TITLE: CARDIOVASCULAR EFFECTS OF MEPIVACAINE AND ETIDOCAINE IN THE AWAKE DOG.

AUTHORS: H.S. Feldman, B.Sc., G.R. Arthur, Ph.D., S.B. Norway, AAS, A.M. Doucette, B.A., B.G. Covino, Ph.D., M.D.

AFFILIATION: Dept. Anesthesia, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115

In a previous study, the cardiovascular effects of intravenous (IV) convulsive doses of lidocaine and bupivacaine were found to be very similar in dogs.[1] However, two of seven dogs developed fatal cardiac arrhythmias following a 30 second IV infusion of bupivacaine. In awake sheep, all animals receiving a high dose of IV bupivacaine developed either arrhythmias and/or transient ECG changes.[2] No arrhythmias were seen with lidocaine. This study compares the cardiovascular effects of convulsive doses of etidocaine and mepivacaine in unanesthetised dogs. Etidocaine and mepivacaine were chosen because of their physicochemical similarities to bupivacaine and lidocaine. (i.e. lipid solubility, protein binding and chemical structure.)

Materials and Methods. Five adult mongrel dogs were used. At least 48 hours prior to experimentation the animals were anesthetized with IV Thiamylal. Catheters were placed into the abdominal aorta and inferior vena cava via the femoral vessels. A cephalic vein catheter was also placed. A modified pulmonary artery (PA) catheter introducer was placed in the right external jugular vein to allow floating of a PA cardiac output catheter while the dog is in the awake state. On the experimental day the animals were secured in the standing position in a canvas sling. Recordings of ECG, arterial blood pressure (ABP), cardiac output (CO), arterial pH, pCO_2, pO_2, Sodium (Na), Potassium (K) were made at control and appropriate times during the experiments. Each animal received etidocaine (4.6 mg/kg) and mepivacaine (13 mg/kg) in a blinded, random cross over design. Each drug administration was separated by at least 48 hour intervals. These mean convulsive doses were determined previously in a separate group of animals. Two animals that received mepivacaine did not convulse, they were given a second dose one hour later (19.5 mg/kg; 1.5 x convulsive dose). Arterial and venous blood samples were drawn at appropriate time intervals for drug concentration determination. Analysis was performed by gas chromatography.

Results. There were no significant differences in recorded data between drug groups during the control period. The mean times to inject drugs were 36 sec (etidocaine) and 35 sec (mepivacaine) with convulsive activity occurring 12 sec (etid) and 17 sec (mepiv) thereafter. Duration of convulsions were 242 ± 50 sec (etid) 291 ± 104 sec (mepiv) (means ± SEM). No abnormal ECG complexes resulted from administration of either drug. Following administration of both drugs, heart rate (HR), CO, and ABP showed a marked increase, with elevation having the longest duration after the termination of convulsions. Blood K^+ concentrations were elevated during seizures in 4 animals of each drug group with Na^+ concentrations remaining relatively stable. No consistent changes were noted for pCO_2, pO_2, or pH during seizure activity. However maximal changes for some of these values were significant (see table). Arterial whole blood concentrations were: Start seizure 145 ± 20 µg/ml mepivacaine HCl, 31.9 ± 1.9 µg/ml etidocaine HCl; End seizure 12.8 ± 2.0 µg/ml mepivacaine HCl, 4.5 ± 0.7 µg/ml etidocaine HCl. (Mean values ± SEM.)

Table. Control and Maximum Values During Seizure Activity (Mean Values ± SEM)

	Mepivacaine		Etidocaine	
	cont	max	cont	max
HR(bpm)	89±7	204±15*	89±4	203±25*
ABP(mmHg)	118±5	185±12*	114±3	176±7*
CO(L/min)	3.6±0.4	6.4±0.9	3.7±0.4	10.4±3.7
pH(units)	7.4	7.5±0.1	7.4	7.3±0.1
pO_2(mmHg)	83±1	100±3*	85±1	87±10
pCO_2(mmHg)	22.7±0.1	18.7±1.3	22.5±0.8	21.4±4.2
Na(mM/L)	143±1	144±2	143±1	146±1
K(mM/L)	3.5±0.1	3.9±0.2	3.6±0.1	4.4±0.4

*Statistically different from control values.

Discussion. Convulsive doses of mepivacaine and etidocaine produced hemodynamic responses very similar to those reported for lidocaine and nonlethal convulsive doses of bupivacaine[1]. Changes in blood gas and electrolyte status remained relatively stable during convulsions which is not in keeping with human data. Mepivacaine, the less potent, less protein bound and less lipid soluble of these two compounds, required doses three times those of etidocaine to produce seizure activity in the dog. Mepivacaine blood concentrations at start and end seizure activity were higher than those found with lidocaine, and etidocaine concentrations were greater than those for bupivacaine. This study suggests that the malignant arrhythmias previously observed following IV bupivacaine in awake dogs may not be related to the high lipid solubility and protein binding of this agent since etidocaine, which is also highly lipid soluble and protein bound, did not cause arrhythmias in the current studies. In addition, the piperidine ring which is common to both bupivacaine and mepivacaine does not appear to be of importance in terms of arrhythmogenic potential as mepivacaine did not cause the development of arrhythmias in this study.

REFERENCES

1. Sage D, Feldman H, Arthur GR, Covino BG. Cardiovascular effects of lidocaine and bupivacaine in the awake dog. Anesthesiology 1983, 59:A210.
2. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA. Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 1984; 60, 10-18.