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Premedication and High-dose Fentanyl Anesthesia for Myocardial Revascularization: A Comparison of Lorazepam Versus *Morphine-scopolamine*

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Using a randomized double-blind placebo-controlled experimental protocol, the authors compared two premedication regimens in 42 patients undergoing elective myocardial revascularization. Group L patients (n = 23) received lorazepam 0.06 mg/kg po 90 min preoperatively, while group M patients (n = 19) received morphine 0.1 mg/kg im, plus scopolamine 0.006 mg/kg im 60 min preoperatively. Anesthesia was induced with fentanyl 100 μg/kg and atracurium 0.50 mg/kg administered over 10 min. The treatment groups did not differ significantly with respect to the degree of sedation or anxiolysis achieved, or the rapidity of induction with fentanyl. Premedication significantly influenced the hemodynamic response to anesthetic induction. Hemodynamics were stable post-induction in group M, but cardiovascular depression was noted in group L. Control heart rate (HR) was lower in group L. The HR, arterial pressure, and cardiac index were significantly lower, following both induction and intubation, in group L. Following sternotomy hemodynamics were identical in both groups. Serum fentanyl concentration was significantly higher during intubation in group L, probably secondary to the pharmacokinetic consequences of a decreased CI. New electrocardiographic evidence of myocardial ischemia did not occur in either group. Based on their findings with fentanyl-atracurium, and their review of the literature, the authors speculate that premedication exerts a significant hemodynamic effect during induction with other narcotic-relaxant combinations. (Key words Anesthesia: cardiovascular. Anesthetics, intravenous: fentanyl. Premedication: lorazepam; morphine; scopolamine. Surgery: myocardial revascularization.

IN PATIENTS UNDERGOING myocardial revascularization during high-dose fentanyl anesthesia, premedication is intended to achieve anxiolysis, sedation, analgesia and amnesia, and to facilitate induction. Narcotics, antimuscarinics, and sedative hypnotics have been used alone or in combination to achieve these goals.[1–5] However, little objective information is available regarding the comparative efficacy and side effects of various premedication regimens. This study was undertaken to compare two commonly used premedication regimens: 1) oral lorazepam, and 2) intramuscular morphine and scopolamine, in patients undergoing coronary artery surgery with high-dose fentanyl anesthesia. The regimens were compared with respect to their sedative and anxiolytic properties, and their influence on the course of anesthesia and surgery.

Materials and Methods

This study was approved by the Ethics Committee of the University of Manitoba, and all patients gave informed consent. We studied 42 patients undergoing elective myocardial revascularization whose left ventricular ejection fraction (EF) was greater than 0.40. Patients with a history of ethanol or drug abuse, or chronic use of sedative-hypnotics were excluded. The patients were randomly assigned one of two groups based on premedication. Patients in group L received lorazepam 0.06 mg/kg po 90 min preoperatively, and patients in group M received morphine 0.1 mg/kg im plus scopolamine 0.006 mg/kg im 60 min preoperatively. The night before surgery, all patients received triazolam 0.006 mg/kg po as a hypnotic. The patients' regular antianginal medications were continued until the time of transfer to the operating room.

Premedications and appropriate placebos were prepared in our Hospital Pharmacy, and these arrived on the ward in coded vials. All patients were given a pill 90 min preoperatively, followed 30 min later by an im injection. Either the pill or the injection was a placebo. Patients, nursing staff, investigators, and attending anesthesiologists were unaware of which premedication was administered. In the operating room, electrocardiographic (ECG) leads II and CS5 were attached. The attending anesthesiologist then inserted intravenous, arterial and pulmonary arterial catheters under local anesthesia. At the discretion of the attending anesthesiologist, fentanyl 50–100 μg iv was administered to supplement premedication during insertion of invasive monitors. Patients then breathed 100% oxygen from an

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anesthetic circuit until a 5-min period of hemodynamic stability was noted. Atracurium 0.05 mg/kg iv was then given. Two minutes later, anesthesia and muscle relaxation were induced by infusing fentanyl 100 μg/kg and atracurium 0.5 mg/kg iv over 10 min. The patients were repeatedly asked to open their eyes and breathe. Loss of consciousness was defined as failure to respond to either command for 15 s. Patients were then manually ventilated by mask. Rigidity was then graded by the attending anesthesiologist as: 1) no rigidity, easily ventilated; 2) moderate rigidity, some ventilation possible; or 3) severe rigidity, unable to ventilate. Endotracheal intubation was performed upon termination of the fentanyl-atracurium infusion. End-tidal carbon dioxide tension (ET CO_2) was monitored throughout and used to evaluate the adequacy of ventilation. Subsequently, the patients were prepared, draped, and operated upon. Clinically significant changes in hemodynamics were treated with appropriate vasoactive agents or volatile anesthetics at the discretion of the attending anesthesiologist. Neither benzodiazepines nor additional fentanyl was administered.

The ECG, systemic arterial pressure (AP), pulmonary arterial pressure (PAP), central venous pressure (CVP), and ET CO_2 were continuously recorded on electromagnetic tape using a Vetter® Model "A" FM tape recorder, and intermittently on paper using an eight-channel Hewlett-Packard® polygraph. Cardiac output in triplicate was measured intermittently by the thermodilution technique using ten milliliters of room temperature 5% dextrose solution. Complete hemodynamic profiles were generated: 1) immediately prior to induction (control), 2) 1 min after completion of narcotic infusion (pre-intubation), 3) 1 min post-intubation, 4) 1 min post-sternotomy, and 5) 1 min after either sternal spread (patients undergoing only aortocoronary vein grafting) or elevation of the left hemi-sternum (patients undergoing left internal mammary artery-coronary grafting). Arterial blood for determination of serum fentanyl concentration was drawn at times 1, 3, and 5, above, and during any hyperdynamic circulatory "event" requiring intervention by the attending anesthesiologist. Serum was separated and frozen at −20° C for later analysis using gas chromatography and nitrogen-phosphorous detection, as previously described.[6] Arterial blood for determination of carbon dioxide tension (Pa_{CO_2}) was drawn at control, 5 and 10 min after the fentanyl infusion began, and 5 min after intubation.

The efficacy of premedication was evaluated with respect to both sedation and anxiolysis, which were graded according to the criteria in table 1. This aspect of the study was carried out in patients 8 through 42 (*i.e.*, n = 35). One of us (RGB) evaluated each patient immediately prior to premedication and on arrival in the operating room. The patients evaluated their level of anxiety, prior to premedication and upon arrival in the operating room, according to an ordinal scale, where zero represented no anxiety and ten represented the greatest conceivable degree of anxiety.

TABLE 1. Criteria for Evaluation of Sedation and Anxiety

Sedation	
Awake:	Alert and oriented, appears no different from normal.
Drowsy:	Heavy eyelids, occasional blinking.
Sleepy:	Marked blinking, slurred speech, indifferent to environment.
Asleep:	Quickly falls asleep when left unattended, needs to be actively aroused when apporoached.
Anxiety	
Marked:	Will spontaneously complain of anxiety.
Moderate:	Anxiousness only expressed when asked specifically.
Mild:	Some apprehension but generally seems relaxed and placid.
Negligible:	Indifferent to external environment, smiling and content.

Side effects specifically looked for included nausea and/or vomiting, dysphoria and/or restlessness, chest pain, dyspnea, or spontaneous complaint of a dry mouth. On approximately the fifth postoperative day, all patients were visited by one of us (RGB) and specifically questioned about recall of intraoperative events.

The polygraphic ECG and hemodynamic records were reviewed. The heart rate (HR), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), rate-pressure product (RPP), and cardiac index (CI) were derived from directly recorded variables according to standard formulae.[7] Alterations from control exceeding 20% in hemodynamic variables were noted. The ST-segment of the ECG was evaluated 0.06 s after the nadir of the S-wave. A diagnosis of ischemia was made when new ST-depression of 0.1 mV or more was noted in either ECG lead.

Statistical analysis of hemodynamic variables, serum fentanyl concentration, and Pa_{CO_2} were made by analysis of variance (ANOVA) for repeated measures. Where ANOVA revealed significant effects ($P \leq 0.05$), the Least Squares Means Test was used to make appropriate comparisons. Bonnferoni's correction was used to compensate for multiple comparisons. A P value less than or equal to 0.05/k (where k equals the number of comparisons) was accepted as significant. Between-groups comparisons of other variables were made as follows: 1) Chi-square or Fischer's Exact Test for contingency tables, 2) Wilcoxon-Mann-Whitney Rank-Sums Test, or the Wilcoxon Signed-Ranks Test for ordinal data, and 3) Students t test for continuous variables. The null hypothesis was rejected when P was less than or equal to 0.05.

TABLE 2. Demographic Variables (Mean ± SD)

	Group L (n = 23)	Group M (n = 19)
Age (years)	58.3 ± 8.1	61.6 ± 7.9
Sex (male:female)	19:4	17:2
Weight (kg)	84.7 ± 15.0	77.3 ± 12.0
B.S.A. (m^2)	1.96 ± 0.20	1.91 ± 0.20
Ejection fraction (%)	63 ± 10	64 ± 11
LVEDP (mmHg)	17 ± 6	15 ± 6
HR (beats/min)*	59 ± 12	61 ± 10
SAP (mmHg)*	116 ± 15	124 ± 17
DAP (mmHg)*	73 ± 11	76 ± 9
Antianginal medication		
β-adrenergic blocking agent	18	15
Calcium entry blocking agent	18	13
Nitrate	14	15
Distal coronary grafts	3.2 ± 1.0	3.6 ± 0.8

* Measured at 0600 h on operative day, prior to premedication.

Results

Twenty-three patients received lorazepam and 19 received morphine-scopolamine premedication. Demographic characteristics of the two groups are compared in table 2. There were no statistically significant differences between groups with respect to age, sex, weight, body surface area, HR, AP, EF, left ventricular end-diastolic pressure, number of distal coronary anastomoses performed, or type of preoperative antianginal medication.

Sedation and anxiety scores as determined by the investigator are shown in figure 1. The groups did not differ with respect to these variables either prior to or following premedication. The patients' self-evaluation of anxiety did not differ between groups at any time. Mean anxiety scores prior to and following premedication were 2.8 ± 1.6 (mean ± standard deviation [SD]) and 3.1 ± 2.0, respectively, in group L, *versus* 3.6 ± 2.4 and 4.5 ± 3.1 in group M. During insertion of invasive monitors, premedication had to be supplemented with fentanyl 50–100 μg iv in three patients from group L and two from group M. The incidence of minor side effects was identical in both groups. Two patients from group L and one from group M complained of dry mouth. Dysphoria was noted in one patient from group L and two from group M.

During induction, loss of consciousness occurred at similar times in both groups. In group L, patients lost consciousness 108 ± 21 s into induction, *versus* 110 ± 36 s in group M. The severity of rigidity did not differ between groups. The mean rigidity score was 1.6 ± 0.7 in group L *versus* 2.0 ± 0.8 in group M. The groups did not differ with respect to Pa_{CO_2}. The Pa_{CO_2} decreased slightly but significantly in both groups after intubation.

Hemodynamic variables are shown in table 3. Analysis of variance revealed significant group-time interactions for HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), CI, and RPP. Values for all these variables were significantly lower 1 min post-induction and 1 min after intubation in group L. Heart rate was also lower at control in group L. Following sternotomy, hemodynamics were identical in both groups.

The incidence of clinically significant systemic arterial hypotension and hypertension is shown in figure 2 (a change from control in SAP exceeding 20% was defined as significant). Hypertension was significantly more frequent in group M immediately post-induction, whereas hypotension was significantly more frequent in group L post-induction, and post-intubation. During induction, but before intubation, hemodynamic changes requiring pharmacologic intervention by the attending anesthesiologist occurred in 13 patients. Nitroglycerin was administered to two patients from group L and five patients from group M. Phenylephrine was administered to five patients from group L and one patient from group M. The incidence of various interventions did not differ significantly between groups.

The serum fentanyl concentration was significantly higher in group L compared to group M ($P < 0.05$,

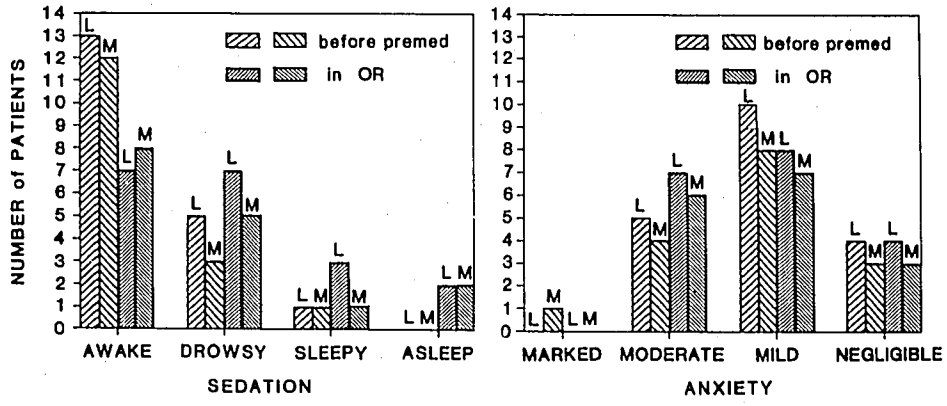

FIG. 1. The number of patients in groups L (lorazepam) and M (morphine-scopolamine) in each sedation or anxiety category, prior to premedication (premed) and upon arrival in the operating room (OR). The distribution of sedation and anxiety categories did not differ between groups at either time.

TABLE 3. Hemodynamic Variables (Mean ± SD)

Variable	Group	Control	Post-induction	1 Min Post-intubation	1 Min Post-sternotomy	1 Min Post-sternal Spread
HR (beats/min)	L	54 ± 9†	51 ± 12†	51 ± 12†	48 ± 12*	50 ± 13
	M	59 ± 13	61 ± 10	62 ± 11	52 ± 9	52 ± 9*
SAP (mmHg)	L	147 ± 27	130 ± 26*†	128 ± 30*†	140 ± 27	137 ± 27
	M	144 ± 24	147 ± 22	149 ± 26	140 ± 16	140 ± 26
DAP (mmHg)	L	68 ± 10	63 ± 13†	63 ± 13†	69 ± 12	68 ± 12
	M	70 ± 10	74 ± 13	75 ± 15	73 ± 9	73 ± 10
MAP (mmHg)	L	93 ± 14	88 ± 17†	86 ± 16†	95 ± 15	94 ± 15
	M	97 ± 14	101 ± 17	102 ± 21	95 ± 13	99 ± 16
MPAP (mmHg)	L	19 ± 5	18 ± 5	19 ± 5	17 ± 4	17 ± 3
	M	19 ± 7	19 ± 5	20 ± 6	15 ± 4	16 ± 5
PCWP (mmHg)	L	12 ± 4	13 ± 4	12 ± 4	11 ± 2	11 ± 3
	M	12 ± 5	13 ± 4	12 ± 5	10 ± 3	11 ± 5
CVP (mmHg)	L	6 ± 3	8 ± 3*	8 ± 3*	8 ± 3	8 ± 3
	M	7 ± 2	8 ± 2	8 ± 2	8 ± 2	7 ± 2
CI ($l \cdot min^{-1} \cdot m^{-2}$)	L	2.47 ± .49	2.15 ± .59*†	2.12 ± .15*†	2.02 ± .39*	2.03 ± .47*
	M	2.45 ± .69	2.53 ± .70	2.44 ± .71	2.00 ± .46	2.00 ± .57
SVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^2 \cdot 10^{-3}$)	L	2.90 ± 0.67	3.10 ± 0.73	3.02 ± 0.55	3.55 ± 0.61*	3.50 ± 0.77*
	M	3.06 ± 0.78	3.14 ± 0.91	3.27 ± 0.92	3.54 ± 0.69*	3.80 ± 0.91*
RPP ($mmHg \cdot beats \cdot min^{-1} \cdot 10^{-3}$)	L	7.97 ± 2.11	6.73 ± 2.64*†	6.69 ± 2.72*†	6.76 ± 2.42*	6.85 ± 2.25*
	M	8.65 ± 3.32	9.01 ± 2.19	9.34 ± 2.60	7.22 ± 1.58	7.33 ± 2.17
PVRI ($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	L	208 ± 82	204 ± 94	255 ± 99	233 ± 93	214 ± 107
	M	226 ± 102	202 ± 67	264 ± 80	224 ± 94	232 ± 89

HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index; SVRI = systemic vascular resistance index; RPP = heart rate × systolic arterial pressure; PVRI = pulmonary vascular resistance index.

* $P \leq 0.0125$ *vs.* control, Least Squares Means Test.

† $P \leq 0.01$ group L *vs.* group M, Least Squares Means Test.

ANOVA). The respective serum fentanyl concentrations in group L and group M were 111 ± 44 *versus* 89 ± 30 ng/ml 1 min post-intubation ($P < 0.01$, Least Squares Means Test), and 31 ± 8 *versus* 25 ± 8 ng/ml 1 min post-sternal spread or elevation. A significant negative correlation was noted between serum fentanyl concentration and CI 1 min post-intubation (fig. 3).

Hyperdynamic cardiovascular responses to either endotracheal intubation or surgery which required intervention by the attending anesthesiologist were noted in 19 patients, 11 from group L and eight from group M. Table 4 lists the elapsed time from induction, the serum fentanyl concentration, and the nature of the noxious stimulus, for each hyperdynamic response. The groups did not differ significantly with respect to these variables.

New ECG changes indicative of ischemia were not observed in any patient. One patient from group M remembered endotracheal intubation. This event was associated with clinically significant hypertension. No patient recalled surgical events.

Discussion

The two premedication regimens used in this study were equally effective and caused few immediate side effects. Their sedative and anxiolytic effects were indistinguishable. Similarly, premedication altered neither the speed of induction nor the severity of rigidity.

In contrast, premedication affected resting HR and substantially altered the hemodynamic response to induction with high-dose fentanyl and atracurium. Heart rate was higher in group M at control, and this effect persisted until sternotomy. The difference in HR at

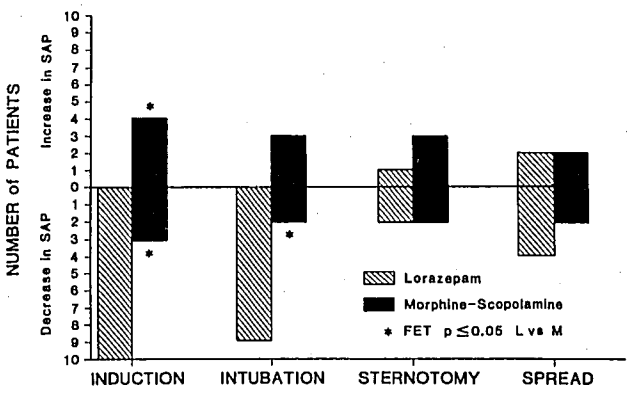

FIG. 2. The number of patients manifesting either an increase or a decrease in systolic arterial pressure (SAP) exceeding 20% of control, at various intervals following induction of anesthesia.

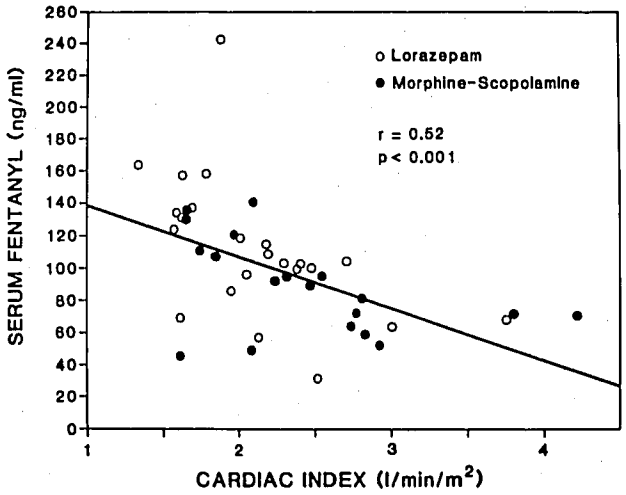

FIG. 3. Regression analysis of the relationship between serum fentanyl concentration and cardiac index at the time of endotracheal intubation.

control was caused by premedication, since HR was identical in both groups before premedication. Following induction, hemodynamic stability was noted in group M, whereas AP and CI were significantly lower in group L. These differences appear to be due to myocardial depression in group L, since CI decreased, CVP increased, and HR was unchanged post-induction in group L. Consequently, hypotension was significantly more frequent in group L. Of interest is the fact that

TABLE 4. Hyperdynamic Responses to Intubation and Surgery

Patient No.	Time from Induction (Hours)	Serum Fentanyl (ng/ml)	Stimulus
Group L			
#35	0.67	30.0	Skin incision
#34	0.75	32.7	Skin incision
#31	0.82	29.0	Sternum elevation
#21	0.88	25.4	Sternum spread
#25	0.95	27.9	Sternum elevation
#10	0.97	20.9	Sternum elevation
#4	1.57	20.8	LIMA dissection
#20	2.10	24.0	LIMA dissection
#2	2.33	23.0	LIMA dissection
#1	2.37	27.3	LIMA dissection
#29	2.50	9.2	Periaortic dissection
Mean ± SD	1.44 ± .74	24.5 ± 6.3	
Group M			
#36	0.23	95.5	Tracheal intubation
#38	0.30	59.5	Tracheal intubation
#5	0.67	21.7	Sternum spread
#33	0.77	23.5	Sternotomy
#24	0.77	37.2	Sternum spread
#26	0.87	20.6	Skin incision
#30	1.40	22.8	Periaortic dissection
#14	2.07	21.6	LIMA dissection
Mean ± SD	0.89 ± .60	37.8 ± 26.9	

LIMA left internal mammary artery, # patient number

hypertension following induction, but prior to intubation, was significantly more frequent in group M. We have previously reported hyperdynamic responses to induction with high-dose fentanyl in patients premedicated with morphine-scopolamine.[8] Premedication with lorazepam appears to significantly decrease the incidence of such responses.

Hyperdynamic responses to noxious stimuli requiring pharmacological intervention by the attending anesthesiologist occurred in 45% of patients. The incidence was similar in both groups. Of the 17 patients who responded to surgical stimuli (table 4), only two had serum fentanyl levels in excess of 30 ng/ml. This suggests that steady-state serum fentanyl concentrations of at least 30 ng/ml would be required to block significant hemodynamic responses to surgical stimulation in the majority of patients. Such a hypothesis regarding required steady-state serum fentanyl concentrations is unlikely to be prospectively tested in coronary or major vascular surgery, in view of the impracticably large fentanyl dose which would be required. Similar conclusions have been reached by other investigators.[9,10] Of note is the finding that two patients in group M responded to intubation, despite serum fentanyl levels of 59 and 95 ng/ml, respectively. The latter level was observed in the patient who recalled intubation. Higher serum fentanyl concentrations may be required during intubation to achieve anesthesia, because CNS effect lags behind serum concentration during induction with narcotics.[11]

An incidental, but noteworthy, finding was that serum fentanyl concentrations at the time of intubation were 24% higher in group L. The effect of premedication on the hemodynamic response to induction probably explains this difference. Since the identical fentanyl dose was administered to both groups, premedication must have influenced the pharmacokinetics of fentanyl. We postulate that the decreased CI in group L delayed redistribution of fentanyl, and/or decreased its' rate of delivery to organs of elimination, resulting in higher fentanyl concentrations. This hypothesis is supported by the finding of a significant negative correlation between CI and serum fentanyl concentration at the time of intubation.

Definitive explanation of the significant effect of premedication on the hemodynamic response to anesthetic induction with fentanyl is not provided by this study. However, the autonomic nervous system is the most likely site of mediation. Increases in serum catecholamine concentrations have been reported to follow induction of anesthesia with high-dose fentanyl in patients premedicated with morphine and scopolamine.[12,13] Conversely, unchanged or decreased serum catecholamines have been noted following anesthetic induction with fentanyl in patients premedicated with benzodiaze-

pines.[14-16] Tomichek *et al.*[17] found that, in patients premedicated with im morphine-scopolamine, the administration of iv diazepam 0.125–0.5 mg/kg immediately prior to anesthetic induction with high-dose fentanyl was associated with lower mean values for AP, SVR, and serum catecholamine concentration, than those from a control group who did not receive diazepam. Thus, administration of benzodiazepines prior to induction, either po or iv, appears to produce a sympatholytic and, hence, cardiovascular depressant effect during the subsequent induction of anesthesia with fentanyl. Theoretically, scopolamine *per se* may also exert a hemodynamic effect in morphine-scopolamine premedicated patients. Scopolamine's antimuscarinic effect may have contributed to the higher control HR in group M. Antimuscarinic drugs also exert a presynaptic effect at sympathetic nerve endings, which facilitates catecholamine release.[18] Thus, the intergroup differences in hemodynamics we observed are likely explained by the sympatholytic effects of lorazepam in group L, and the antimuscarinic-sympathomimetic effects of scopolamine in group M. The results of Tomichek *et al.*[17] indicate that, when both a benzodiazepine and an antimuscarinic are administered, the effect of the former may predominate.

Although pre-anesthetic medication significantly influenced hemodynamics during fentanyl-atracurium anesthesia, new electrocardiographic ST-segment changes of myocardial ischemia were not noted in either group. Thus, since both regimens were associated with similar degrees of sedation and anxiolysis and a comparable incidence of hyperdynamic responses to surgery, neither regimen was demonstrably superior.

Based on our findings with fentanyl-atracurium, we speculate that premedication significantly influences the hemodynamic response to induction with other narcotic-relaxant combinations. Clearly, such a hypothesis requires prospective evaluation. If correct, our theory explains why induction with fentanyl-pancuronium in patients premedicated with morphine-scopolamine has been reported to cause tachycardia, hypertension, and myocardial ischemia,[4,19,20] while hemodynamic stability has been reported to follow induction with fentanyl-pancuronium in patients whose premedication included a benzodiazepine.[1,2,5,15,16,21] Similarly disparate responses to sufentanil-pancuronium are also resolved if premedication is considered.[16,22-27] Good results have been obtained with sufentanil-vecuronium in patients premedicated with morphine-scopolamine.[26,27] Conversely, recent reports of clinically significant bradyarrythmias and hypotensive episodes after sufentanil-vecuronium occurred exclusively in patients in whom benzodiazepines were administered prior to induction.[24,28,29] The benzodiazepine-sufentanil-vecuronium combination appears to produce profound sympatholysis.

Most clinicians probably select a premedication on the basis of their personal opinion regarding its efficacy as a sedative and anxiolytic, with less regard for its potential influence on the hemodynamic response to induction. Our results suggest that a different approach is indicated. While important differences in the quality of sedation and anxiolysis were not apparent, premedication significantly altered hemodynamics. When choosing a premedication for patients undergoing myocardial revascularization under high-dose narcotic anesthesia, the potential for significant hemodynamic effects resulting from the interaction between the premedication, the narcotic, and the neuromuscular relaxant deserves careful consideration.

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