Title: MIDAZOLAM ON STIMULATORY RESPONSES TO HYPOTENSION: PREINDUCTION VS DURING ANESTHESIA

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Midazolam, a potent benzodiazepine, has been used for premedication, sedation and induction of anesthesia. Although the clinical effects of midazolam are short acting, the duration of its effects on intraoperative responses to stress has not been demonstrated. The purpose of this study was to determine midazolam's ability to suppress elevations in plasma catecholamines, cortisol and renin activity due to hypotensive stress when given preinduction and during anesthesia.

Methods

Eighteen beagle dogs were induced with thiopental, intubated and mechanically ventilated to achieve a normal $PaCO_2$. Anesthesia was maintained with 2% enflurane in N_2O-O_2 (1:2). A percutaneous catheter was inserted into the femoral artery and a Swan-Ganz catheter was floated into the pulmonary artery. Mean arterial blood pressure (MAP), mean right atrial pressure (RAP), mean pulmonary artery pressure (PAP), and mean pulmonary capillary wedge pressure (PCWP) were measured. Cardiac output was determined by thermodilution and heart rate (HR) was continuously monitored using Lead II ECG. Peripheral vascular resistance index (PVRI), cardiac index (CI) and left ventricular stroke work index (LVSWI) were then calculated from the measured hemodynamic data. The dogs were divided into three groups. One group (preinduction) was administered midazolam, 0.2 mg/kg IV, ten minutes before induction of anesthesia (1½ hours prior to the induced hypotensive stress). The other groups received either midazolam or saline during anesthesia (4 minutes before the induced stress). Neuro-endocrine blood samples and hemodynamic measurements were taken pre-stress; at 2, 10 and 20 min. during the hypotension; and 10 min. post-recovery of the blood pressure. The 20 min. period of hypotensive stress was achieved by lowering mean blood pressure 30% from baseline using a nitroprusside infusion. Cortisol was measured by radioimmunoassay and catecholamines were measured by the trihydroxyindole method. Statistical analysis consisted of ANOVA and Duncan's multiple range test. A probability of less than .05 was considered significant.

Results

Both epinephrine and norepinephrine were significantly increased during the hypotension in the control group. However, when midazolam was given preinduction or during anesthesia these elevations were suppressed. Cortisol levels also increased in the control group at the 10 and 20 minute periods ($p<.05$). Midazolam administered during anesthesia suppressed the cortisol stimulation in the early phases of hypotension, but not at the 20 minute period. Administration of midazolam preinduction had no effect on the hypotension-induced increase in cortisol. The hemodynamic responses observed in the three groups were similar. Reductions in MAP, CI and LVSWI occurred during the induced hypotension, and there was a slight reduction in PCWP. HR and PVRI remained stable in the control group, but decreased in both midazolam groups.

Discussion

Midazolam is generally considered to be a short-acting drug. However, the duration of the effects of midazolam on stress responses has not been clearly defined. The findings of this study show that midazolam effectively suppressed the adrenergic stress response whether it was administered prior to anesthesia, 1½ hours before the hypotension, or during anesthesia, immediately before the hypotension. Although injections at both times were effective, the adminstration during anesthesia provided a slightly greater suppression. Midazolam was less effective in suppressing the cortisol increase when administered just prior to the stress and was ineffectual when given before induction of anesthesia. Although the entire time course of midazolam's actions on stress responses has not been established, these results suggest that midazolam may be of potential clinical value as a premedicant in short procedures where it would be desirable to suppress stress-induced surges in catecholamines.