Title: HEMODYNAMIC RESPONSES TO FENTANYL OR DIAZEPAM-FENTANYL ANESTHESIA IN PATIENTS ON CHRONIC NIFEDIPINE THERAPY

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Introduction: High-dose fentanyl anesthesia is a widely accepted technique for patients undergoing coronary artery bypass (CAB) surgery because it produces minimal hemodynamic changes. Diazepam is often used to supplement fentanyl anesthesia to guarantee unconsciousness. Although intravenous diazepam alone produces minimal cardiovascular effects, in combination with fentanyl it produces significant decreases in mean arterial pressure (MAP) and systemic vascular resistance (SVR).[1] Severe hypotension during fentanyl-metocurine anesthesia has also been reported in patients taking large doses of nifedipine.[2] Our study investigated hemodynamic interactions between fentanyl-nifedipine, fentanyl-diazepam, and fentanyl-diazepam-nifedipine during anesthesia for CAB surgery.

Methods: Twenty-four patients (41-69 years) giving informed consent to the institutionally approved protocol were randomized to receive either fentanyl (F) anesthesia or diazepam-fentanyl (DF) anesthesia. Six patients chronically taking nifedipine received F anesthesia (Group N-F); 6 patients chronically taking nifedipine received DF anesthesia (Group N-DF); 6 patients not taking nifedipine received F anesthesia (Group F); and 6 patients not taking nifedipine received DF anesthesia (Group DF). Exclusion criteria included a myocardial infarction within 6 weeks of surgery, chronic benzodiazepine ingestion, or hypertension not controlled by a diuretic and/or a beta-blocker. Patients were given their usual morning doses of nifedipine and beta-blockers. Premedication consisted of morphine 0.15-0.2 mg/kg and scopolamine 0.3-0.4 mg im 90 min prior to induction of anesthesia. Upon arrival in the OR, two intravenous, radial arterial and triple-lumen pulmonary arterial catheters were inserted under local anesthesia. Ringer's lactate 8-15 ml/kg was infused intravenously, if necessary, to maintain a pulmonary capillary wedge pressure (PCWP) of $\geq$ 10 mmHg prior to and during induction of anesthesia. All patients breathed 100% oxygen throughout the study. After control measurements were obtained, diazepam 0.25 mg/kg was administered over 1 min in Groups N-DF and DF. Four min later fentanyl was infused at a rate of 400 µg/min to a total dose of 50 µg/kg in all 4 groups. After loss of consciousness, pancuronium in 1-2 mg increments was administered to a total dose of 0.1 mg/kg. Hemodynamic measurements were made prior to induction of anesthesia while breathing room air, 3 min after diazepam (before fentanyl), 3 min after fentanyl 25 µg/kg and 3 min after 50 µg/kg. Measurements included heart rate (HR), systolic, mean and diastolic arterial pressures, mean and diastolic pulmonary arterial pressures, PCWP, central venous pressure, and cardiac output; cardiac index (CI) and SVR were calculated. Data were evaluated by two way and repeated measures analysis of variance with $p<0.05$ considered statistically significant.

Results: The hemodynamic data for the 4 groups are shown in the Table (mean±SEM). There was no significant difference in the age, weight, or medical history in any of the groups. Twenty of 24 patients were receiving beta-blockers. Doses of nifedipine in Group N-F and Group N-DF were similar (42±7 vs 33±3 mg). Control values were comparable for all groups. The most clinically and statistically significant drug interaction ($p<0.001$) was the decrease in MAP in both groups given diazepam prior to fentanyl (N-DF and DF). When the 2 diazepam groups (N-DF and DF) were combined, the decrease in MAP was associated with a statistically significant decrease in SVR, without changes in HR, CVP or CI. Hypotension did not occur following fentanyl anesthesia in patients chronically receiving nifedipine (Group N-F).

Discussion: The observed diazepam-fentanyl interaction confirms previous work.[1] The absence of hypotension during fentanyl-pancuronium anesthesia in our nifedipine patients, in contrast to the marked hypotension reported during fentanyl-metocurine anesthesia,[2] may have been due to smaller daily doses (20-60 mg) of nifedipine that our patients were receiving. However, plasma nifedipine levels at surgery may not have differed since our patients received their usual morning dose and Freis and Lappas's patients received their last dose of nifedipine the night before surgery. On the basis of these findings, the current recommendation for the discontinuation of nifedipine 36 hours prior to CAB surgery with fentanyl anesthesia (Physician's Desk Reference, 1983, p. 1580) seems unwarranted.

References:

1. Tomichek RC, et al, Diazepam-fentanyl interactions - hemodynamic and hormonal effects in coronary artery surgery. Anesth Analg 62:881-4, 1983.
2. Freis ES, Lappas DG: Chronic administration of calcium entry blockers and the cardiovascular responses to high doses of fentanyl in man. Anesthesiology 57:A295, 1982.

		Control	Diazepam	F 25 µg/kg	F 50 µg/kg
Group F	MAP	84±3	-	91±7	91±6
	HR	57±4	-	67±3	67±3
	CI	2.5±.2	-	2.7±.2	2.7±.2
	SVR	1250±100	-	1330±130	1350±140
Group N-F	MAP	87±5	-	83±4	83±6
	HR	60±2	-	67±4	71±5
	CI	2.5±.3	-	2.9±.3	3.0±.4
	SVR	1320±140	-	1110±160	1120±170
Group N-DF	MAP	89±2	91±7	71±7	74±7
	HR	68±5	68±4	63±4	62±4
	CI	3.2±.5	3.1±.4	3.0±.3	2.9±.3
	SVR	1180±180	1230±200	960±200	1050±220
Group DF	MAP	85±5	85±7	68±4	72±5
	HR	64±7	65±6	67±6	64±6
	CI	2.7±.3	2.8±.2	2.8±.3	2.8±.2
	SVR	1200±110	1180±130	940±110	980±90