Title : PORCINE MALIGNANT HYPERTHERMIA: A METHOD TO PRODUCE DANTROLENE PROPHYLAXIS AND THERAPEUSIS

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Introduction. This study tests the hypothesis that the 95 percent effective (ED_{95}) muscle relaxant dose of dantrolene intravenously provides prophylaxis (P) therapeusis (T) for malignant hyperthermia (MH) challenge in swine. Dantrolene has been shown P and T for MH in swine[1] and is recommended orally for suspect MH human patients prior to anesthesia[2]. A lyopholized intravenous dantrolene preparation is being evaluated for human MH crisis. Dantrolene dose necessary to achieve P and T in swine has varied between 1-10 mg/kg. Human dantrolene MH dose recommendations are empirical.

Methods.

Dantrolene Dose Response:

Foretoe flexion tension, indirectly stimulated, was quantitated and used to determine the dose response to intravenous dantrolene, 0.5 mg/kg/2 min. in 4 MH susceptible swine. Subjects breathed oxygen 100 percent spontaneously. Cardiopulmonary parameters monitored were: arterial pressure, CO_2, O_2, pH; electrocardiogram; peak exhaled CO_2; expired gas volume; and peak negative inspiratory effort. Thiopental anesthesia was used.

Dantrolene Prophylaxis and Therapeusis:

Four other MH swine each underwent three separate MH challenges. MH challenge was succinylcholine, 1 mg/kg, i.v. and halothane, 1.5 percent, inspired after thiopental induction. Before the first challenge the ED_{95} dantrolene dose, 3.5 mg/kg, i.v., was given. Inspired halothane was reduced to 1.0 percent after 30 min. and discontinued after 60 min. and subjects allowed to recover. After MH had become established from the second challenge, halothane was discontinued and dantrolene (ED_{95} dose) was given intravenously. Subjects were hyperventilated with oxygen without any additional therapy and allowed to recover spontaneously after 60 min. After MH had become established from the third challenge, halothane was discontinued, hyperventilation instituted and no therapy given. Monitored parameters during these three MH challenges were: indirectly evoked foretoe twitch tension; arterial lactate, pressure, CO_2, O_2, pH; electrocardiogram; peak exhaled CO_2; and rectal temperature. Student's T test was used for paired data and analysis of variance for group data. P values < 0.05 were considered significant.

Results.

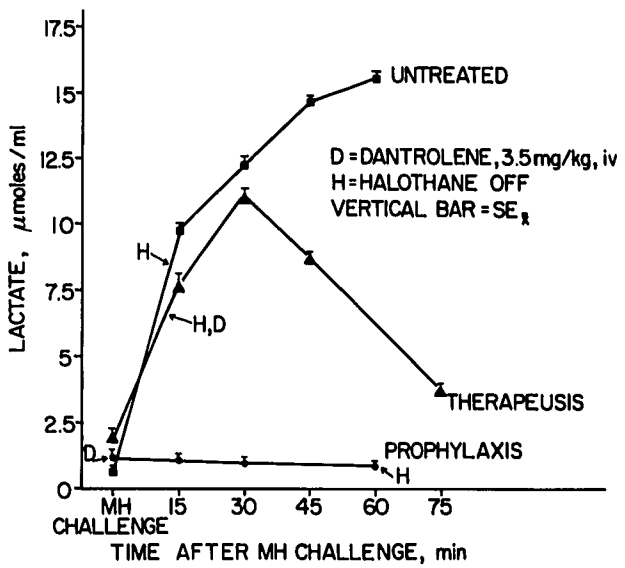
Dantrolene Dose Response:

The ED_{95} relaxant dantrolene i.v. dose was determined to be approximately 3.5 mg/kg producing 93 percent twitch depression. Dantrolene total dose was 7.5 mg/kg. No significant change in monitored cardiopulmonary parameters was observed.

Dantrolene P and T:

None of the subjects given dantrolene P showed signs of MH. Arterial lactate and oxygen were stable, and rectal temperature fell. Twitch depression produced by dantrolene did not differ from that of the dose response group. All P subjects recovered uneventfully. All of the T subjects developed MH when challenged the second time within 15 min. The ED_{95} dantrolene dose produced twitch depression similar to the dose response group. Arterial lactate rose significantly, then fell rapidly after dantrolene administration. Dantrolene successfully reversed the syndrome and all T subjects recovered. All subjects developed MH when challenged a third time within 16 min. The severity of the syndrome was comparable to that of the previous MH episode. Arterial lactate rose significantly and remained elevated. All subjects died within 70 min.

Discussion. We confirmed our hypothesis that the dantrolene ED_{95} relaxant dose is prophylactic and therapeutic for a porcine MH challenge. The changes in arterial lactate,



a sensitive indicator of increased MH muscle metabolism, supports these conclusions. Dantrolene did not produce cardiopulmonary depression. We propose that in any MH subject the attainment and maintenance of dantrolene maximum indirectly evoked twitch depression should render the individual in a P and T condition for MH. The muscle relaxant dose response to oral or intravenous dantrolene has not been ascertained in man. When determined, the ED_{95} dose would provide a basis for initial dose recommendations in human MH subjects.

References.

1. Gronert GA, Milde JH, Theye RA: Dantrolene in porcine malignant hyperthermia. Anesthesiology 44:433-495, 1976
2. Pandit SK, Kothary SP, Cohen PJ: Orally administered dantrolene for prophylaxis of malignant hyperthermia. Anesthesiology 50:156-158, 1979