (fig. 6).
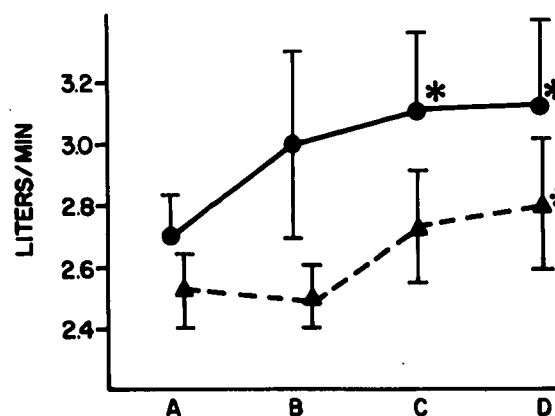

Fig. 2. Effects of diazepam and midazolam maleate on heart rate (mean beats/min ± SEM). See legend to figure 1 for explanation of *A–D*.

Fig. 3. Effects of diazepam and midazolam maleate on cardiac output (mean liters/min ± SEM). See legend to figure 1 for explanation of *A–D*.

at all doses. Midazolam maleate produced a 15 per cent increase in heart rate with all three doses (fig. 1). Diazepam did not alter heart rate significantly at any dose. Mean arterial pressure was decreased by midazolam maleate at 1 and 10 mg/kg, while diazepam had no significant effect on this variable (fig. 2). A slight but significant increase in cardiac output was found with the two higher doses of midazolam maleate (fig. 3). This moderate increase may be related to the tachycardia that occurred with the higher doses of midazolam maleate. However, diazepam, 2.5 mg/kg, produced a significant increase in cardiac output independent of the existence of any significant increase in heart rate. The increase in cardiac output and decrease in mean arterial pressure associated with the higher dosages of midazolam maleate were associated
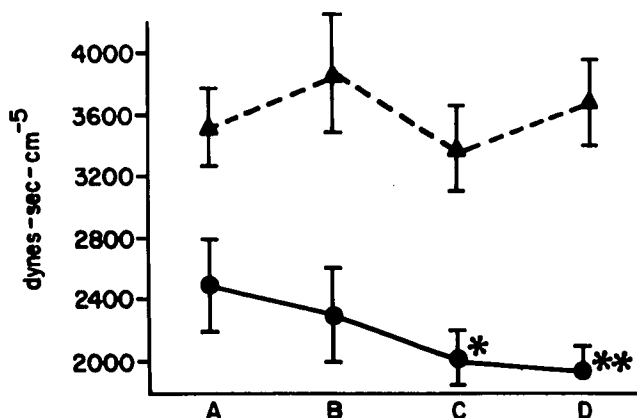

Fig. 4. Effects of diazepam and midazolam maleate on systemic vascular resistance (dynes·sec·cm⁻⁵ ± SEM). See legend to figure 1 for explanation of *A–D*.

Discussion

The doses of midazolam maleate and diazepam administered intravenously were comparable to, above, and below those that are clinically efficacious for induction of anesthesia. Previous studies by Fragen et al.[5] and Reves et al.[6] established that such doses, which produce induction of anesthesia in 90–100 per cent of subjects, are 0.2 mg/kg for midazolam maleate and 0.3 mg/kg for diazepam.

A time course for evaluation of effects that reflected the time of maximum pharmacologic effect following intravenous administration was used. The above-described studies established that induction occurred within 80–150 sec with midazolam maleate and 94–158 sec with diazepam.[5,6] In addition, the 45-min interval between dosages takes into account the 30-min first-phase half-life of diazepam[8] in dogs and a half-life of less than 8 min for midazolam maleate.¶ This half-life represents the distribution of drug from the central compartment to the peripheral tissue space. In dogs the elimination-phase half-lifes are 7.6 hours for diazepam[8] and 1.1 hours for midazolam maleate.¶

The published clinical reports of studies using midazolam maleate as an induction agent for anesthesia confirm the lack of deleterious effects of this agent on the cardiovascular system.[5,6] Neves et al. reported that with induction dosages of 0.1–0.3 mg/kg no hypotension or other cardiovascular instability occurred.[6] In agreement, Fragen et al. reported that only two of 25 patients showed decreases in mean arterial pressure of 25 per cent or more when an average of 0.15 mg/kg was used for induction.[5] Four patients were reported to have 25 per cent or greater increases in heart rate with this dose.

¶ Runser RH, Hoffmann–La Roche Inc., Nutley, New Jersey: Personal communication.
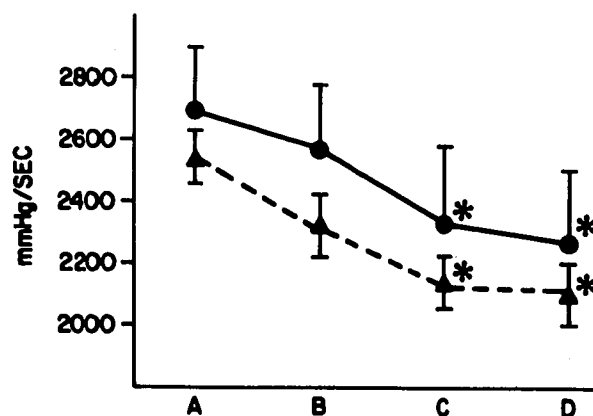

Fig. 5. Effects of diazepam and midazolam maleate on LV_{max} dP/dt (mean torr/sec ± SEM) as an index of myocardial contractility. See legend to figure 1 for explanation of A–D.
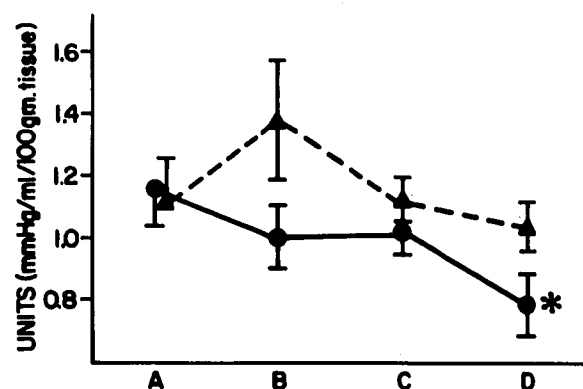

Fig. 6. Effects of diazepam and midazolam maleate on coronary vascular resistance (mean resistance units ± SEM). See text for explanation of calculation and legend to figure 1 for explanation of A–D.

As in the above-mentioned clinical studies, both hypotension and tachycardia were seen in the present study. The maximum change in these variables, 20 per cent, occurred with 1.0 and 10.0 mg/kg. The in-

TABLE 1. Comparative Effects of Midazolam Maleate and Diazepam on Stroke Work, Stroke Volume, and Regional Coronary Blood Flow (Means ± SEM)

	Midazolam Maleate				Diazepam			
	0	0.25 mg/kg	1.0 mg/kg	10.0 mg/kg	0	0.5 mg/kg	1.0 mg/kg	2.5 mg/kg
Stroke work (g M/kg)	1.8 ± 0.5	2.0 ± 0.5	1.7 ± 0.5	1.4 ± 0.3	2.2 ± 0.2	1.9 ± 0.2	1.9 ± 0.3	1.9 ± 0.2
Stroke volume (ml/beat)	25 ± 4	26 ± 4	26 ± 4	25 ± 3	25 ± 3	23 ± 2	23 ± 2	22 ± 2
Right ventricular flow (ml/min/100 g)	76 ± 6	77 ± 6	75 ± 9	90 ± 11	65 ± 6	64 ± 6	72 ± 9	71 ± 12
Septal flow (ml/min/100 g)	111 ± 10	116 ± 11	103 ± 11	122 ± 14	120 ± 14	115 ± 15	125 ± 12	126 ± 12
Left ventricular flow (ml/min/100 g)	108 ± 12	110 ± 8	102 ± 10	120 ± 21	113 ± 13	111 ± 15	124 ± 21	123 ± 15

crease in heart rate could possibly be reflex in origin, due to the decrease in mean arterial pressure, but it also occurred at the dose level of 0.25 mg/kg, which did not produce significant hypotension.

Cardiac output, stroke volume, and stroke work were maintained despite significant decreases in mean arterial pressure and contractility at the two higher doses of midazolam maleate. The decrease in arterial pressure was reflected in a decrease in systemic vascular resistance, which would be expected, since cardiac output was maintained or slightly increased. Such data indicate that minimal alterations in stability of the circulatory system are evident with relatively large doses of midazolam maleate.

As shown previously by numerous investigators, diazepam in clinically effective doses exerts minimal effects on the cardiovascular system in patients who have normal or diseased hearts.[9-12] In the present study, a similar lack of effect of diazepam on the circulatory system was seen even in doses that exceed the usual induction dose five- to sevenfold.

Conflicting reports have been presented relative to the effects of benzodiazepines on coronary blood flow. Diazepam has been reported to increase coronary blood flow in anesthetized animals following thoracotomy with[13] or without[14] cardiopulmonary bypass. However, such an increase in coronary flow has not been confirmed in clinical studies in unanesthetized patients undergoing coronary angiography.[10,12] Coronary blood flow was not altered by any dosage of diazepam or midazolam maleate, confirming the effects in conscious patients described above.

As shown previously, midazolam maleate compares favorably with diazepam as a hypnotic for induction of anesthesia.[6] While both agents minimally alter cardiovascular function, the water solubility of midazolam maleate and the lesser injection-site irritation it causes are advantages that dictate further clinical trials.

References

1. Langdon DE, Harlan JR, Bailey RL: Thrombophlebitis with diazepam used intravenously. JAMA 223:184–185, 1973
2. Siebke H, Ellertsen BB, Lind B: Reactions to intravenous injections of diazepam. Br J Anaesth 48:1187–1189, 1976
3. Graham CW, Pagano RR, Katz RL: Thrombophlebitis after diazepam—can it be prevented. Anesth Analg (Cleve) 56:409–413, 1977
4. Von Dardel O, Mebious C, Mossberg T: Diazepam in emulsion form for intravenous usage. Acta Anaesthesiol Scand 20:221–224, 1976
5. Fragen RJ, Gahl F, Caldwell N: A water-soluble benzodiazepine, RO 21-3981, for induction of anesthesia. ANESTHESIOLOGY 49:41–43, 1978
6. Reves JG, Corssen G, Holcomb C: Comparison of two benzodiazepines for anaesthesia induction: Midazolam and diazepam. Can Anaesth Soc J 25:211–214, 1978
7. Buckberg GD, Luck JC, Payne DB, et al: Some sources of error in measuring regional blood flow with radioactive microspheres. J Appl Physiol 31:598–604, 1971
8. Klotz V, Antonin KH, Bieck PR: Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig and rat. J Pharmacol Exp Ther 199:67–73, 1976
9. Dalen JE, Evans GL, Banas JS, et al: The hemodynamic and respiratory effects of diazepam (Valium). ANESTHESIOLOGY 30:259–263, 1969
10. Cote P, Gueret P, Bourassa MC: Systemic and coronary hemodynamic effects of diazepam in patients with normal and diseased coronary arteries. Circulation 50:1210–1216, 1974
11. Cote P, Campeau L, Bourassa MG: Therapeutic implications of diazepam in patients with elevated left ventricular filling pressure. Am Heart J 91:747–751, 1976
12. Formanek A, Korbuly D, Moore R, et al: The effect of Valium on myocardial blood flow. Radiology 121:541–544, 1976
13. Abel RM, Reis RL, Staroscik RN: Coronary vasodilation following diazepam (Valium). Br J Pharmacol 38:620–631, 1970
14. Daniell HB: Cardiovascular effects of diazepam and chlordiazepoxide. Eur J Pharmacol 32:58–65, 1975