Title : ELECTROPHYSIOLOGIC EFFECTS OF INTRAVENOUS DANTROLENE ON DOG HEARTS

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Introduction. A common characteristic abnormality associated with malignant hyperthermia (MH) is the development of cardiac arrhythmias. Frequently, ventricular rhythm disturbances are the cause of death during the anaesthetic-induced pyrexic crisis. Reviewing clinical reports of the MH treatment by dantrolene, reversal of ventricular arrhythmias was noted to occur more rapidly than could be explained by dantrolene's relaxant effect on skeletal muscle and by the correction of acid-base disturbances. This phenomenon as well as recent electrophysiologic studies on isolated dog[1] and sheep[2] Purkinje fibers are the basis for hypothesizing that dantrolene has a direct antiarrhythmic effect. The present investigation was designed to assess by intracardiac electrophysiologic study (IES) whether intravenously administered dantrolene has primary effects on electrophysiologic basic parameters in healthy dogs.

Methods. Six adult beagle dogs of either sex weighing 22 – 28 kg were studied by programmed electrical stimulation of the heart. According to the usual guidelines, these dogs in normothermic situation were anaesthesized with xylazin (0.1 ml/kg) and ketamine (10 mg/kg) im. Anaesthesia was maintained with ketamine (10 mg/kg/hr) and diazepam (0.1 mg/kg/hr) intravenously. Blood gas analysis were repeated several times during the study to ensure a steady state. Catheters were passed through femoral veins using Seldinger technique and positioned in the heart under fluoroscopic guidance. These included a bipolar catheter in the right atrium and right ventricular apex as well as a bipolar catheter, which was placed across the tricuspid valve to record His-bundle potentials. ECG-leads I, II, III and intracavitary leads from right atrium, right ventricular apex and His-bundle were recorded simultaneously. With the use of single test stimulus technique during atrial and ventricular pacing at a basic cycle length of 510 ms, the refractory periods of the atrium, the AV-node and the right ventricle were determined. There was no retrograde conduction in all dogs. Standard definitions for electrophysiologic parameters were used.[3] After assessment of IES control data, dantrolene was administered by an infusion in a dose of 10 mg/kg over 15 min and all measurements were repeated immediately, 30, 60 and 90 min after application of dantrolene. Blood samples for determination (thin-layer chromatography) of serum concentration of dantrolene and its metabolites, 5-hydroxydantrolene and acetylated dantrolene, were drawn before and every 15 min after application of dantrolene up to the end of the study. Statistical analysis was performed by the paired student t-test.

Results are summarized in the table (SCL = sinus cycle length, ERP = effective refractory period, FRP = functional refractory period, P = p-wave, A = atrium, AVN = AV-node, H = His-bundle, V = ventricle) and presented as mean ± 1 SD (ms).

	pre-drug	post-dantrolene				
	control	immediately	30 min	60 min	90 min	mean 0–90 min
SCL	626±55	632±35	602±32	606±27	614±53	614±35
QRS	60±12	60±12	60±12	60±12	60±12	60±12
PQ	114± 9	118±11	114±11	114± 9	114± 9	115±10
QT	270±19	278±19	274±18	266±11	268±15	272±15
PA	17± 6	17± 6	18± 6	17± 6	18± 6	18± 6
AH	66± 5	75± 6	79± 9	79± 9	76± 5	77± 6
HV	35± 6	38± 5	38± 5	38± 5	39± 6	38± 4
A-ERP	122±11	156±38	138±25	148±22	150±20	148±25
A-FRP	180±16	205±30	187±10	193±10	198±17	196±11
AVN-ERP	≤A-FRP	≤A-FRP	≤A-FRP	≤A-FRP	≤A-FRP	≤A-FRP
AVN-FRP	294± 2	293±26	288±10	288±10	283±19	287±15
V-ERP	146± 9	158± 4	156± 7	158±19	160±25	158±15

Dantrolene did not significantly alter CL, QRS complex, PQ, QT, PA and HV intervals during sinus rhythm. The AH interval increased from 66 ± 5 to 77 ± 6 ms. Concerning refractory periods, dantrolene administration resulted in a significant increase of A-ERP from 122 ± 11 to 148 ± 25 ms and of A-FRP from 180 ± 16 to 196 ± 11 ms ($p < 0.05$) as well as an increase of V-ERP from 146 ± 9 to 158 ± 15 ms. AVN-FRP did not change. Mean maximum plasma dantrolene concentration of 11.6 ± 3.7 µg/ml occurred immediately after drug infusion. The terminal half life of dantrolene ranged from 0.8 to 3.7 hr. Mean maximum plasma concentration of 5-hydroxydantrolene amounted to 1.4 ± 0.4 µg/ml after 90 min. Acetylated dantrolene could not be detected in blood.

Discussion. We conclude, that intravenous dantrolene has primary effects on electrophysiologic basic parameters. The observed prolongation of the refractory periods of the right atrium and ventricle, induced by a high dose of dantrolene, persisted for 90 min. These in-vivo results seem compatible with those from in-vitro dog Purkinje fibers showing an increase of action potential duration and of ERP. Our findings support the hypothesis that the beneficial effects of dantrolene on MH associated cardiac arrhythmias may be related to its intrinsic activity on the electrophysiologic properties of the heart, but require further investigations in dogs with induced ventricular arrhythmias.

References.

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