Title: DANTROLENE DOSE RESPONSE IN AWAKE MAN

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Introduction. Dantrolene sodium (DS), an inhibitor of skeletal muscle electromechanical coupling is recognized as a therapeutic agent in malignant hyperthermia (MH) in man.1,2 Current therapeutic dose recommendations are empirical. We examined the muscle relaxant dose response in awake man to the lyophilized DS formulation. Concurrent cardiopulmonary response and pharmacokinetic data was obtained.

Methods. Subjects were twelve volunteers, nine males and three females, ranging in age from 28-59 years, weighing 76 kg mean (range 59-90). Indirectly evoked thumb adduction was quantitated by stimulating the ulnar nerve at the wrist with needle electrodes, using supramaximal voltage, frequency 0.1 Hz, and duration 0.4 msec. Hand grip strength (GS) and subjective weakness (SW) score (0-10; full strength, 0=paralyzed) were monitored. Cardiopulmonary function was assessed by quantifying forced vital capacity (FVC), peak expiratory flow rate (PEFR), percent end-tidal carbon dioxide concentration (ETCO₂), mean arterial pressure (MAP) by Dinamap device, and heart rate (HR). Dantrolene 33 mg/kg was given in bolus 0.1 mg/kg doses every 5 min until the twitch had not decreased for three doses (plateau). Following each cumulative 0.2 mg/kg dose, venous blood was obtained for whole blood dantrolene level (DBL). Subjects had intermittent assessment of GS, SW, and DBL for 48 hours following initial dantrolene. Statistical significance was assumed at the p<.05 levels.

Results. Dantrolene dose response, percent twitch depression versus cumulative dose, is shown in Figure 1. Plateau depression was reached between 2.2 - 2.5 mg/kg. Mean maximal depression was 75 percent (range 63-85%). GS was significantly depressed after 0.4 mg/kg and remained so for 24 hr. Maximal depression was 60 percent of control. SW score was 5 immediately following DS and subjects did not feel that strength was fully recovered for 48 hr following last DS. ETCO₂ was not affected. MAP increased and HR remained unchanged. Peak DBL was 4.2 μg/ml and calculated blood T½ was 12.1 hr.

Discussion. The ED₉₅ twitch depressant dose of DS has proven prophylactic and therapeutic for an MH anesthetic challenge in pigs.3 We conclude that DS, 2.5 mg/kg, would be similarly effective in man. What duration of protection would be expected from this dose? In our subjects, DS 1.6 and 1.4 mg/kg produced 95 and 93 percent maximal twitch depression respectively. The blood levels after these doses were 2.8 and 2.4 μg/ml, preceding to these blood levels by 10 to 13 hours following initial dantrolene. Thus, MH susceptible patients are predicted to have protection for 13 hours following DS 2.5 mg/kg iv.

DS 2.5 mg/kg was found efficacious in therapy of acute MH crisis in man.2 Approval for this project was obtained from the local Institutional Review Board.

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References.

Figure 1. Dose-response relationship obtained with dantrolene, iv., given in 0.1 mg/kg-1 incremental doses every 5 min while monitoring percent depression (DE) of indirectly evoked adductor pollicis twitch in awake man. Cumulative dantrolene shown on a logarithmic scale. Straight line represents least squares regression line for cumulative doses through 1.1 mg/kg.