TITLE: EFFECT OF MIDAZOLAM AND FLUMAZENIL ON THE ACTIVITY OF CARDIAC SYMPATHETIC BRANCH

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Midazolam (MDZ) is often used for anxiolysis in the perioperative period. It has been reported that small doses of MDZ may produce transient cardiovascular depression by lowering skeletal muscle sympathetic efferent nervous activity (1). The present study was undertaken to determine whether MDZ depressed central sympathetic outflow innervating the heart and to ascertain if subsequently administered flumazenil (FMZ), a specific benzodiazepine antagonist, could reverse the effect of MDZ on sympathetic tone.

Eight cats were initially anesthetized with 30ml/kg ketamine IM, intubated and mechanically ventilated. Baseline anesthesia was maintained with 70% nitrous oxide and 0.4% halothane in oxygen. Postganglionic compound action potential from the stellate cardiac nerve (SCN) was recorded following left thoracotomy. Heart rate (HR), mean arterial pressure (MAP) and pulse density (PD) of SCN at 1 sec intervals were measured and stored in a digital data recorder. A bolus of 0.15 mg/kg MDZ was administered followed by another dose of MDZ 0.15mg/kg 90 sec later. FMZ (0.1mg/kg) was administered 5 min after MDZ administration. Results were compared with repeated measures ANOVA.

The results are summarized in the table shown below. MDZ produced hypotension and a sustained decrease in sympathetic tone. FMZ restored MAP and SCN activity changes induced by MDZ to the control level, suggesting that MDZ depressed sympathetic tone via GABAergic pathway.

The present study provides evidence that MDZ produces a marked reduction in SCN activity. This depressant effect of MDZ on the sympathetic nerve innervating the heart caused a drop in the BP even though effect of MDZ on HR was not demonstrated. MDZ may produce a limited ability of the autonomic nervous control of the heart.

Table: Hemodynamics and cardiac sympathetic activity

	CONTROL	MDZ 0.15mg/kg	MDZ 0.3mg/kg	FMZ 0.1mg/kg
MAP (mmHg)	132±15	118±18*	118±20*	132±17
HR (bpm)	176±23	183±18	182±18	169±27
PD (spikes/sec)	55±16	35±13*	37±12*	60±26

values are mean±SD, * P<0.05 vs control

REFERENCE: 1. Anesthesiology 71:A297, 1989.

A398

TITLE: GLUTATHIONE DEPLETION EXACERBATES HALOTHANE-ASSOCIATED HEPATOTOXICITY IN GUINEA PIGS.

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Halothane(H)-associated centrilobular necrosis in guinea pigs has been linked to covalent binding to hepatic proteins by oxidative biotransformation reactive intermediates.[1] Since glutathione (GSH) is a known protectant against toxicants that form reactive intermediates, the effect of its depletion on H binding and resultant hepatotoxicity was studied.

Outbred male Hartley guinea pigs (600-700 g) were injected ip with either 1.6 g/kg buthionine sulfoximine (BSO; N=16) or vehicle (V; N=16) 24 hr prior[2] to exposure to 1% v/v H, F_IO_2=0.40, for 4 hr. At the end of exposure (0 hr) one-half of the animals were terminated, cardiac blood drawn, and livers frozen. Remaining animals were bled at 0, 24, 48, and 72 hr with termination at 96 hr. Control groups included animals killed 24 hr after V or BSO injection (N=4) for determination of hepatic GSH concentrations[3], and BSO-treated animals that were not anesthetized (N=3) or were exposed to 1.7% isoflurane (N=3) and bled at the same times as H-exposed animals. 0 hr plasma samples from H-exposed animals were analyzed for trifluoroacetic acid and fluoride ion as indicators of H biotransformation.[1] All plasma samples were analyzed for ALT levels. Liver sections were evaluated by light microscopy. Protein and lipid, isolated from liver tissue collected at 0 hr, were analyzed for bound organic fluorine.[4]

Hepatic GSH levels decreased from 2.8 ± 0.1 to 0.5 ± 0.1 μmoles/g liver (N=4, p<0.01) 24 hr after BSO administration. H biotransformation was unaffected by BSO treatment as indicated by 0 hr metabolites. Bound organic fluorine to protein increased from 1.40 ± 0.17 (V+H) to 2.10 ± 0.45 (BSO+H) nmoles F^- released/mg protein (N=8, p< 0.01). H binding to lipid was unaffected. H-associated hepatotoxicity was exacerbated by GSH depletion. ALT levels at 72 hr: V+H = 213 ± 179, BSO+H = 550 ± 461* units/ml, at 96 hr: V+H = 107 ± 82, BSO+H = 449 ± 532* units/ml (N=6-8, *p<0.05 vs V+H, control = 21 ± 2 units/ml, N=8). Incidence and severity of centrilobular necrosis was significantly increased in BSO+H animals as well. There was no hepatic injury in any of the control groups.

Low hepatic GSH concentrations may leave critical targets more vunerable to covalent binding by H oxidative reactive intermediates, producing an increased susceptibility to H-associated hepatotoxicity.

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