Title: INFLUENCE OF LIDOCAINE AND BUPIVACAINE ON ISOLATED GUINEA PIG ATRIA IN THE PRESENCE OF ACIDOSIS AND HYPOXIA

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Introduction. In vivo local anesthetic potencies of amide local anesthetics are proportional to their relative cardiovascular toxicity measured in intact anesthetized dogs whose blood gas and acid-base status is normal [(1)]. However, it has been suggested [(2)] that the more highly lipid soluble agents such as etidocaine and bupivacaine may have enhanced toxicity in the presence of hypoxia or acidosis.

This study investigated differences between lidocaine and bupivacaine depression of isolated atrial activity when perfusate conditions were changed to resemble hypoxia, acidosis, and asphyxia (hypoxia and acidosis).

Method. Guinea pig atria were rapidly dissected and suspended in a bath containing Kreb's-Henselite (KH) solution. The bath was maintained at 37.0-37.5°C and aerated with one of three gas mixtures. The tip of one atria was secured to the base of the bath and the opposite end fastened to a force displacement transducer with diastolic tension adjusted to 1 g. After equilibration, the tissue was exposed to one of the following drug concentrations: lidocaine 50µg/ml, bupivacaine 5µ/ml, bupivacaine 10µg/ml. Spontaneous heart rate (HR) and contractile force (CF) were measured for 60 minutes. The atria and a perfusate sample were then removed, and drug concentrations assayed using a standard gas chromatographic technique.

Combinations of gas mixtures and KH or KH modified by reducing $NaHCO_3$ content produced the perfusate conditions presented in Table I. The relatively high pO_2 chosen for hypoxic conditions was necessary to prevent atrial death. Results are expressed as the mean ± SEM and were compared using Student's t-test for unpaired data.

Results:

		GAS MIXTURE		
		A O_2 95% CO_2 5%	B O_2 70% CO_2 30%	C O_2 30% CO_2 10% N_2 60%
Normal Kreb's		"Normal"	"Acidosis I"	"Hypoxia"
	pH	7.40±0.01	6.70±0.05	7.36±.001
	pO_2	474.5±43.04	377.8±22.97	201.6±4.19
	pCO_2	22.43±1.36	166.9±9.03	25.6±1.31
		"Acidosis II"		"Acidosis/ Hypoxia"
Modified Kreb's	pH	6.89±0.03		6.83±0.02
	pO_2	549.4±31.35		213.0±6.43
	pCO_2	22.28±0.90		22.5±0.44

Table 1: Perfusate pH, pO_2, and pCO_2 for 5 conditions tested (mmHg) mean ± SEM.

HR and CF were unchanged from controls in atria exposed to the 4 test conditions without drug. Addition of lidocaine or bupivacaine caused an immediate sustained decrease in CF under all conditions (p<0.01). HR was significantly depressed under all conditions except lidocaine and hypercarbia ("acidosis I") where the increase wa not significantly different from controls.

Under conditions of "hypoxia" and "acidosi II" the effect of lidocaine was not distinguishabl from bupivacaine 5µg/ml or 10µg/ml.

Under "normal" conditions, maximum HR and C changes were greatest for bupivacaine 10µg/m (-61.51 ± 9.59% and -66.39 ± 8.65%) which wa significantly different from lidocain (-33.79 ± 1.42% and -37.84 ± 8.43%) (p<0.05) Bupivacaine 5µg/ml produced maximum HR and C depressions of -45.13±18.32% and -60.64±9.06% (no significantly different from lidocaine).

With hypercarbia ("acidosis I") maximum HR an CF changes were greatest for bupivacaine 10µg/m (-59.81 ± 14.15% and -78.24 ± 8.79%) with n significant difference between the two bupivacain concentrations. Both bupivacaine 5µg/ml an 10µg/ml caused significantly greater HR and C depression than lidocaine (+27.70 ± 16.41% an -46.98±2.52%).

The greatest atrial depression was seen wit bupivacaine under "acidosis/hypoxia" conditions One death occured in the bupivacaine 5µg/ml grou and 5 of 6 preparations died with bupivacain 10µg/ml. Maximum changes in HR (Fig. 1) and C (Fig. 2) with all 3 drug concentrations differe significantly from one another (p<0.01).

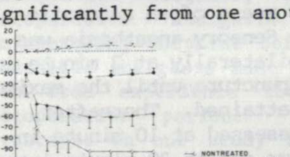

Fig. 1

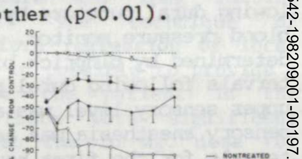

Fig. 2

Discussion: Under "normal" conditions bupivacaine was 5-10 times as toxic as lidocaine to some extent reflecting their relative local anesthetic potencies. Hypoxia or metabolic acidosis did not alter this ratio, but hypercarbia increased bupivacaine toxicity relative lidocaine. Bupivacaine cardiotoxicity was strikingly enhanced relative to lidocaine with "acidosis/hypoxia" and was dose-dependent. The explanation for these changes is not clear. Isolated atria in protein-free perfusate may not reflect in vivo toxicity.

References:

1. Liu P, Feldman HS, Covino BG, et al: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982; 61:317-322.

2. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiol 1979; 51:285-287.

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