Title: MIDAZOLAM-N_2O INDUCTION IN ISCHEMIC HEART DISEASE PATIENTS

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Introduction. Midazolam maleate (M), a new water soluble 1-4 benzodiazepine, has minimal cardiovascular effects during intravenous induction of anesthesia in patients with ischemic heart disease breathing 100% oxygen [1]. The present study examined the hemodynamics during midazolam anesthetic induction in a similar group of patients breathing 50% N_2O.

Methods. Six patients electively scheduled for myocardial revascularization surgery were studied (after informed consent and approval by the Institutional Review Board for Human Use.) Premedication consisted of morphine sulfate 0.1 mg/Kg IM and scopolamine 6-8 ug/Kg IM 60-90 minutes prior to induction. In a pre-induction area, catheters were placed in 2 peripheral veins, a radial artery, and the pulmonary artery via the right internal jugular vein (Edwards Swan-Ganz triple lumen thermodilution catheter). ECG (V_5 and II), heart rate (HR), rhythm, systemic systolic/diastolic (SBP/DBP), and mean blood pressure ($\overline{MAP}$), mean right atrial pressure ($\overline{RAP}$), pulmonary artery systolic/diastolic (PASP/PADP) and mean pressure ($\overline{PAP}$), pulmonary artery occluded pressure ($\overline{PAO}$), thermodilution cardiac output in duplicate (CO), and ABG's were measured serially. Derived data consisted of cardiac index (CI), stroke index (SI), heart rate systolic blood pressure product (RPP), systemic (SVRI) and pulmonary vascular resistance indexed (PVRI), and left (LVSWI) and right ventricular stroke work indexed (RVSWI). Measurements were made at the following time periods: 1) pre-induction area baseline breathing room air (Air), 2) operating room baseline breathing 100% oxygen (repeated every 5 minutes until values stable $\pm$ 10% and mean reported) (O_2), 3) operating room 4-5 minutes after breathing 50% N_2O (N_{4-5}), 4) 1-2 minutes after midazolam maleate induction (0.2 mg/Kg IV over 5-10 seconds) (M_{1-2}), 5) 4-5 minutes after midazolam (M_{4-5}). Ventilation was monitored continuously by end expired CO_2, documented by ABG's at each measurement period, and assisted when respiratory depression or apnea occurred. The results from these patients receiving midazolam plus nitrous oxide were compared with those of a similar group of ten patients with ischemic heart disease premedicated identically and induced with M (0.2 mg/Kg) while breathing 100% oxygen. The data was analyzed using multifactorial analysis of variance and the New Duncan's Multiple Range Test with $p < 0.05$ considered significant.

Results. The study group consisted of 5 men and 1 woman, mean age 55 years, weight 77 Kg, BSA 1.9 m^2. Five patients had 3 vessel coronary disease and one had left main stenosis. Three patients had LVEDP $\geq$ 14 at catheterization, 5/6 were on propranolol, and at surgery 3-5 grafts were performed on all patients. All patients were successfully induced with midazolam and N_2O. No adjuvant anesthetic, inotropic, or antiarrhythmic drugs were required throughout the study period and intravenous crystalloid was limited to "keep open". The measured and derived hemodynamic responses for patients induced with midazolam and N_2O in Table I demonstrate (M_{1-2} and M_{4-5}) a small increase in HR and $PaCO_2$ with a significant decrease in $\overline{MAP}$, $\overline{PAP}$, $\overline{PAO}$, SI, SVRI, LVSWI, and RVSWI. No patients demonstrated ECG (II, V_5) changes indicative of ischemia, or arrhythmias.

Discussion. Despite some statistically significant hemodynamic variations, the data indicates that M - (0.2 mg/Kg) plus N_2O (50%) has relatively minor effects on the cardiovascular system of patients with ischemic heart disease. The most striking changes during the study period occurred after transfer of patients into the operating room (increases in MAP, $\overline{PAP}$, $\overline{PAO}$, RPP, SVRI, and LVSWI). These changes were persistent ($\pm$ 10%) as documented by repeat hemodynamic measurements every 5 minutes for up to 20 minutes despite all patients being well sedated, non-stimulated, usually sleeping, and breathing O_2 in the O.R. These hemodynamics also persisted during the 5 minutes of 50% N_2O breathing. Anesthetic induction with M after 5 minutes of 50% N_2O resulted in return of most of the above parameters toward the (Air) baseline. The hemodynamic responses of M plus N_2O are similar to those previously reported for M plus O_2 [2] (differing statistically only as noted in Table I) and those of diazepam. [1, 2] Interestingly, $\overline{PAO}$ and $\overline{PAP}$ decreased to a greater degree after M + N_2O than after M + O_2 and when $\overline{PAO}$ was initially elevated. [1] Since midazolam maleate is a relatively short acting drug it may be necessary to add adjuvant anesthetic agents to maintain appropriate levels of anesthesia. These results indicate that 50% N_2O can be safely added to midazolam induction in patients with ischemic heart disease.

References.

1. Reves JG, Samuelson PN, Lewis S.: Midazolam maleate induction in patients with ischemic heart disease-hemodynamic observations, Can Anaesth Soc J, (in press).
2. Samuelson PN, Lell WA, Kouchoukos NT: Study of hemodynamics during anaesthetic induction in patients for coronary artery bypass grafting (Abstr), V European Congress of Anaesth. Excerpta Medica No. 452, pp 277-278, 1978.

MEASUREMENT PERIOD:

VARIABLE:	AIR	O_2	N_{4-5}	M_{1-2}	M_{4-5}
HR	69±4.3*	68±6.4	65±7.7	75±5.1	71±3.4
MAP	93±5.2	106±6.0	109±6.5†	96±6.0	82±7.4†
$\overline{RAP}$	8±0.6	10±1.3	10±1.0	9±0.9	9±0.9
$\overline{PAP}$	21±1.4	23±1.9	24±2.2	19±0.9†∝	18±1.5†∝
$\overline{PAO}$	13±0.7	17±1.5†	18±2.0†	13±1.4†∝	12±1.5†∝¥*
RPP x 10^3	9.4±.75*	10.6±1.23	10.5±1.50	9.9±.52	7.9±.69
CI	2.8±.19	2.±.29	2.7±.53	2.6±.27	2.3±.18
SI	41±2.2	40±1.8	41±3.0	34±2.8†∝	32±2.6†∝
SVRI	668±79.2	812±107.4	888±138.6†	746±79.7	701±58.8∝
PVRI	63±10.0	54±8.5	57±5.0	53±6.0*	67±11.6
LVSWI	45.0±3.72	47.9±2.55	51.2±4.67	39.6±5.25†∝	31.5±5.11††∝
RVSWI	7.2±1.31	7.0±.83	8.2±1.25	4.7±.49†∝	4.2±.49†∝
$PaCO_2$	42±1.5	42±2.2	43±1.5	44±1.6	41±1.7

Where: † $p < 0.05$ $\bar{x}$ versus Air, † $p < 0.05$ $\bar{x}$ versus O_2, ∝ $p < 0.05$ $\bar{x}$ versus N_2O, ¥ $p < 0.05$ M_{1-2} versus M_{4-5}, * $p < 0.05$ M + N_2O versus M + O_2 Study. And, HR (beats/min); MAP, $\overline{RAP}$, $\overline{PAP}$, $\overline{PAO}$, $PaCO_2$ (mm Hg); RPP (beats·mm Hg/min); CI (L/min/m^2), SI (ml/min/m^2), SVRI, PVRI (dynes·sec·cm^{-5}/m^2), LVSWI, RVSWI (g·m/m^2).