Dantrolene sodium was administered intravenously to 12 adult volunteers to assess muscular and cardiopulmonary response. Pharmacokinetic results were obtained from whole blood drug concentration. Indirectly evoked thumb adduction was quantitated. Hand-grip strength and subjective weakness score (10 equal to full strength, 0 equal to paralyzed) were assessed. Cardiopulmonary variables included forced vital capacity (FVC), peak expiratory flow rate (PEFR), percentage of end-tidal carbon dioxide (ETCO₂), indirect mean arterial pressure (MAP), and heart rate (HR). Commercially available dantrolene for intravenous administration 0.55 mg/ml was administered in bolus doses of 0.1 mg/kg every 5 min until a plateau in twitch depression was achieved. Monitored variables were assessed either after each dose or following each cumulative 0.2 mg/kg dose over approximately 2 h. Intermittently during the subsequent 46 h, grip strength, subjective weakness, and blood levels were assessed. An average maximal twitch depression of 75% was reached at 2.2–2.5 mg/kg cumulative dantrolene dose. Significant depression of grip strength was observed after a dantrolene dose of 1.0 mg/kg and remained for 20 h. Subjective weakness was 4.7 after dantrolene and slowly returned to 10 by 48 h. FVC and PEFR were not depressed significantly from control levels. ETCO₂, MAP, and HR were unchanged. Maximum dantrolene blood level was 4.2 µg/ml at 2.9 h after the initial dantrolene dose. A near steady state existed for 5.5 h following the last dantrolene dose with a blood level of 3.6 µg/ml. Then blood levels declined slowly following first-order kinetics with a 1/2 elimination of 12.1 h. Based on these results, the authors predict that the acute intravenous administration of dantrolene, 2.4 mg/kg, will achieve MH prophylaxis or therapeutics in humans. (Key words: Hyperthermia; malignant. Neuromuscular relaxants; dantrolene. Pharmacokinetics: dantrolene.)

DANTROLENE SODIUM (Dantrium®), an intracellular muscle relaxant,¹ has become recognized as a prophylactic and therapeutic agent in human malignant hyperthermia (MH).²–⁶ Dose recommendations for treatment of this disorder using a lyophilized formulation of dantrolene sodium for parenteral use are empiric. In swine, a near maximal twitch depressant dantrolene dose produced a state of prophylaxis and therapeutics for MH.⁷ Although dose-response studies for oral dantrolene have been accomplished,⁸ dose response for intravenous dantrolene in humans has not been reported. This study determines the relationship between the intravenous dose of lyophilized dantrolene and depression of adductor pollicis muscle twitch in awake man. Concurrent response of cardiopulmonary variables and pharmacokinetic information was obtained. Results allow for better recommendations for the management of MH-susceptible patients.

Methods

Subjects were 12 volunteers ranging in age from 28–59 years (mean 35.7 ± 2.8 SE) weighing 75.8 kg ± 3.5 SE (range 57–90). There were nine men and three women. All were in good health, taking no medication, and had normal physical examinations referable to neurologic and cardiopulmonary systems. The acute phase of the experiment was carried out in the Anesthesiology Research Laboratory, then subjects were observed overnight in the Clinical Research Center of the University of Texas Medical Branch, Galveston, Texas.

This study was approved by the Institutional Review Board of the University of Texas Medical Branch, Galveston, Texas. Informed consent was obtained from each subject.

After the subject assumed a semirecumbent position, intravenous catheters were placed in each antecubital fossa, the right for dantrolene administration, the left for intermittent blood sampling, using a heparin flush system.

Following bupivacaine, 0.5%, field block, two 25-gauge needle electrodes were placed subcutaneously over the right ulnar nerve just proximal to the wrist. Thumb adduction was quantitated using a Stanec Adductor Pollicis Monitor transducer and hand restraint.** A Grass Model S48 stimulator was set to deliver 1.5 times voltage for threshold of maximal stimulus (0.1 Hz, 0.04 ms duration), and resting tension of the adductor pollicis was adjusted to 100 g. Twitch tension

---

** Stanec, Inc., 15 Secor Road, Scarsdale, New York 10583.
was recorded on a Gould Model 2400. A train of four consisted of four stimuli administered 0.5 s apart (2 Hz). Grip strength, kg, was quantitated in the left hand with a Jamar Hand Dynamometer and head lift was assessed by asking subjects to maintain neck flexion for 5 s.

Systolic and diastolic blood pressure, pulse rate, and mean arterial pressure (MAP) were obtained using a Dinamap Model 845. Electrocardiogram was monitored continuously with a Datasec Model 870. Forced vital capacity (FVC) and peak expiratory flow rate (PEFR) were obtained using a Hewlett-Packard 9825A computer, 4730A flow transducer, and 2107B pneumotachograph. End-tidal carbon dioxide (ETCO₂) was monitored for 1 min at the mouthpiece with a Perkin-Elmer 1100 mass spectrometer, and from the resultant wave form on a Gould 2400 Recorder, respiratory rate was counted. A control period of 1 h prior to dantrolene administration was used to establish monitoring and obtain baseline values.

Dantrolene was reconstituted by adding sterile water, 60 ml, to a vial containing dantrolene, 20 mg, mannitol, 5 g, and sufficient sodium hydroxide to yield a pH of approximately 9.5. The final concentration was dantrolene 0.33 mg/ml. Adequate drug was dissolved and pooled in an empty plastic iv solution bag (Travenol) to administer 2.5 mg/kg to each subject. Bolus iv dantrolene doses 0.1 mg/kg, were given every 5 min until the twitch tension had no further decrease following three successive injections (plateau in dose response). Except for the initial two subjects, recovery of muscle function was not assessed because of slow recovery of twitch and associated discomfort from nerve stimulation and immobility.

Measurements were begun 2 min following any dose, allowing time for dantrolene effect on twitch tension to stabilize. After every dose twitch tension, blood pressure, MAP, pulse rate, train of four, ETCO₂, and respiratory rate were recorded. Subjects were questioned about any subjective alteration of mental status. After each odd dose, beginning at 0.1 mg/kg, head left was assessed. After each even dose beginning at 0.2 mg/kg, grip strength, FVC, and PEFR were recorded and a 5-ml sample of heparinized venous blood was obtained for determination of whole blood dantrolene level, utilizing a spectrophotofluorometric technique. After dantrolene produced maximal twitch tension depression, subjects walked approximately 30 meters. Twitch, blood pressure, and ECG monitoring were discontinued. A subjective weakness score was obtained by having the volunteer rate overall strength by responding to the command, "Rate how much strength you have now," ranging from 10 (full) to zero (paralyzed). Subjects were observed closely for the next 4 h. Every 30 min after the last dantrolene dose, the following were monitored: grip strength, dantrolene blood level, FVC, PEFR, and subjective weakness. Six hours after the first dantrolene dose, the acute monitoring phase of the experiment was terminated and subjects walked 200 meters to another area for overnight observation and the evening meal.

Grip strength, dantrolene blood level, and subjective weakness score were obtained at 7, 8, 9, 10, 11, 12, 16, 20, 24, 28, 32, and 48 h following the initial dantrolene dose in the last nine subjects.

Subjects had the following clinical laboratory determinations done within 2 weeks before the study, then repeated 1 month after dantrolene administration: hemoglobin, hematocrit, white blood cell count, urinalysis, glucose, alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), cholesterol, blood urea nitrogen (BUN), phosphorus, calcium, creatinine, bilirubin, uric acid, creatine phosphokinase (CPK), and pregnancy test on women.

Mean values at each cumulative dantrolene dose and at various times after dantrolene were compared with the mean control value by the method of Dunnett. Changes in variable responses versus blood dantrolene levels were compared by regression analysis. Student's paired t test was used to compare biochemical values before and after dantrolene administration. Significance was assumed at the P < 0.05 level. Values are expressed as mean ± standard error of the mean (SE) unless otherwise indicated.

Results

NEUROMUSCULAR

An exponential relationship was observed between percentage of depression of twitch tension and cumulative dantrolene dose (Fig. 1). Cumulative dantrolene dose to achieve a maximal twitch depression (plateau) was 2.4 ± .03 mg/kg and varied among subjects as follows: 2.2 (n = 1), 2.3 (n = 5), 2.4 (n = 1), and 2.5 (n = 5) mg/kg. Following each dose, twitch tension reduction stabilized by 2–3 min, and there was no recovery before the next dose. Dantrolene administration occurred over approximately a 2-h period. Averaged among subjects, maximal twitch depression was 75.3 ± 1.4% (range 69–85%). No difference in dose response was observed in men versus women. There was poor correlation between maximal twitch depression and body weight (r = 0.2). In the two subjects in whom twitch recovery was followed, by 6 h after last dantrolene dose, one had recovered from 85 to 67% twitch depression, and by 3 h, the other had recovered from 69 to 57% blockade.
Grip strength progressively diminished with dantrolene dose (Fig. 2). The average control grip strength was 37 kg ± 2.9. Significant depression was observed over doses ranging from 1.0–2.4 mg/kg and remained depressed after initial dantrolene for at least 20 h (Fig. 2). Maximal depression in grip strength was 42 ± 4% (range 18–60%) and occurred after dantrolene 2.2 mg/kg (Fig. 2). Subjectively, subjects rated weakness as 4.7 ± 0.5 immediately after the last dantrolene dose and did not report a feeling of normal strength until 48 h after initial dantrolene (Fig. 3). All subjects complained of fatigue at 24 h. Strength by this time was subjectively normal in the arms but weakness was present in the legs and was noted especially while walking down stairs. Grip strength correlated very well with subjective weakness score during recovery (r = 0.91). Train-of-four (T4) ratio was not changed significantly from control after any drug dose. Initial T4 ratio was 0.94 ± 0.02 and after the final dantrolene dose it was 0.95 ± 0.02. Head lift was performed easily and successfully without fade at all doses tested.

CENTRAL NERVOUS SYSTEM

Central nervous function was altered subjectively in all subjects. Description of this effect varied among dizzy, floating, and lightheaded. Subjects rated the alteration from minimal to marked immediately after the last dantrolene dose. The alteration progressively diminished and was absent by 48 h. Four subjects noted a definite increase in effect when moving the head, which was described as a dysequilibrium. Nausea and vomiting occurred in one subject, 5 h after completion of the dose response. Bilateral ptosis was noted in eight subjects. Difficulty swallowing the evening meal and one episode of choking was related by one subject 10 h after the last dantrolene dose was administered.

RESPIRATORY AND CARDIOVASCULAR

Peak expiratory flow rate, vital capacity, end-tidal carbon dioxide, and respiratory rate did not change significantly during dantrolene administration. Similarly, there were no significant changes in mean arterial pressure or heart rate.

A Wenckebach heart block was observed in one subject during the dose response when the sinus rate fell...
below 60 beats/min. The rhythm was not detected 24 h later during a 10-min monitoring period. Follow-up 24-h continuous electrocardiographic monitoring at 1 and 5 weeks after the study revealed the Wenckebach rhythm during sleep at slow sinus rates.

**Pharmacokinetics**

As dantrolene administration proceeded, an essentially linear increase in whole blood dantrolene concentration was observed. Maximum blood dantrolene concentration of $4.2 \pm 0.2 \mu g/ml$ (±SD) occurred at 2.9 ± 1.0 h after the first dose (Fig. 4). Essentially, a near steady state existed for about 5.5 h after the last dose, with a mean blood dantrolene level of $3.6 \pm 0.2 \mu g/ml$. Although blood dantrolene levels relatively were unchanged in each subject, an overall trend for a decrease in the blood dantrolene concentration was observed during this period. Subsequently, the blood dantrolene level slowly declined following first-order kinetics with a $t_{1/2}$ elimination of $12.1 \pm 1.9$ SD h based on the terminal linear portion of the blood drug concentration–time curve (Fig. 4). A mean of the coefficients of correlation of $-0.981$ (range from $-0.968$ to $-0.992$) was determined for each subject between the logarithms of the blood drug levels and the corresponding blood collection times for the terminal linear portion of the blood drug elimination curve. The mean of the residual blood dantrolene concentration present from 20–24 h after initial drug dose was $1.7 \mu g/ml$, while the mean of that present from 48–50 h was $0.3 \mu g/ml$ (Fig. 4).

**Correlation with Blood Dantrolene Level**

High correlation coefficients were observed between increasing blood dantrolene concentration and percentage of depression of grip strength, $r = 0.95$ (Fig. 5) and percentage of depression of twitch, $r = 0.91$ (Fig. 5). During recovery, fall of blood dantrolene concentration correlated well with return of grip strength, $r = 0.95$, but grip strength return preceeded blood level decline (Fig. 5).

**Biochemical**

Serum enzyme levels tended to be higher within 1 month following dantrolene administration, but significant differences could not be declared when compared with predantrolene levels. Serum SGOT changed from $24 \pm 2$ to $32 \pm 4$ IU/l, SGPT changed from $26 \pm 4$ to $40 \pm 11$ IU/l, serum LDH changed from $141 \pm 9$ to $149 \pm 5$ IU/l, and CPK changed from $119 \pm 18$ to $155 \pm 23$ IU/l.

**Discussion**

Previous studies in swine showed that a dose of intravenous dantrolene (3.5 mg/kg), which was 95% of the maximal muscle depressant dose, proved both prophylactic and therapeutic for a halothane-succinylcholine anesthetic challenge. The threshold effective dose for MH management would be difficult to determine experimentally in swine and ethically impossible to discover in humans. However, in the present study in humans, the dose of dantrolene that produced maximal
muscle depression was 2.4 mg/kg, which resulted in a
dantrolene blood level of 4.2 µg/ml and a mean twitch
depression of 75%. Dantrolene doses of 1.4 and 1.6
mg/kg produced 93% and 95% of maximal depression
associated with dantrolene blood levels of 2.4 and 2.8
µg/ml, respectively. These blood levels were observed
between 10 and 13 h after initial drug dosage (Fig. 4).
We predict that patients receiving dantrolene, 2.4 mg/
kg, would have a similar duration of perianesthetic MH
prophylaxis or therapy. Based on the prolonged
half-life of blood dantrolene, it is tempting to suggest
that a prophylactic blood level would exist 10–13 h after
initial drug dosing (Fig. 4). However, caution is neces-
sary in this interpretation for several reasons. First, al-
though a good relationship was observed between twitch
depression and blood dantrolene levels during drug ad-
ministration, this relationship is unknown for the elim-
nation phase for dantrolene. Second, it has been re-
ported to us (J. Conklin, Biopharmaceutics Unit, Nor-
wich Pharmaceuticals, personal communication), that
2.4 mg/kg dantrolene administered intravenously over
shorter periods of time resulted in shorter half-life.
Dantrolene dose response in malignant hyperthermia-
susceptible and normal swine is not different.11 We
assume that a similar relationship exists in humans. These
results provide a basis for less empiric dantrolene pro-
phylactic and therapeutic management of MH in hu-

A multi-center study to establish the efficacy of in-
travenous dantrolene in the acute therapy of MH crisis
has been reported.2 All of the patients who developed
clinical evidence of MH survived when dantrolene was
administered promptly. The mean dose of dantrolene
that was needed to reverse the crisis was 2.5 mg/kg.
This supports the findings of our study and our rec-

Clinicians have administered oral dantrolene sodium
capsules in single doses of 1–2 mg/kg four times a day
for one or two days preoperatively for prophylaxis of
MH.4,5,12 Blood dantrolene levels achieved with these
doses are unknown, and a failure of oral dantrolene
therapy to prevent MH in humans has been reported.12
A single oral dose of 100 mg in eight adults produced
only 49% twitch depression, with a peak blood level of
1.2 µg/ml.8 However, the time to peak blood level var-
ed among subjects from 1–12 h. In six children who
received oral dantrolene 4–12 mg · kg · day−1 for two
weeks, blood level plateaued at less than 2 µg/ml after
2–3 days.13 These doses are in the range suggested for
MH prophylaxis,5–5 but the blood level is below that we
predict adequate for MH management. Four paraplegic
adults who received oral dantrolene, 400 mg/day, for
several weeks did reach blood levels (3 µg/ml) that we
would predict adequate for MH prophylaxis.14 Thus,
current recommendations for oral dantrolene in MH
prophylaxis may be inadequate in some patients.

In addition to the uncertainty of how humans absorb
and metabolize orally administered dantrolene, gas-
testinal side effects (i.e., nausea, vomiting, and diar-

Fig. 5. Percentage of depression of adductor pollicis twitch strength
(○), hand grip strength during dantrolene administration (●), and
hand grip strength during recovery from drug effect (■), versus whole
blood dantrolene, µg/ml. Values are mean ± SEM.

Heptic injury has been reported as a complication of the long-term dantrolene administration in a small
percentage of patients.18,19 Liver function as measured by SGOT and SGPT did not change during this acute
dantrolene exposure.
Because of the limitations of oral dantrolene medication for MH prophylaxis, we believe an alternative approach is to administer preoperative dantrolene immediately before anesthetic induction. We would pool enough vials of reconstituted lyophilized dantrolene in a sterile container to provide a 2.4 mg/kg dose. The contents would be infused over 10–15 min. Intravenous administration rapidly will achieve a more predictable dantrolene blood level with consequent twitch depression than will oral administration. Our study results suggest that the prolonged dantrolene blood level following 2.4 mg/kg will provide protection of adequate duration for the MH-susceptible patient for most surgical procedures. For initial acute treatment of an MH crisis in humans, we would bolus inject a similar total dantrolene dose as rapidly as the lyophilized vials could be reconstituted. With this dantrolene dose gastrointestinal side effects are alleviated and cardiopulmonary depression is not expected.

Oral administration of dantrolene has been recommended after an MH crisis to prevent recrudescence. However, many patients will have alteration of gastrointestinal physiology, which may preclude oral therapy. An alternative approach could be continued intravenous dantrolene therapy in the postanesthetic period. No respiratory depression was observed in volunteers who were awake. However, the postoperative MH patient will likely have additional depression produced by drugs and pain and should be monitored intensively.

Acute intravenous administration of dantrolene 2.4 mg/kg, in healthy humans carries minimal morbidity and moderate economic cost. The drug cost can be weighed against the cost of additional hospitalization. It has become common practice to hospitalize known MH-susceptible patients for one or two days before surgery while they are receiving oral dantrolene therapy. Added hospitalization also will be required if MH occurs because of inadequate dantrolene blood levels after oral dosing.

Individual vials containing 20 mg lyophilized dantrolene and 5 g mannitol require 60 ml sterile water for reconstitution. Most MH patients should weigh less than 100 kg. We recommend that 13 vials of drug be immediately available for administration. When administered, a urinary catheter for bladder decompression should be in place before diuresis commences.

In conclusion, humans who are awake achieve maximal skeletal muscle depression of 75% when given dantrolene, 2.4 mg/kg, intravenously. Based on previous studies, this degree of resultant muscle depression is considered adequate to prevent malignant hyperthermia during most anesthetic administrations. For initial therapy of acute MH crisis, the rapid intravenous administration of a similar dose is recommended. Significant cardiopulmonary depression is not expected.

The authors thank Pat Huber, Pat Turk, Deborah Willingham, G. L. Holovac for technical assistance and Mary Jane Kelly for clerical assistance. They thank John Conklin for assistance with pharmacokinetic data and Mary Elizabeth Kolb and Dennis Worthen for review.

References