TITLE: THE EFFECT OF CONVULSIONS ON LIDOCAINE AND BUPIVACAINE PHARMACOKINETICS IN THE DOG.

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The rapid intravenous (IV) administration of convulsive doses of bupivacaine (BUP), but not lidocaine (LID), has been reported to cause ventricular arrhythmias in cats[1], sheep[2], and dogs[3]. Slow infusions of both agents have not been reported to cause cardiac abnormalities. Differences in the pharmacokinetic properties of local anesthetics may exist between convulsive and non-convulsive states. The present study was initiated to compare the pharmacokinetics of LID and BUP following rapid IV administration in dogs, which produced convulsive activity, and after slow IV infusion of the same dose which did not cause convulsions.

Materials and Methods. In the first part of the study, 5 adult mongrel dogs were given an IV convulsive dose of BUP (3.4 mg/kg n = 4, 5.1 mg/kg n = 1) and LID (11 mg/kg n = 3, 16.5 mg/kg n = 2) over 30 seconds. Blood samples were taken at regular intervals for 4 hours (venous) and 90 minutes (arterial) after drug administration. Four additional animals were utilized for the second part of the study. IV infusions of BUP (3.4 mg/kg) and LID (11 mg/kg) were made over 15 minutes. Arterial blood samples were drawn both during the infusion and for 4 hours thereafter. Drugs were administered in a random, crossover manner with a 48 hour recovery period between each experiment. Drugs were injected into a cephalic vein. Blood drug concentrations (CB) were determined using a gas chromatographic technique. Pharmacokinetic analysis of CB data was based on a 2 compartment model using SIMPLEX (provided by JA Clements, Heriot Watt Univ, Edinburgh), a computer program using non-linear regression analysis. Pharmacokinetic data in the infusion study was based on arterial CB and in the bolus study on venous CB. In the bolus group, extrapolation of arterial CB (using the β value determined from venous CB) yielded pharmacokinetic data essentially the same as for venous CB.

Results. All animals receiving 30 sec bolus injections of drug convulsed. During convulsive activity, heart rate (HR), arterial blood pressure (ABP) and cardiac output all increased: LID--HR + 109%, ABP + 54% and CO + 150%; BUP--HR + 128%, ABP + 62% and CO + 150%. No animals receiving slow IV infusions convulsed and only minor increases in HR and ABP were observed. The greatest increase in HR was in the lidocaine group at end infusion (HR + 60%). Pharmacokinetic data is presented in the table. The only statistically significant difference found was for clearance (Cl) in the two LID groups. Although a similar trend was seen with BUP, this was not statistically significant. Values for steady-state volume of distribution ($V_D ss$) were essentially the same for both rates of drug administration. The longer half life of elimination ($t_{1/2}\beta$) after rapid IV administration was associated with one animal in each drug group (LID, $t_{1/2}\beta$ = 111 min, BUP $t_{1/2}\beta$ = 80 min).

Table. Pharmacokinetic Parameters for Lid. and Bup. in the Dog ($\bar{x}$ ± SD, * $p < .05$)

	Lidocaine		Bupivacaine	
	Bolus	Infusion	Bolus	Infusion
$t_{1/2}\beta$ (min)	75 ± 25	46 ± 11	46 ± 21	40 ± 12
$V_D ss$ (l/kg)	2.9±1.4	2.3±0.5*	1.4±0.4	1.2±0.3
Cl (ml/min/kg)	30 ± 8	56 ± 13*	25 ± 5	33 ± 5

Discussion. Rapid administration of BUP and LID produced dramatic hemodynamic changes during convulsive activity but slow IV infusions of both drugs produced only minor hemodynamic changes. The reduced Cl values seen after rapid drug administration may be related in part to sustained CB values during convulsive activity. Although CO increased during convulsive activity, blood supply to the hepatic circulation may be reduced due to a greater increase in supply to muscle vascular beds, this caused by the increased demand for oxygen during the violent muscle activity associated with convulsions. Pharmacokinetic data presented here for LID and BUP differs from that reported for man. This is due to the relatively greater hepatic blood flow in the dog[4] and greater hepatic extraction ratios for LID[5] and BUP[6] in the dog. It is possible that sustained local anesthetic CB values during convulsions, associated with an increased coronary blood flow, cause an increase in drug uptake by cardiac tissue thus precipitating cardiac abnormalities.

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