Title: EFFECT OF 2 CALCIUM ENTRY BLOCKERS ON NEUROLOGICAL OUTCOME AFTER 10 MINUTES VENTRICULAR FIBRILLATION CARDIAC ARREST IN DOGS

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Introduction. In dogs after cardiac arrest (CA) administration of calcium entry blockers (CEB) ameliorates cerebral hypoperfusion (1,2), but amelioration of neurological deficit (ND) by a CEB given after CA remained to be demonstrated in a long-term CA model with intensive care (3). That was accomplished by this study.

Methods. 27 fasting, healthy mongrel dogs received N2O/O2-halothane-pancuronium anesthesia for preparation. Intravascular catheters were established for fluid/drug administration, blood analysis, pressure monitoring and cardiac output (CO) measurements by the thermodilution technique. Ventricular fibrillation (VF) was induced by external AC shock with the dogs ventilated on room air. A CA time of 10 min was allowed. Restoration of spontaneous circulation (ROSC) was accomplished according to standardized protocol with external CPR, IPPV/100% O2 and intra-aortic injection of epinephrine plus NaHCO3 in a bolus of Ringers Lactate. ROSC was accomplished within 5 min CPR. Lidoflazine (L) 1 mg/kg was given to 11 dogs IV immediately upon ROSC, and repeated at 8 h and 16 h PI. Verapamil (V) 0.1 mg/kg was given to 5 dogs and repeated at 5 h, 10 h and 15 h PI. (Results of only 5/11 dogs with L, and no results with V were reported 1 yr ago.) The control (C) dogs (n=11) received the same volume of placebo and were studied concurrently with L and V dogs, in randomized sequence. Continuously monitored were: HR, MAP, rectal temperature, CVP, EKG, EEG, sagittal sinus and cisternal pressure (SSP/ICP). Intermittently measured were: CO, blood gases, arterial and sagittal sinus O2 contents, serum electrolytes, hct, blood sugar and diuresis. MAP was controlled at 105-15 mmHg with norepinephrine (NE) and trimethaphan, PaO2 > 100 and PaCO2 at 30 mmHg. The dogs were weaned to spont. ventilation at 20-24 h and post-CPR intensive care life support with normotension, normoxia, normocarbia, normothermia and control of other variables for 96 h. Outcome was evaluated as neurological deficit (ND) score after an established scoring system (0% ND=no deficit and 100% ND=brain death); and by Overall Performance Categories (OPC) (#1=normal, 2=slightly disabled, 3=severely disabled, conscious, 4=vegetative, 5=brain dead). Brain damage was also assessed by increase of brain specific creatine phosphokinase (CPKBB) in cisternal fluid (CSF) (4). At 96h the best ND was recorded and the dogs sacrificed by perfusion-fixation for histopathological studies.

Results. ROSC was accomplished within 40"-4'40", and there was no difference in total insult time between groups. The patterns of return of EEG activity and pupillary light reflexes were the same in all groups. ICP/SSP increased transiently to 25-30 mmHg 1 min after ROSC and returned to preinsult values of 8-10 mmHg 10-15 min PI, with no difference between the 3 groups. The pattern of Ca-ss O2 changes were the same in all groups, with an initial fall (hyperemic phase) and then an increase to reach a plateau 2-4 h PI (hypoperfusion phase). Outcome, represented by the best ND and OPC is shown in the table. Both ND and OPC were significantly better in L-treated dogs. 5/11 L dogs and 0/11 control dogs achieved OPC #1 (normal) ($p < 0.01$). CSF-CPKBB was also lower as a reflection of less brain damage, but the difference from the control group was not significant because of a wide range. There was good correlation between outcome, as reflected by ND% (and OPC), and maximum CPKBB activity at 48 h) (4=0.77), as well as histopathologic damage scores. L was well tolerated by the cardiovascular system and CO was better preserved than in the control and the V-groups in which C.O. decreased more in the first hrs post-CA. Both L and V dogs needed more NE initially, but the total dose was the same, except that NE support was needed when V was repeated. L and V seemed to protect against ventricular ectopia. Atrio-ventricular and intra-ventricular conduction defects caused brady-arrhythmias which were more pronounced in the V than the L groups.

Summary and Conclusion. Lidoflazine (but not verapamil), with this mode of administration, ameliorated brain damage in dogs post-CA, in terms of ND scores and better overall outcome. L resulted in normality in 5/11 L dogs; while all 11 control dogs remained severely damaged. CSF-CPKBB was also lower in 5/11 L treated dogs and correlated well with ND and outcome. The beneficial effect was not reflected by an improvement of brain oxygen supply/demand ratio. L, but not V, seemed to ameliorate the severe impairment of the cardiovascular system which can be observed after long CA in dogs.

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Table.

	n	Best Outcome ND%	Best Outcome OPC	OPC 1	Max CPKBB U/L	Max CPKBB n
Contr	11	33.7±11	3.1±0.9	0/11	46±26	11
Lido	11	18.5±14*	1.9±0.9	5/11**	35±33	10
Verap	5	27.2±7.6	2.6±0.9	0/5	12±13	4

*$p < 0.05$ vs control. **$p < 0.01$ vs control.