TITLE: THE EFFECT OF BENZODIAZEPINE PREMEDICATION ON THE TOXICITY OF BUPIVACAINE

AUTHORS: C.M. Bernards, M.D.; R.L. Carpenter, M.D.; S.M. Rupp, M.D.; D.L. Brown, M.D.; B.V. Morse, D.V.M.; R.C. Morell, M.D.; G.E. Thompson, M.D.

AFFILIATION: Department of Anesthesiology, Virginia Mason Clinic, Seattle, WA 98111; Department of Veterinary Medicine, University of Washington, Seattle, WA 98111

INTRODUCTION: Benzodiazepines are frequently administered as anxiolytics prior to regional anesthesia. Additionally, by raising seizure threshold, they provide some protection from central nervous system toxicity of local anesthetics. However, previous studies of the effect of benzodiazepine premedication on the cardiovascular toxicity of local anesthetics have produced conflicting results.[1,2] We, therefore, assessed the effects of midazolam and diazepam on the CNS and cardiovascular toxicity of bupivacaine in awake swine.

METHODS: In 30 swine, under N_2O/Halothane anesthesia, both femoral arteries were cannulated and a pacing pulmonary artery catheter inserted. Anesthesia was discontinued. One hour later diazepam (0.15 mg/kg), midazolam (0.06 mg/kg), or saline was injected intravenously in a blinded randomized manner. Five minutes later, an infusion of bupivacaine (2 $mg \cdot kg^{-1} \cdot min^{-1}$) was begun. Blood pressure (BP), heart rate (HR), and intracardiac ECG were continuously monitored and the animals were observed for seizures.

The bupivacaine infusion was continued until mean arterial pressure fell to 30 mm Hg. Animals were then intubated, ventilated with 100% oxygen, and open cardiac massage begun. Cardiopulmonary resuscitation continued as per ACLS protocol until successful or until 25 minutes had elapsed. Arterial blood gasses, electrolytes, bupivacaine levels and catecholamine levels were measured at standard intervals. Differences among groups were assessed by ANOVA and were considered significant for $p < 0.05$.

RESULTS: The groups did not differ in any baseline variable. Control animals experienced dysrhythmias earlier than animals premedicated with midazolam or diazepam (table 1). BP and HR increased during the first 2 minutes of bupivacaine infusion in the control group but not in the benzodiazepine groups (fig. 1). The dose of bupivacaine required to produce cardiovascular collapse and the plasma bupivacaine levels at collapse did not differ among the groups. We were less successful in resuscitating diazepam premedicated animals (table 1). Animals premedicated with a benzodiazepine were less likely to experience seizures (table 1).

DISCUSSION: The infrequency of seizures in the benzodiazepine treated groups confirms earlier reports that benzodiazepines raise the threshold for local anesthetic induced seizures. An important observation was that benzodiazepines suppressed manifestations of CNS toxicity, i.e. seizures, without affecting the threshold for cardiovascular collapse. This finding suggests that patients who receive accidental IV injections of bupivacaine after benzodiazepine premedication may progress directly to cardiovascular collapse without manifesting CNS toxicity as a warning sign.

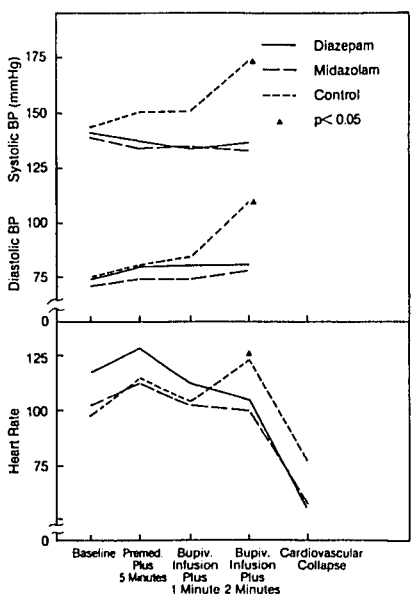
The mechanism by which benzodiazepine premedication delayed the onset of dysrhythmias and prevented elevations in BP and HR during bupivacaine infusion is unclear. We hypothesize that bupivacaine stimulates the sympathetic nervous system (SNS) just as it stimulates the amygdala to cause seizures. SNS stimulation could explain the observed elevations in BP and HR as well as earlier dysrhythmias. Benzodiazepine premedication may inhibit stimulation of SNS neurons just as it prevents seizures by inhibition of neurons within the amygdala.

Table 1: Effect of benzodiazepine premedication on bupivacaine toxicity

Group	Control (N = 10)	Midazolam (N = 10)	Diazepam (N = 10)
Seizures (%)	100*	20	0
Time to first dysrhythmia (sec)	119 ± 18*	170 ± 56	162 ± 42
Successfully resuscitated (%)	90	100	60*

values are mean ± S.D. *$p < 0.05$

FIGURE 1



REFERENCES:
1. deJong RH, Bonin JD: Benzodiazepines protect mice from local anesthetic convulsions and death. Anesth Analg 60:3385-389, 1981.
2. Gregg RV, Turner PA, Denson DD, Coyle DE: Does diazepam really reduce the cardiotoxic effects of high dose I.V. bupivacaine? Anesth Analg 67:9-14, 1988.