J Anesth (1994) 8:28–31

Journal of
Anesthesia

The effects of low-dose midazolam for induction of high-dose fentanyl anesthesia for coronary artery bypass graft

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Abstract: A small dose of midazolam 0.06 mg/kg or diazepam 0.15 mg/kg was used for induction of high-dose fentanyl (50 μg/kg) anesthesia in patients undergoing coronary artery bypass grafting operation. Hemodynamic variables were measured 5 min after the injection of midazolam or diazepam, after the end of the fentanyl infusion, and following endotracheal intubation. Midazolam and diazepam caused a slight but significant decrease in mean arterial pressure (−9.8% and −11.8%, respectively) and a further significant depression was observed in the diazepam group but not in the midazolam group after fentanyl. Although the cardiac index was maintained in patients who received midazolam, a significant decrease was observed in the diazepam group (−28.5%) after administration of fentanyl. Heart rate was decreased in the diazepam group but not in the midazolam group. Therefore, a small dose of midazolam may be a suitable induction agent for high-dose fentanyl anesthesia in patients with coronary artery disease.

Key words: Hypnotics, Midazolam, Diazepam, Analgesics, High-dose fentanyl anesthesia, Surgery, Coronary artery bypass grafting, Hemodynamics

Introduction

A combination of benzodiazepines with opiates is frequently used for induction of high-dose fentanyl anesthesia in patients with ischemic heart disease because of its hypnotic properties. However, diazepam and flunitrazepam have been reported to cause a moderate to severe drop in the systemic arterial pressure when combined with a large dose of fentanyl, or even alone [1,2]. Midazolam, a new water-soluble benzodiazepine, has been reported to have a minimal cardiovascular depressant effect in healthy volunteers [3,4]. On the other hand, the combination of midazolam, heavy premedication, and high-dose fentanyl anesthesia showed a moderate degree of cardiovascular depression even if it did not cause severe depression [5]. The present study was designed to evaluate the effect of small dose of midazolam as a sedative adjunct during the induction of high-dose fentanyl anesthesia as compared with diazepam in patients undergoing coronary artery bypass grafting operation.

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Received for publication on December 28, 1992; accepted on April 21, 1993

Methods

Twenty-two patients, electively scheduled for myocardial revascularization surgery, were randomly divided to receive either midazolam ($n = 9$) or diazepam ($n = 13$). The study was approved by our institutional ethics committee, and informed consent was given by all patients. All patients received morphine sulfate 0.1 mg/kg and scopolamine 5 μg/kg as premedication, given intramuscularly 60 min before induction. The characteristics of the two patient groups are shown in Table 1. Patients with a left ventricular ejection fraction less than 0.5 or a coexisting valvular disease were excluded. There was no statistically significant difference between the groups in age, sex, body weight, or preoperative medications.

Upon arrival in the operating room, ECG leads (II and modified V5) were attached, and a peripheral i.v. cannula and 20-gauge radial artery catheter were placed under local anesthesia. A 7F Swan-Ganz thermodilution catheter had been introduced into the pulmonary artery by a cardiovascular surgeon under fluoroscopy the day before the operation. The ECG and the measured pressures were recorded continuously via an 8-channel recorder. Cardiac output (CO) was measured in triplicate by the thermodilution method (Cardiac Output Computer 9520A, Edwards Laboratories, Irvine, CA).

Prior to the induction of anesthesia, when the patients' hemodynamics stabilized in the operating room,

Table 1. Patient characteristics

	Midazolam	Diazepam
n	9	13
Age (years)	53 (38–64)[a]	58 (49–69)[a]
Sex (male/female)	5/4	6/7
Weight (kg)	70 (53–97)[a]	57 (50–73)[a]
Concurrent Medications		
Calcium antagonists	9	13
Nitrates	8	12

[a] mean (range).

the first hemodynamic measurement was performed to obtain control values. Thereafter, either midazolam 0.06 mg/kg or diazepam 0.15 mg/kg was injected into the peripheral vein over 15 s. During the induction, the patients breathed 100% oxygen and were later ventilated with a mask to maintain normocapnea. Five minutes after the administration of benzodiazepine, the second hemodynamic measurement was performed. Loss of consciousness was confirmed by the disappearance of eyelid reflex and nonresponse to verbal commands to avoid waking before fentanyl infusion. A mixture of fentanyl 50 μg/kg and pancuronium 0.15 mg/kg was then infused over 10 min, followed by the third hemodynamic measurement. The fourth hemodynamic measurement was done 1 min after the endotracheal intubation. The patient whose systolic blood pressure decreased to less than 80 mmHg or 60% of the control value received appropriate treatment and was excluded from further study and statistic analysis.

Demographic data of both groups were compared by one-way analysis of variance (ANOVA) followed by Scheffe tests, and for nonparametric values by chi-square analysis. Statistical analyses were performed using the paired Wilcoxon test for comparison of hemodynamic variables within the same subject and the unpaired Wilcoxon U test for comparison between the midazolam and diazepam group. Statistical significance was defined as $P < 0.05$. Data are presented as mean ± SEM.

Results

There was no statistically significant difference between the groups in terms of age, sex, body weight, or preoperative medications.

There were four excluded cases in the diazepam group and one in the midazolam group. Consequently, the data were taken from 8 patients in the midazolam group and 9 patients in the diazepam group. There was

Table 2. Hemodynamic changes

		Control (baseline)	After BDZ	After fentanyl[a]	Postintubation[b]
HR	M	74.00 ± 4.76	71.00 ± 4.35	73.13 ± 4.48	73.00 ± 3.61
(beats/min)	D	76.00 ± 3.36	68.11 ± 3.38*	68.56 ± 4.03*	72.00 ± 6.16
MAP	M	109.75 ± 5.28	94.38 ± 5.43*	101.50 ± 5.99	105.80 ± 6.32
(mmHg)	D	109.33 ± 4.01	98.67 ± 4.44*	84.56 ± 5.13*#	94.83 ± 8.77
PAP	M	18.63 ± 1.70	14.38 ± 1.37*	15.88 ± 0.89	17.80 ± 1.00
(mmHg)	D	19.00 ± 1.57	16.11 ± 1.52	17.11 ± 1.61	19.17 ± 3.71
PCWP	M	10.38 ± 1.33	7.63 ± 1.38*	8.50 ± 1.05	10.60 ± 1.51
(mmHg)	D	9.89 ± 1.69	8.00 ± 1.28	8.67 ± 1.19	12.17 ± 3.53
CVP	M	2.75 ± 0.72	2.45 ± 0.86	3.69 ± 0.96	4.34 ± 1.13
(mmHg)	D	2.16 ± 0.68	2.42 ± 0.70	4.36 ± 0.76*	3.51 ± 0.90
CI	M	3.52 ± 0.20	3.12 ± 0.20*	3.12 ± 0.19*	3.29 ± 0.32
(l/min · m^2)	D	3.79 ± 0.17	3.14 ± 0.13*	2.60 ± 0.16*#	2.80 ± 0.21*
SV	M	82.51 ± 6.06	76.08 ± 5.59	74.14 ± 5.97	77.84 ± 9.04
(ml/stroke)	D	75.14 ± 4.67	69.61 ± 3.56	56.98 ± 2.44*#	56.01 ± 1.35*
SVRI	M	2462.50 ± 127.11	2372.88 ± 99.92	2536.51 ± 139.67	2529.63 ± 142.00
(dyn · sec · cm^{-5} · m^{-2})	D	2296.10 ± 137.07	2483.06 ± 159.84*	2514.48 ± 175.20	2622.64 ± 190.64
PVRI	M	200.26 ± 33.87	183.57 ± 23.46	194.87 ± 19.91	184.37 ± 29.37
(dyn · sec · cm^{-5} · m^{-2})	D	196.45 ± 16.06	206.77 ± 22.94	264.39 ± 26.89*	206.54 ± 26.17
LVSWI	M	64.78 ± 4.16	52.57 ± 4.54*	54.71 ± 4.81	58.79 ± 6.95
(g · m^{-2}/m^2)	D	67.70 ± 3.83	57.41 ± 3.60*	40.05 ± 3.85*#	43.57 ± 2.56*
RVSWI	M	10.21 ± 0.82	7.04 ± 0.35*	7.08 ± 0.52*	8.13 ± 0.69
(g · m^{-2}/m^2)	D	11.91 ± 1.54	8.42 ± 0.76*	6.65 ± 0.82*	8.20 ± 1.80*

HR, heart rate; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; CVP, central venous pressure; CI, cardiac index; SV, stroke volume; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke work index; M, midazolam; O, diazepam.

* $P < 0.05$ *vs* baseline.

# $P < 0.05$ midazolam vs diazepam in their corresponding periods.

Values are mean ± SEM.

[a] 5 min after the injection of either midazolam or diazepam.

[b] 1 min after the endotracheal intubation.

no significant difference in excluded cases between the two groups.

All hemodynamics are shown in Table 2.

Five minutes after the injection of midazolam or diazepam, a significantly greater decrease in the mean arterial pressure (MAP) from the baseline level was seen in each group (−14% and −10%, respectively). After the addition of fentanyl, a further significant decrease (−23%) was observed in the diazepam group, whereas MAP was maintained in the midazolam group. The diazepam group showed a significantly lower MAP than the midazolam group after fentanyl. MAP increased in both groups after endotracheal intubation.

The heart rate (HR) in the diazepam group was significantly low both at 5 min after diazepam and after fentanyl induction compared with the control period. HR in the midazolam group did not change significantly during the study period. Throughout the induction, no arrhythmias were observed, and no ECG changes indicative of ischemia were observed.

Midazolam and diazepam significantly decreased the cardiac index (CI) by 11% and 17%, respectively, from control values 5 min after the injection of benzodiazepines. After fentanyl induction, CI decreased further in the diazepam group, whereas no further decrease was observed in the midazolam group, and the difference between the two groups was significant. CI increased slightly in both groups following endotracheal intubation; the diazepam group still remained significantly lower than the control value.

Stroke volume (SV) decreased 5 min after the injection of benzodiazepines. A further decrease of the SV was obtained in the diazepam group after the infusion of fentanyl, reflecting the change in the CI, and a significant difference was observed between the two groups.

Mean pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) decreased after the injection of midazolam. However the extent of the decrease was not significant between midazolam and diazepam. These parameters tended to be similar throughout the induction in both groups.

There were no major changes in the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) during the induction of anesthesia with midazolam and fentanyl.

Left ventricular stroke work index (LVSWI) and right ventricular stroke work index (RVSWI) decreased significantly 5 min after the injection of benzodiazepines. A significantly greater decrease from the baseline level in the diazepam group compared with midazolam was seen in the LVSWI after the fentanyl infusion. The decrease in LVSWI in the diazepam group persisted even after the endotracheal intubation, while LVSWI returned to the control level in the midazolam group.

Discussion

The benzodiazepines have an established place in anesthetic practice as sedative hypnotics during the induction of high-dose fentanyl anesthesia. Recently, midazolam has been adopted widely as the induction agent because of its smaller depressive effect on the cardiovascular system [6–8]. Forster et al. [3] reported that midazolam 0.15 mg/kg i.v. decreased the systolic arterial pressure by 5% 3 min after the injection in healthy unpremedicated volunteers. However, patients with ischemic heart disease usually receive heavy premedication and are anesthetized by narcotics to prevent psychic stress. It is well known that the combination of the benzodiazepines and other sedative agents or narcotics causes a synergistic effect in hemodynamics. Therefore, the same induction dose of midazolam used in healthy adults may lead to severe cardiovascular depression in patients with coronary artery disease.

Midazolam 0.06 mg/kg or diazepam 0.15 mg/kg injected intravenously prior to fentanyl induction was followed by a moderate decrease in MAP by 10% or 12%, respectively, from the baseline values. The falls in systemic blood pressure following the intravenous injection of both drugs were smaller than those reported by other investigators [9–13]. Samuelson et al. [9] showed a decrease in MAP of more than 20% 5 min after the injection of midazolam 0.2 mg/kg or diazepam 0.5 mg/kg in patients with ischemic heart disease. A negative inotropic effect has been reported with very high doses of midazolam (over 1 mg/kg) in animal experiments [14]. Although we could not find any reports of a dose-dependent negative inotropic effect of midazolam in patients with coronary artery disease, we suppose that the different reductions in MAP 5 min after the benzodiazepines reported in the present study and in other investigations may be due to a dose-dependent negative inotropic effect of these benzodiazepines. It has been reported that diazepam has a direct myocardial depressant effect when it is administrated with high-dose fentanyl to a greater [1,15] or lesser degree [2]. In our previous study [16], MAP, CI, SV, and LVSWI in the diazepam group showed greater depression from the control values after the fentanyl infusion (50 μg/kg), whereas the midazolam group maintained these hemodynamic values. These depressions observed in the diazepam group generally did not recover, even after endotracheal intubation. The hypotension following fentanyl infusion in the diazepam group was most likely caused by a decrease in the CI in our study because SVR did not change significantly during the induction.

Heart rate showed a significant decrease from the baseline value in the diazepam group, though no changes were noted in the midazolam group during the induction. It has been demonstrated using a pressor test

that both benzodiazepines reduce baroreflex sensitivity [17], and a statistically positive correlation has been reported between the results of pressor and depressor tests [18]. Thus, in our study, it seemed that the attenuated baroreflex depression in the midazolam group, compared with the diazepam group, was due to hypotension.

The hypnotic effect of both benzodiazepines was satisfactory during the induction in our study. The dosages compared were selected on the basis of clinical and laboratory data showing midazolam to be approximately 2 to 2.5 times as potent as diazepam [5,10,11,19]. Though the ED_{95} for loss of consciousness in midazolam and diazepam are 0.2 mg/kg [20] and 0.5 mg/kg [21,22], respectively, in healthy unpremedicated patients, the doses used in this study were smaller because of premedication with morphine and scopolamine intramuscularly.

It is concluded that the combination of midazolam 0.06 mg/kg i.v. with high-dose fentanyl infusion (50 μg/kg) show smaller cardiovascular depressant effects than the combination of diazepam 0.15 mg/kg i.v. and high-dose fentanyl.

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