

THE ANTI-ARRHYTHMIC EFFECTS OF VERAPAMIL AND PROPRANOLOL IN AMINOPHYLLINE TOXIC DOGS.

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INTRODUCTION: Phosphodiesterase inhibition, stimulation of catecholamine synthesis and release as well as altered calcium kinetics are actions of aminophylline possibly responsible for its arrhythmogenic properties. These cardiac effects can result in potentially lethal arrhythmias. In an effort to better understand these arrhythmogenic properties and to provide a more rational approach to pharmacologic management, we explored the usefulness of the calcium blocker Verapamil and the beta adrenoceptor blocker propranolol in aminophylline toxic dogs. Verapamil was studied because of its effects on cyclic AMP mediated calcium kinetics.

METHOD: Eighteen dogs were intubated and ventilated after induction of anesthesia (pentobarbitone 30 mg/kg and pancuronium 0.1 mg/kg). Electrocardiogram, arterial blood pressure and left ventricular end diastolic pressure were continuously monitored and recorded. Cardiac output and systemic vascular resistance were computed by thermodilution technique. Serum electrolytes including calcium, arterial blood gases and serial aminophylline levels were measured. All animals were rendered toxic by aminophylline infusion, an initial dose of 50 mg/kg over 5 minutes with subsequent doses of 10 mg/kg over 30 seconds. Twenty minutes after each aminophylline infusion, the dog was challenged with phenylephrine (10 to 20 ug/kg). This resulted in short duration hypertension and reproducible emergence of ventricular arrhythmias. The dogs continued to receive additional aminophylline infusions until these arrhythmias became persistent for greater than a 120 second observation period. Arrhythmias were defined as frequent PVC's ventricular tachycardia, or ventricular fibrillation. The dogs were divided into three groups of six animals each. Group I (control) received no anti-arrhythmics whereas Group II received Verapamil 0.2 mg/kg and Group III received propranolol 0.1 mg/kg for the treatment of persistent ventricular arrhythmias.

RESULTS: All dogs in Group I died of ventricular arrhythmias when the serum aminophylline level reached 152 ± 23.3 ug/ml (mean + SD). There was no statistically significant difference between the serum aminophylline level at the time of persistent ventricular arrhythmias in all three groups. In Group II, these arrhythmias were promptly terminated by verapamil. Apart from its anti-arrhythmic effect, Verapamil produced a fall in blood pressure (-33%) and systemic vascular resistance. In Group III propranolol resulted in rapid but partial arrhythmia control, three dogs required additional doses of propranolol. Significant changes observed with the administration of propranolol included heart rate slowing, PR interval prolongation and a decrease in cardiac index. Subsequent challenge with phenylephrine could not reinstitute these arrhythmias in Group II while transient ventricular ectopics were seen in four dogs in Group III.

DISCUSSION: Verapamil and propranolol exerted an anti-arrhythmic effect in aminophylline induced ventricular arrhythmias. The efficacy of Verapamil was independent of a reduction in blood pressure and systemic vascular resistance as subsequent phenylephrine induced hypertension could not reinstitute these arrhythmias. Propranolol appeared less effective since it did not completely suppress the arrhythmias in three dogs and could not prevent emergence of PVC's in four following repeat phenylephrine challenge. Although mechanisms of anti-arrhythmic action remain speculative, these observations suggest that Verapamil and perhaps propranolol hold promise in pharmacologic management of aminophylline induced cardiac arrhythmias. Further development of this animal model may be useful for the better understanding of ventricular arrhythmias.