Title: CORONARY HEMODYNAMIC RESPONSES FOLLOWING REVERSAL OF BENZODIAZEPINE INDUCED SEDATION WITH FLUMAZENIL IN PATIENTS WITH CORONARY ARTERY DISEASE

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Introduction. Flumazenil, a specific antagonist of benzodiazepines, has been proposed for reversal of the residual sedative effects of benzodiazepines. Since benzodiazepines are often used in patients with coronary artery disease (CAD), it is important to establish the hemodynamic safety of reversal in these patients. By analogy with naloxone,[1] it can be speculated that accelerated and increased hemodynamic response might be observed after flumazenil even if the hemodynamic tolerance of this reversal is considered as good.[2] The present study was designed to assess in a double blind trial the effect of reversal with flumazenil on coronary circulation, myocardial metabolism and left ventricular (LV) performance in patients with CAD.

Methods. Eleven unpremedicated patients undergoing cardiac catheterization and coronary angiography for CAD (NYHA class 2,3) were randomly allocated in two groups: placebo (P) and flumazenil (F). Institutional approval was obtained and all patients gave informed consent. All cardiac medications were continued until the night preceeding the procedure. Sedation was performed during catheterization using intravenous flunitrazepam 30 to 40 mcg/kg. A Swan-Ganz catheter was inserted into pulmonary artery to measure cardiac output. A double microtipped manometer catheter was placed in the left ventricle to obtain simultaneously LV and aortic pressures. A thermodilution catheter was positioned in the coronary sinus to measure coronary sinus blood flow (CBF). The following parameters were calculated by a catheterization data analysis computer system (Hewlett Packard 5600M): LVend diastolic pressure (LVEDP), mean aortic pressure (MAP), maximum velocity of shortening (Vmax), cardiac index (CI), systemic vascular resistance (SVR) and total coronary resistance (CTR). Arterial and coronary sinus blood samples were analyzed for oxygen and lactate contents. Myocardial oxygen consumption (MVO_2) and lactate extraction (Alact - CSlact/Alact) were then calculated. Sedation was evaluated on an analog scale. Measurements were obtained during steady state sedation and 5, 10 and 15 min after F or P (administered by 0.3 mg increment every 30 sec up to 1 mg). Data were compared using ANOVA.

Results. No difference concerning clinical data was found between the two groups. Sedation scores were signficantly lower after F. No significant hemodynamic changes were observed in the P group. HR, CI, SVR, CTR and Vmax were not significantly altered in F group. MAP and LVEDP were significantly increased following F administration. Myocardial oxygen consumption, coronary sinus blood flow and myocardial lactate extraction were not altered after F administration. One patient in each group had lactate production at one period but no ECG changes were observed throughout the study.

m±SD		Control	5 min	10 min	15 min
HR (bts/min)	P	79±12	78±15	80±15	80±14
	F	71±10	87±11	70±9	65±12
MAP (mm Hg)	P	85±21	82±20	81±19	80±18
	F	89±6	96±7*	98±9*	94±5
LVEDP (mm Hg)	P	8±4	6±6	6±4	7±4
	F	8±5	12±5*	13±7*	11±7*
MVO_2 (ml/min)	P	11±3	13±2	13±2	13±2
	F	13±3	14±2	14±3	14±3
CBF (ml/min)	P	135±23	128±20	126±21	127±19
	F	135±45	129±23	133±19	129±22
Lactate extraction%	P	41±12	43±12	40±11	45±10
	F	39±14	41±13	31±27	31±27

* $p < 0.01$ versus control

Discussion. This study shows that reversal of benzodiazepine induced sedation by flumazenil is not associated with major alteration of LV function and of coronary circulation in patients with CAD. However, the increase in LVEDP and in MAP may be detrimental in some patients. The small number of patients included in this study does not demonstrate definitely the safety of flumazenil in patients with CAD in other circumstances like major surgery. It only indicates that by contrast to naloxone, flumazenil induces a smooth recovery without major adverse circulatory reactions. Its use in patients with CAD, nevertheless, should be careful especially when LVEDP is high.

References

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2. Sage DJ, Close A, Boas RA. Br J Anaesth 59:459-464, 1987

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