Title: REVERSAL OF MIDAZOLAM'S EFFECT ON AUTONOMIC RESPONSES IN DOGS BY THE BENZODIAZEPINE ANTAGONIST - RO15-1788

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Introduction. Clinical and laboratory studies have demonstrated the effectiveness of midazolam and other benzodiazepines in inducing or supplementing anesthesia, inhibiting seizures and decreasing catecholamine responses to perioperative stresses. Recent attention has focused on investigational drugs that are specific benzodiazepine antagonists because of their clinical potential for reversing benzodiazepine actions in the postanesthesia period. Studies on the antagonist RO15-1788 have demonstrated its ability to rapidly and completely reverse anesthesia induced in volunteers with midazolam. The question answered in this study was whether RO15-1788 reverses other benzodiazepine effects, namely midazolam's action on the catecholamine response to hypotensive stress.

Methods. The responses to increasing doses of RO15-1788 were studied in twelve mongrel dogs and compared to nine dogs without RO15-1788, all anesthetized with pentobarbital. Each dog was intubated and mechanically ventilated with 100% oxygen to maintain normocapnea, 35-45 mm Hg. Catheters were inserted in the forelimb vein and in both femoral arteries, and a thermal dilution Swan-Ganz catheter was placed at the wedge position. Lead II EKG and urine output were monitored. Systemic and pulmonary arterial pressures were measured directly, while total peripheral resistance, cardiac index and left ventricular stroke work index were calculated from measured variables. After one hour of normotension four of the treatment groups received midazolam 0.2 mg/kg IV; the control group received saline. Five minutes later all dogs received nitroprusside 0.1% infusion to reduce the mean blood pressure 30% from baseline. Twenty minutes after the blood pressure had been reduced, three groups of dogs were administered the antagonist RO15-1788 intravenously at doses of 0.5 mg/kg (.5RO), 1.0 mg/kg (1.0RO) and 4.0 mg/kg (4.0RO). The control (C) and midazolam (M) groups were administered saline. After an additional fifty five minutes the nitroprusside was discontinued and the blood pressure allowed to recover to normotension. Hemodynamic measurements and plasma catecholamine samples (HPLC-EC assay) were obtained at 12 time periods during the study. The results were statistically analyzed within and between treatment groups using ANOVA, Duncan multiple test and non-paired t.

Results. Important results are shown in the TABLE. Administration of 0.5 and 1.0 mg/kg of the antagonist to midazolam-treated dogs caused progressive increases in EPI, CI, LVSWI and NE toward values obtained in the control group (C). This contrasts the declining/no change values in the midazolam group (M) without the antagonist. Responses of the 4.0 mg/kg group were less than the 1.0 mg/kg group and greater than the midazolam without RO15-1788 group (M). Baseline values, not shown, were not statistically different between the five groups, nor were the baseline and recovery values for individual treatment groups.

TABLE: HEMODYNAMIC AND CATECHOLAMINE RESULTS

		NP	+20	RO ↓ +55	+75	NP OFF	R+20	M
EPI	C		237±44*	303±60	288±71+		51±31	
pg/ml	M		100±33	205±55	117±43		19±8	
	0.5RO		83±38	195±100	240±74		6±1	
	1.0RO		120±40	245±82	236±21*		36±12	
	4.0RO		71±18	67±18*	103±54		5±1	
NE	C		443±168	455±116	548±123		84±24	
pg/ml	M		265±71	413±88	363±69		69±18	
	0.5RO		330±148	467±201	468±172		127±78	
	1.0RO		455±120	498±162	505±123		215±113	
	4.0RO		533±143	482±106	460±93		295±17	
CI	C		4.90±.84	4.89±.72	5.03±.72		3.56±.62	
	M		3.74±.10	4.43±.29	4.28±.27		3.78±.39	
	0.5RO		4.40±.26	5.10±.29	5.44±.30*		5.00±.29*	
	1.0RO		5.15±.25	6.15±.42*	6.53±.60*		5.19±.27*	
	4.0RO		5.63±.18*	6.12±.28*	5.93±.42*		5.23±.57*	
LVSWI	C		29±4	29±3	30±4		46±6	
	M		23±1	28±2	27±1		54±6	
	0.5RO		30±3	36±3	37±2*		73±10	
	1.0RO		30±2	37±1*	38±3*		75±5*	
	4.0RO		35±2*	43±4*	43±5*		77±11	
HR	C		180±14	180±12	177±13		120±5	
	M		162±9	169±9	169±10		111±8	
	0.5RO		172±14	169±5	166±10		117±17	
	1.0RO		206±10	199±8*	204±13		122±12	
	4.0RO		187±12	169±11	162±4		118±16	

MEAN ± SEM, * P < .05 and +P=0.08 compared to "M"

Discussion. The benzodiazepine antagonist RO15-1788 will reverse anesthesia induced with midazolam, however these results may only reflect an antagonistic action at higher consciousness sites. Results obtained in this study demonstrate that benzodiazepine antagonism with RO15-1788 extends to other sites associated with autonomic catecholamine responses to hypotension, i.e., brainstem. There is however a marked difference in the magnitude of reversal between the two responses. The volunteers awoke within 2 minutes after RO15-1788, while the catecholamine reversal developed slowly, achieving significance near the end of the study. Additional time may be required for maximum reversal. The parallel increases in CI and LVSWI are consistent with the inotropic activity of increased epinephrine in the presence of afterload reduction. Heart rate remained elevated but constant during the hypotension. In summary, RO15-1788 reversed midazolam's action on catecholamines without adversely affecting hemodynamic stability. It would appear that in the near future benzodiazepine reversal will be as common as narcotic and neuromuscular blockade reversal.