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Title : THE PHARMACOLOGIC MODEL OF MALIGNANT HYPERTHERMIA(MH)

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A Malignant Hyperthermia-like syndrome may be induced in laboratory rabbits by the administration of caffeine during halothane anesthesia.[1] The present studies further define the relation between pharmacologically induced and naturally occurring MH. To this end, CO_2 production, venous blood gas changes, the effect of dantrolene, pavulon, and enflurane were studied in the pharmacologic model of MH.

Methods. Rabbits were anesthetized with either halothane(1.2%) or enflurane(2%). After tracheotomy ventilation was controlled at a volume and rate sufficient to yield a control $Paco_2$ of 35 torr. Arterial and central venous catheters were placed from the femoral vessels. One hour later pancuronium (0.2 mg/Kg) was administered producing complete depression of indirect twitch. After this, all animals were ventilated and received caffeine 120 mg every 20 minutes until death. Five animals were anesthetized with halothane during caffeine administration (group I), 4 with enflurane during caffeine administration (group II) and 6 others were given dantrolene (3.5 ml/Kg) in the presence of halothane prior to pavulon and caffeine administration (group III).

Arterial and central venous blood gases, electrolytes, right hind limb tension, CO_2 production, and rectal temperature were measured. Body temperature was not permitted to fall below 38.5°C, by the use of intermittent external heating.

Results. Dantrolene by itself produced 70% twitch depression. Pancuronium produced 100% twitch depression for the duration of the experiment. As shown in figures 1 and 2 and the table, none of the animals developed elevation of muscle or rectal temperature. However, the animals in groups I and II displayed significant muscle rigidity after 3 doses of caffeine (360 mg); the dantrolene treated animals did not. CO_2 production rose significantly in all rabbits except those who received dantrolene.

In all groups, arterial Pco_2 remained unchanged or declined later in the experiment. However, venous Pco_2 rose steadily in all animals. All animals (regardless of dantrolene administration) experienced progressive metabolic acidosis and hyperkalemia. There was no difference in extent of elevation of venous Pco_2, decline in pH, or rise in serum K^+ among groups. Four of 6 animals treated with dantrolene survived 600 mg of caffeine, while only 2 of 5 untreated animals survived this dose of caffeine.

Discussion. This study shows in greater detail than before, the similarity between the pharmacologic model and naturally occurring MH. Progressive muscle rigidity, acidosis and hyperkalemia occurred during caffeine administration in both halothane and enflurane anesthetized rabbits. Both agents are known to be associated with naturally occurring MH. CO_2 production also increased, and the venous blood gas changes are similar to those noted in MH susceptible swine during an episode of MH.2 Failure of arterial Pco_2 to rise may be secondary to changes in cardiac output (not measured). Other have also noted delayed rise in Pco_2 in MH.[2] Paralysis with pancuronium did not afford protection from MH contrary to the suggestion of others,[3] nor did it aggravate MH. In this study, body temperature did not show a consistent rise during caffeine-halothane administration. This may be related to suppression by pancuronium of caffeine-induced seizure activity observed in unparalyzed rabbit.[1]

Dantrolene administration was associated with longer survival and diminished CO_2 production, but the degree of metabolic acidosis, hyperkalemia and muscle rigidity were not different between dantrolene and untreated animals. This would suggest that this dosage of dantrolene in the face of exposure to agents that provoke MH, provides only partial protection to MH. Treatment of MH should therefore include cessation of stimulating agents in addition to dantrolene administration.

The pharmacologic model of MH should be useful in evaluation of proposed treatment regiments in MH.

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TABLE I: Measurements during caffeine administration prior to (Pre) caffeine, after 360 mg caffeine and prior to last dose of caffeine (Final).

	Leg tension (g)			K+(meq/L)			Arterial pH		
	Pre	360 mg	Final	Pre	360 mg	Final	Pre	360 mg	Final
Group I N=6	119 ±6	132 ±6.4	135 ±21	4.6 ±.09	5.19* ±.48	6.15* ±1.5	7.30 ±.02	7.18* ±.04	6.96* ±.02
Group II N=6	115 ±6	136 ±8.4	138 ±18	4.5 ±.06	5.68* ±.49	6.17* ±1.2	7.34* ±.03	7.21* ±.06	6.93* ±.04
Group III N=5	120 ±8	118 ±6	131 ±20	4.36 ±.28	5.26* ±.46	8.09* ±.48	7.24 ±.04	7.13* ±.03	6.97* ±.04

*p< .01 compared to stabilization period by t test

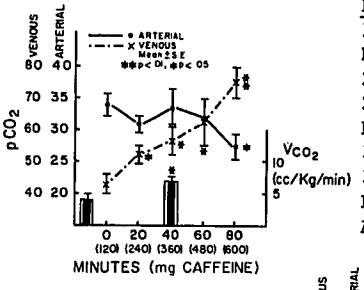

Figure 1: Arterial and venous Pco_2 and $\dot{V}_{CO_2}$ in rabbits given caffeine anesthetized with 1.2% halothane. Student's t test tested significance of differences between pre and post caffeine time periods.

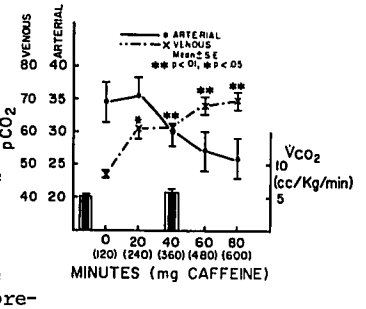

Figure 2: Same as figure 1, except animals were pretreated with dantrolene 3.5 mg/Kg.

References.

1. Durbin CG, Rosenberg H: J Pharm Exp Ther 210:70-74, 1979
2. Gronert GA, Theye RA: Anesthesiology 44: 36-43, 1976
3. Hall GM, Lucke JN, Lister D: Br. J. Anaesth 48:1135, 1976