Title: VERAPAMIL DOSE HAVE PROLONGED INTERACTIONS WITH HALOTHANE

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Introduction. Verapamil has been used in the therapy of supraventricular arrhythmias and ischemic heart disease. Its action in the presence of inhalation agents have been reported. We report the alterations observed in the hemodynamic effects of halothane after a small clinically relevant dose of verapamil, together with the nature of calcium reversal of halothane-induced myocardial depression in the presence of verapamil.

Methods. Anesthesia was induced in 14 mongrel dogs with 30 mg/kg pentobarbital and maintained on 2 mg/kg i.v. pentobarbital (pentobarbital is known to exhibit ATP dependent calcium effects in dogs, but non-halothane anesthesia was necessary for control measurements). The dogs were divided into two equal groups: Group I, the control group and Group II, the verapamil pretreated group. Femoral arterial lines and Swan-Ganz catheters were placed in all dogs. A 7F Millar Microtip catheter was inserted via a left ventricular stab wound to measure left ventricular pressure. Dp/dt was measured at ventricular pressure of 40 torr (dp/dt/40). A bipolar atrial pacemaker was passed via the left external jugular vein and all dogs were paced at a rate of 150 beats/min. Arterial Po2 was maintained above 100 torr and PCO2 between 35-45 torr. Cardiac output (CO) was measured by thermodilution (E for M Cardiac Output Computer). Temperature was maintained at 36-37°C. In Group I animals following 45 min stabilization, control measurements were made. Animals were then maintained at 1% halothane (end tidal) for 30 min and measurements repeated. Depending on hemodynamic effects, CaCl2 was infused at a rate of 1.2 - 4 mg/kg/min. Following 5 min of stabilization of hemodynamic parameters, repeat measurements were made. Group II animals were treated exactly the same except following control measurements, 2 mg/kg verapamil was given over 10 min. After 45 min, repeat hemodynamic measurements were made. Halothane exposure and calcium reversal were performed as in Group I.

Results. In the control group, CO decreased by 32% (p < 0.01) and dp/dt/40 decreased by 40% (p < 0.01) following exposure of 1% halothane. Systemic vascular resistance (SVR) was unchanged (Table I). In Group II, 45 min after administration of 2 mg/kg verapamil, hemodynamic measurements were unchanged (Table I). Following exposure of Group II animals to 1% halothane, CO was unchanged. However, dp/dt/40 decreased by 26% (p < 0.05) while SVR decreased by 29% (p < 0.01). Infusion of CaCl2 in verapamil pretreated dogs increased serum ionized calcium (Ca++) from 1.83 ± 0.39 to 2.62 ± 0.43 (p < 0.01) mEq/L with no statistically significant change in CO, SVR, or LVEDP. However, dp/dt/40 increased from 73 ± 8.7% control to 108.6 ± 8.7% control (p < 0.02) (Table II).

Discussion. Effects of halothane in Group I are consistent with earlier studies in which heart rate was controlled. Following a dose of verapamil (Group II), whose hemodynamic effects were no longer apparent, halothane induced markedly different results. Contractility as measured by dp/dt/40 was similarly reduced in both groups; however, there was a large and statistically significant reduction in SVR in the verapamil pretreated group. This suggests prolonged subclinical effects of verapamil on the peripheral vasculature. Blood levels are undetectable and hemodynamic changes are gone by 30 min after single intravenous injection of verapamil in the dog. Maintenance of CO in the presence of a decreasing dp/dt/40 following halothane in Group II could be explained on the basis of the large decreases in SVR. In Group II, halothane depression was easily reversed with calcium infusion. Dp/dt/40 returned to control when mean Ca increased from 1.8 to 2.62 mEq/L. This prolonged interaction between halothane and verapamil is contrary to earlier studies. SVR returned to normal within 10 min of verapamil administration during 1% halothane anesthesia in that study. This difference could be explained on the basis of the order of administration of halothane and verapamil or possibly an interaction peripherally with pentobarbital.

Single intravenous doses of verapamil, as may be used intraperoperatively, produce persistent hemodynamic interactions in the dog anesthetized with pentobarbital. In this setting, halothane reduces SVR, preserves CO, and reduces contractility as measured by dp/dt/40. In the presence of verapamil, halothane induced myocardial depression is readily reversed by CaCl2 infusion. However, decreases in SVR are resistant to CaCl2 infusion, even at high levels of serum Ca++.

References.

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