Title: VERAPAMIL ATTENUATION OF THE MALIGNANT HYPERTHERMIA SYNDROME IN SUSCEPTIBLE PIGS

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Introduction. Calcium antagonists block the entry of extracellular calcium into cells. These drugs have been used most successfully to treat cardiovascular problems such as hypertension, angina pectoris, and cardiac arrhythmias (1). Smooth and cardiac muscle cells require the influx of extracellular calcium for excitation-contraction coupling to occur. In contrast, skeletal muscle cells contain large amounts of intracellular calcium stored in the sarcoplasmic reticulum (SR) and do not require an influx of extracellular calcium for excitation-contraction coupling to occur (1). In spite of this information, verapamil, a prototype calcium antagonist, was reported to prevent muscle contracture using an in vitro preparation of skeletal muscle strips from patients susceptible to Malignant Hyperthermia (MH) (2). An in vivo experiment was undertaken to further define the effectiveness of verapamil in preventing MH.

Methods and Materials. Eight Poland China pigs inbred to enhance susceptibility to halothane induced MH were obtained (3). Each pig was tested for susceptibility by monitoring core temperature (T°C) and muscle tone during a brief exposure to halothane and oxygen. All eight pigs were found to be highly susceptible as evidenced by a rapid increase in T°C and rigidity (4). The halothane was removed immediately and all eight pigs recovered uneventfully. One month later these same eight pigs were again exposed to halothane and nitrous oxide anesthesia. However, each pig received intravenous verapamil prior to (0.5 mg/kg loading dose) and during (0.035 mg/kg/min infusion) halothane exposure. These doses are roughly five times the recommended human doses for cardiovascular maladies. Core temperatures (T°C), electromyographic (EMG) activity, blood pressure (BP), heart rate (HR), and electrocardiogram (ECG) were monitored throughout. When surgical levels of anesthesia were obtained, a carotid artery cutdown was performed to facilitate BP and arterial blood gas (ABG) monitoring. The pigs were also intubated and ventilation controlled as soon as possible during the halothane-oxygen exposure.

Results. Verapamil in very high intravenous doses did not prevent MH in susceptible Poland China pigs. Each pig studied, when exposed to halothane experienced an increased T°C, rigidity, and metabolic abnormalities consistent with MH. However, the onset of signs and symptoms was significantly prolonged by verapamil. In the control group onset of signs of MH occurred within one to five minutes (mean 2) on exposure to halothane. T°C increase and rigidity were present early in all eight pigs. In the verapamil group, the onset of an increased T°C was slowed to twenty-five to forty-four minutes (mean 36) and rigidity slowed to twenty to fifty-five minutes (mean 38). In fact, in the verapamil group, all pigs initially had a decrease in core T°C when exposed to halothane (5°C to 21°C). Vital signs remained stable during this initial phase of cooling. ABG’s obtained during the cooling phase already showed metabolic abnormalities consistent with MH. There was then a phase of rapid T°C increase with tachycardia, hypotension, and severe metabolic disturbances. ABG’s obtained during hypercarbia (PCO2, 80 to 200), hypoxia (PO2, 40 to 80) and combined metabolic and respiratory acidosis (PH 6.6 to 7.3). All pigs tested eventually died of the syndrome.

Discussion. In MH, abnormal calcium disposition in the cell appears to be involved in the persistent muscle contraction and resultant "metabolic furnace" (5). Drugs such as Dantrolene and Proclainamide, that effect the disposition of intracellular calcium have been useful in the treatment of MH. Calcium antagonists have been suggested as possibly useful on the basis of in vitro experiments (2). This experiment suggests that Verapamil can slow down but not prevent MH in susceptible pigs. This is not surprising in that skeletal muscle contains a large pool of intracellular calcium. Even with calcium influx blocked, repeated cycles of contraction and relaxation, or in the case of MH, continuous contraction, can occur. Verapamil does cause vasodilatation (1) and vasodilatation slows the onset of MH (6). Yet, the eventual outcome is the same: Unrelenting utilization of oxygen and energy substrate, massive heat production, metabolic disturbances and eventual death. To be useful in MH, calcium antagonists would have to be more effective in modulating the disposition of calcium already inside the skeletal muscle cells.

References.