Dose-Response Characteristics of Midazolam for Reducing Diaphragmatic Contractility

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A sedative dose of midazolam decreases contractility of the diaphragm, but no data are available concerning the relationship between dose and diaphragmatic contractility. We studied the dose-response characteristics of midazolam for reducing the diaphragmatic contractility in dogs. Animals were divided into three groups of eight each: Group 1 received no study drug, Group 2 was infused with a sedative dose of midazolam (0.1 mg/kg initial dose plus 0.1 mg · kg^{-1} · h^{-1} maintenance dose), and Group 3 was infused with an anesthetic dose of midazolam (0.1 mg/kg initial dose plus 0.5 mg · kg^{-1} · h^{-1} maintenance dose). We assessed the diaphragmatic contractility by transdiaphragmatic pressure (Pdi). With an infusion of midazolam in Groups 2 and 3, Pdi at low-frequency (20 Hz) and high-frequency (100 Hz) stimulation decreased from the baseline values ($P < 0.05$), and the integrated electrical activity of diaphragm (Edi) at 100-Hz stimulation decreased from the baseline values, whereas Edi at 20-Hz stimulation did not change. Compared with Group 1, Pdi and Edi for each stimulus decreased during midazolam infusion in Groups 2 and 3 ($P < 0.05$). The decrease in Pdi and Edi was more in Group 3 than in Group 2 ($P < 0.05$). We conclude that midazolam decreases, in a dose-dependent manner, contractility of the diaphragm in dogs.

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Volatile anesthetics (halothane, enflurane, isoflurane, and sevoflurane) impair the contractile properties of the diaphragm (1–4). In addition to these anesthetics, midazolam, widely used for sedation, decreases contractility of the diaphragm (5). However, the relationship between the dose of midazolam and diaphragmatic contractility has not been reported. The purpose of this study was, therefore, to determine the dose-response characteristics of midazolam for reducing contractility of the diaphragm in dogs.

Methods

Institutional approval for the study was obtained from the animal care and use committee of the University of Tsukuba School of Medicine. Twenty-four healthy adult dogs, 14 males and 10 females, weighing 10–15 kg (12.4 ± 1.6, mean ± SD), were anesthetized with pentobarbital (25 mg/kg initial dose plus 2 mg · kg^{-1} · h^{-1} maintenance dose) IV to abolish spontaneous movement. Muscle relaxants and analgesics were not used. The animals' tracheas were intubated with a cuffed tracheal tube, and lungs were mechanically ventilated with a mixture of oxygen and air (fraction of inspired oxygen 0.4) to maintain Pao_2 >100 mm Hg, $Paco_2$ 35–40 mm Hg, and arterial pH 7.35–7.45. The right femoral artery was cannulated to monitor arterial blood pressure and to obtain blood samples for blood gas analysis. The right femoral vein was cannulated to allow the administration of fluids (lactated Ringer's solution 10 mL · kg^{-1} · h^{-1}), pentobarbital, and bicarbonate to keep the plasma HCO_3^- concentration within normal ranges. The left femoral vein was cannulated for the administration of midazolam. A pulmonary artery catheter was advanced via the right external jugular vein into the pulmonary artery for measuring cardiac output by the thermodilution technique. Rectal temperature was continuously monitored and maintained at 37°C ± 1°C by use of a heating pad.

Transdiaphragmatic pressure (Pdi) was measured by means of two thin-walled latex balloons: one was positioned in the stomach and the other, in the middle third of the esophagus. The balloons were connected to a differential pressure transducer and an amplifier. Both phrenic nerves were exposed at the neck, and the stimulating electrodes were placed around them. Supramaximal electrical test 0.1-ms stimuli were applied for 2 s at frequencies of 20 and 100 Hz with an electrical stimulator. Diaphragmatic contractility was evaluated by measuring the maximal Pdi generated by

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Table 1. Hemodynamic Data

Variable	Group	Baseline	No study drug (Group 1) / Sedative dose of midazolam (Group 2) / Anesthetic dose of midazolam (Group 3)
HR (bpm)	1	141 ± 15	142 ± 17
	2	143 ± 10	133 ± 10*†
	3	140 ± 12	123 ± 10*†‡
MAP (mm Hg)	1	130 ± 15	131 ± 17
	2	132 ± 12	121 ± 11*†
	3	131 ± 11	110 ± 10*†‡
RAP (mm Hg)	1	5 ± 2	5 ± 2
	2	5 ± 2	5 ± 1
	3	5 ± 2	5 ± 2
MPAP (mm Hg)	1	12 ± 2	12 ± 1
	2	12 ± 2	11 ± 2*†
	3	12 ± 2	10 ± 1*†‡
PAOP (mm Hg)	1	8 ± 2	8 ± 1
	2	8 ± 1	7 ± 2*†
	3	8 ± 2	6 ± 1*†‡
CO (L/min)	1	2.2 ± 0.5	2.2 ± 0.6
	2	2.2 ± 0.4	1.8 ± 0.4*†
	3	2.3 ± 0.4	1.3 ± 0.5*†‡

Values are mean ± SD.
HR = heart rate; MAP = mean arterial pressure; RAP = right atrial pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; CO = cardiac output; Group 1 = no study drug; Group 2 = midazolam 0.1 mg · kg^{-1} · h^{-1}; Group 3 = midazolam 0.5 mg · kg^{-1} · h^{-1}.
* $P < 0.05$ versus baseline.
† $P < 0.05$ versus Group 1.
‡ $P < 0.05$ versus Group 2.

test stimuli after airway occlusion at functional residual capacity. Transpulmonary pressure—the difference between airway and esophageal pressure—was kept constant when the airway was closed at functional residual capacity to maintain the same lung volume before each phrenic nerve stimulation. End-expiratory diaphragmatic geometry and muscle fiber length during contraction were kept constant by placing a close-fitting plaster cast around the abdomen and lower one third of the rib cage throughout the experiment. The electrical activity of the crural and costal parts of diaphragm (Edi-cru and Edi-cost, respectively) was recorded by two pairs of fishhook electrodes placed through a midline laparotomy. Electrodes were positioned into the anterior portion of the crural part near the central tendon and the anterior portion of the costal part (away from the zone of apposition) in the left hemidiaphragm. Each pair was placed in parallel fibers 5–6 mm apart. The abdomen was then sutured in layers. The signal was rectified and integrated with a leaky integrator with a time constant of 0.1 s and was regarded as the integrated diaphragmatic electrical activity (Edi-cru and Edi-cost, respectively).

Table 2. Changes in Pdi (cm H_2O)

Frequency (Hz)	Group	Baseline	No study drug (Group 1) / Sedative dose of midazolam (Group 2) / Anesthetic dose of midazolam (Group 3)
20	1	15.5 ± 2.0	15.4 ± 1.8
	2	15.3 ± 1.8	12.1 ± 2.1*†
	3	15.4 ± 2.1	9.8 ± 2.0*†‡
100	1	21.1 ± 2.0	20.9 ± 2.3
	2	20.9 ± 2.2	18.3 ± 2.0*†
	3	20.9 ± 2.1	15.6 ± 1.9*†‡

Values are mean ± SD. Pdi = transdiaphragmatic pressure; Group 1 = no study drug; Group 2 = midazolam 0.1 mg · kg^{-1} · h^{-1}; Group 3 = midazolam 0.5 mg · kg^{-1} · h^{-1}.
* $P < 0.05$ versus baseline.
† $P < 0.05$ versus Group 1.
‡ $P < 0.05$ versus Group 2.

The dogs were randomly divided into three groups of eight each. Baseline measurements of Pdi, Edi-cru, Edi-cost, and hemodynamic variables—including heart rate, mean arterial pressure, mean pulmonary arterial pressure, pulmonary artery occlusion pressure, and cardiac output (CO)—were recorded in each group. Group 2 was infused with a sedative dose of midazolam (0.1 mg/kg initial dose plus 0.1 mg · kg^{-1} · h^{-1} maintenance dose), and Group 3 was infused with an anesthetic dose of midazolam (0.1 mg/kg initial dose plus 0.5 mg · kg^{-1} · h^{-1} maintenance dose). In both groups, midazolam was continuously administered IV with an electrical infusion pump for 60 min. Immediately after the cessation of midazolam administration, Pdi, Edi-cru, Edi-cost, and hemodynamic variables were measured. In Group 1, no study drug was administered, and the same measurements were performed as those in other groups. The design performed in this experiment, including the duration of the study drug administration and measurements of several variables, was in accordance with our previous study (5).

All values were expressed as mean ± SD. Statistical analysis was performed with analysis of variance with Bonferroni's adjustment for multiple comparison and Student's *t*-test, where appropriate. $P < 0.05$ was considered significant.

Results

No differences in baseline hemodynamic variables were observed among the groups. With an infusion of midazolam in Groups 2 and 3, heart rate, mean arterial

Table 3. Changes in Edi

Variable	Frequency (Hz)	Group	Baseline	No study drug (Group 1) / Sedative dose of midazolam (Group 2) / Anesthetic dose of midazolam (Group 3)
%Edi-cru	20	1	100.0 ± 0.0	100.1 ± 6.7
		2	100.0 ± 0.0	99.1 ± 4.8
		3	100.0 ± 0.0	99.1 ± 4.8
	100	1	100.0 ± 0.0	100.0 ± 2.7
		2	100.0 ± 0.0	88.8 ± 5.1*†
		3	100.0 ± 0.0	75.5 ± 6.3*†‡
%Edi-cost	20	1	100.0 ± 0.0	100.3 ± 5.5
		2	100.0 ± 0.0	99.5 ± 3.8
		3	100.0 ± 0.0	98.8 ± 8.4
	100	1	100.0 ± 0.0	99.0 ± 3.9
		2	100.0 ± 0.0	89.5 ± 5.1*†
		3	100.0 ± 0.0	77.5 ± 4.3*†‡

Values are % of baseline, mean ± SD. Edi = integrated diaphragmatic electrical activity of the crural (Edi-cru) and costal (Edi-cost) parts; Group 1 = no study drug; Group 2 = midazolam 0.1 mg · kg^{-1} · h^{-1}; Group 3 = midazolam 0.5 mg · kg^{-1} · h^{-1}.
* $P < 0.05$ versus baseline.
† $P < 0.05$ versus Group 1.
‡ $P < 0.05$ versus Group 2.

pressure, mean pulmonary arterial pressure, pulmonary artery occlusion pressure, and CO decreased from baseline values ($P < 0.05$). In Group 1, no hemodynamic changes were observed (Table 1). The Pdi values obtained at each stimulus in all groups are shown in Table 2. No changes in Pdi were observed throughout the experiment in Group 1. With an infusion of midazolam in Groups 2 and 3, Pdi at both stimuli decreased from baseline values ($P < 0.05$). The decrease in Pdi was more in Group 3 than in Group 2 ($P < 0.05$). The changes of Edi-cru and Edi-cost (%Edi-cru and %Edi-cost, respectively) from baseline values in all groups are shown in Table 3. There were no changes in Edi-cru and Edi-cost in Group 1. In Groups 2 and 3, both Edi-cru and Edi-cost values at 100-Hz stimulation during midazolam administration were less than those obtained during baseline ($P < 0.05$). The decrease in Edi was more in Group 3 than in Group 2 ($P < 0.05$).

Discussion

The pressure generated by the diaphragm (Pdi) after a given electrical stimulation depends on its length and geometry (6). A major determinant of length and geometry of the diaphragm is lung volume. In this experiment, lung volume was strictly controlled; the airway was occluded at end-expiratory lung volume during the measurements, and the end-expiratory transpulmonary pressure was monitored and kept constant before each stimulus. The deformation of thoracoabdominal structures was also avoided by placing a cast around the abdomen and lower one third of the rib cage. Therefore, changes in Pdi observed in this study can be regarded as the result of changes in the diaphragmatic contractility.

Because the dogs were anesthetized with pentobarbital, the combined effects of midazolam and pentobarbital on contractility of the diaphragm were examined. However, the dose (2 mg · kg^{-1} · h^{-1}) of pentobarbital used in this study does not affect diaphragmatic contractility (4). This was also in agreement with our results in Group 1, showing no change in Pdi throughout the experiment.

We demonstrated that Pdi at 20-Hz and 100-Hz stimulation decreased from baseline values ($P < 0.05$) with an infusion of midazolam and that Edi-cru and Edi-cost values at 100-Hz stimulation during midazolam administration were less than those obtained during baseline ($P < 0.05$) in Groups 2 and 3. We also demonstrated that decrease in Pdi and Edi was more in Group 3 than in Group 2 ($P < 0.05$). These suggest that midazolam decreases diaphragmatic contractility in a dose-dependent manner. The precise mechanism by which midazolam depresses contractility of the diaphragm with a reduction of electromyographic activity (as assessed by Edi) is not known. It has been suggested that selective loss of force at 20-Hz stimulation is closely related to the impairment of excitation-contraction coupling (7) and that selective loss of force and electromyographic activity at 100-Hz stimulation indicates the failure of neuromuscular transmission (8,9). Therefore, the decrease in Pdi at both stimuli with reduced Edi at 100-Hz stimulation during midazolam administration is presumably associated with the impairment of excitation-contraction coupling and the failure of neuromuscular transmission.

Diaphragmatic contractility depends on the energy supplies to the diaphragm, which are related to its blood supply, and CO is one of major factors determining blood flow to the diaphragm (10). The decrease in CO observed in Groups 2 and 3 with an infusion of midazolam may have led to a decrease in

the diaphragmatic blood flow and thereby may have decreased contractility of the diaphragm. We demonstrated that CO decreased from baseline values with an infusion of midazolam ($P < 0.05$) in Groups 2 and 3, and we also demonstrated that CO was less in Group 3 than in Group 2 ($P < 0.05$). Thus, the difference in Pdi between Groups 2 and 3 ($P < 0.05$) during midazolam administration may be attributed to the difference in CO, which is related to the diaphragmatic blood flow.

In conclusion, midazolam decreases contractility of the diaphragm in dogs in a dose-dependent manner. The inhibitory effect of midazolam on diaphragmatic contractility may be related to the impairment of excitation-contraction coupling and the failure of neuromuscular transmission or the decrease in blood flow to the diaphragm.

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