

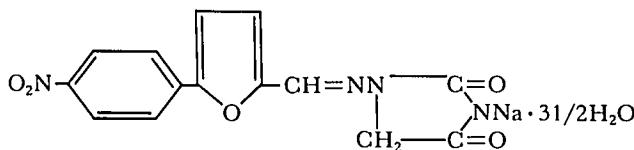
Dantrolene in Human Malignant Hyperthermia

A Multicenter Study

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Anesthesiologists from 65 institutions participated in a multicenter study to assess the efficacy of lyophilized intravenous dantrolene sodium in treating anesthetically related malignant hyperthermia (MH). Of 21 patients treated with the drug, eight were judged to have unequivocal MH and were treated according to study protocol. Three were judged to have probable MH and were also treated according to study protocol. All 11 recovered without sequelae from MH and without adverse drug effects. A mean dantrolene dose of 2.5 mg/kg in these patients produced significant changes in clinical and biochemical parameters suggestive of decreased cellular metabolism. Four patients with unequivocal MH were treated with intravenous dantrolene more than 24 h after the diagnosis of MH; this delay in treatment excluded them from the protocol. Although there was some reversal of clinical signs in these patients, the mortality rate was 75 per cent, which is comparable to that reported without dantrolene. The six remaining patients had episodes of questionable MH during or subsequent to anesthesia and were treated with dantrolene. There was insufficient evidence to justify an unequivocal or probable diagnosis of MH, and they, therefore, were not included in the study. All survived and had no adverse drug reactions. Dantrolene therapy resulted in a statistically significant lower mortality rate than would be expected in MH patients. The study supports animal data suggesting that dantrolene is specific in reversing MH. (Key words: Complications: malignant hyperthermia. Hyperthermia: malignant. Neuromuscular relaxants: dantrolene.)

Dantrolene sodium¹ is hydrated: 1-[[(5-(4-nitrophenyl)-2-furanyl)methylene]amino]-2,4-imidazolidinedione sodium salt; it has low water solubility and high lipid solubility and therefore crosses cell membranes easily. The structural formula for the hydrated salt is:



The drug is a direct-acting skeletal muscle relaxant in that it dissociates excitation-contraction coupling in the muscle by inhibiting the release of calcium ions from the sarcoplasmic reticulum (SR) through actions on the transverse tubular membrane-SR coupling, on SR directly, or on both.² At therapeutic doses, the drug acts specifically on skeletal muscle and has no appreciable

effect on cardiac or smooth muscle. It has been demonstrated to be effective in porcine models of MH, which are similar to human MH.³⁻⁶

The need for human clinical trials to establish the efficacy and safety of dantrolene in treating human MH was apparent. Since the incidence of MH has been reported as ranging from 1:15,000 to 1:50,000 patients exposed to general anesthetics,⁷ a multicenter approach offered the best chance of evaluating the efficacy of intravenous dantrolene in a sufficient number of patients in a relatively short period of time.

Materials and Methods

This was an unblinded study from September 1977 to May 1979 with anesthesiologists from 65 institutions in the United States and Canada acting as investigators. All of the investigators committed themselves to a standardized protocol and case report form which were approved by the appropriate Institutional Review Boards. Every investigator was given sixty vials of drug, each containing a sterile lyophilized mixture of 20 mg dantrolene sodium, 3,000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 ml sterile water without preservatives.

Correct diagnosis of MH and adherence to protocol methodology were essential to evaluation of drug therapy. However, the clinical signs of MH vary in kind and degree, and the facilities and procedures for monitoring and laboratory tests differ among institutions. Furthermore, a crisis situation makes data collection and timing of laboratory tests difficult. Therefore, all cases reported from the study were reviewed by anesthesiologists considered expert in MH.

Clinical evidence (*e.g.*, tachycardia, dysrhythmia, muscle rigidity, increased temperature, cyanosis and/or mottling) prompted a suspicion of MH. The diagnosis was usually established by acid-base analysis and occasionally, when blood gases were not drawn, by correlation of the clinical picture with results of muscle biopsy (caffeine-halothane contractures). Presence of myoglobin in the urine and rise in CPK furnished additional evidence of skeletal muscle damage. Patients who had a cardiac arrest or delay of more than 6 h prior to treatment with intravenous dantrolene were excluded from statistical analysis.

Protocol therapy included stopping all inhalational

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TABLE I. Protocol Treated MH Patients

History	Early Signs of MH	Confirmatory Signs	Treatment*	Results Within 30 min	Comments
Category A: Unequivocal MH-Primary Presenting Signs-					
Patient 1 Female White 12 yr Weight 36.5 kg Pancoectomy with ileostomy Induction: halothane, $\text{N}_2\text{O}-\text{O}_2$ Maintenance: above + pancuronium 3.6 mg	105 min after induction HR ↑ 130 → 160 → 230/min over 25 min and temperature from 37° to 41.1°C (over 15 min). PVCs were noted.	$pH = 6.92$ $\text{PCO}_2 = 98 \text{ mmHg}$ $\text{BE} = -15.2 \text{ mEq/l}$ Myoglobinuria.	Procainamide, 400 mg NaHCO_3 , 1.6 mg/kg Dantrolene, iv, 1.6 mg/kg	HR = 230 → 150 Temperature → 34.7°C $\text{PCO}_2 = 33 \text{ mmHg}$ $\text{BE} = -3.7$	- Recovered.
Patient 2 Female White 10 yr Weight 30 kg Dwyer procedure for scoliosis Induction: thiopental Maintenance: halothane, $\text{N}_2\text{O}-\text{O}_2$, <i>d</i> -tubocurarine	65 min after induction HR ↑ 100 → 125 → 140/min over 15 min, temperature from 34.8° to 36°C in 10 min. There was cyanosis + skin mottling.	$pH = 7.30$ $\text{PCO}_2 = 36 → 58 \text{ mmHg}$ $\text{BE} = -8.3 \text{ mEq/l}$	Iced Ringer's lactate Furosemide, 40 mg NaHCO_3 , 1.2 mEq/kg Dantrolene, iv, 2.7 mg/kg	$pH = 7.58$ $\text{PCO}_2 = 23 \text{ mmHg}$ $\text{BE} = -0.2$ Temperature = 36 → 34°C Normal skin color.	† CPK, 833 units. Recovered.
Patient 3 ¹² Male White 7 mo Weight 7 kg Excision of hemangioma-facial nerve graft Induction: fentanyl + thiopenal + pancuronium Maintenance: $\text{N}_2\text{O}-\text{O}_2$ + thiopenal + fentanyl	First Episode: 3 h after induction, temperature 36.5 → 37.6°C over a 40-min period, HR 130 → 160/min.	First Episode: 30 min after induction $pH = 7.25$ $\text{PCO}_2 = 35 \text{ mmHg}$ $\text{BE} = -11 \text{ mEq/l}$ 1 h after induction, $\text{PCO}_2 = 35 \text{ mmHg}$ $\text{BE} = -15 \text{ mEq/l}$	First Episode: NaHCO ₃ , 2.9 mEq/kg Droperidol No dantrolene	First Episode: Patient appeared to do well except for mild metabolic acidosis. Discharged to ward the following morning.	First Episode: Patient appeared to do well except for mild metabolic acidosis. Discharged to ward the following morning.
Patient 4 Male Black 18 yr Wt 85 kg Inguinal herniorrhaphy Induction: thiopental, sed	Second episode occurred in ward 24 h after surgery: HR 120 → 180/min, temperature 37.6 → 39°C despite cooling blanket.	Second Episode: $pH = 7.3$ $\text{PCO}_2 = 36 \text{ mmHg}$ $\text{BE} = -11 \text{ mEq/l}$ Positive muscle biopsy To produce 1 g tension <u>Patient</u> <u>Control</u> Caffeine 0.8 mM 6 mM Caffeine + halothane 0.3 mM 4 mM	Second Episode: Droperidol, 1.6 mg NaHCO_3 , 2.6 mEq/kg Dantrolene, iv, 7 mg/kg Oral, 1 mg/kg	Second Episode: Temperature dropped to 37°C, HR slowed markedly, BP stabilized and there was increased responsiveness.	No recognized anesthetic trigger. † CPK, 744 units. Recovered.
Patient 4 Male Black 18 yr Wt 85 kg Inguinal herniorrhaphy Induction: thiopental, sed	PVCs noted 5 min after induction. Within next 15 min BP unstable and HR from 75 → 110/min, temperature ↓ 37 → 38°C.	$pH = 7.1$ $\text{PCO}_2 = 86 \text{ mmHg}$ $\text{BE} = -7.3 \text{ mEq/l}$ Myoglobinuria.	Lidocaine, 50 mg Propranolol, 0.1 mg Cold IV fluids NaHCO_3 , 1 mEq/kg Furosemide, 100 mg Droperidol, 10 mg Dantrolene, iv, 1 mg/kg	In first 5 min after dantrolene admin., temperature dropped 1°C, NSR. After 20 min, temperature ↓ to 36.5°C $pH = 7.43$	† CPK, 141,400 units. Recovered.

TABLE 1. (Continued)

History	Early Signs of MH	Confirmatory Signs	Treatment*	Results Within 30 min	Comments
Maintenance: halothane, N ₂ O · O ₂	hypertension. Anesthesia discontinued 65 min after induction. At that time HR was 115/min and temperature 39°C. Despite cooling, temperature ↑ to 39.5°C		P _{CO₂} = 36 mmHg BE = -0.2 mEq/l HR = 130 → 97/min		↑ CPK, 300 units Patient had 12 previous anesthetics, nine with halothane, and three with sch. In three of these when anesthesia lasted over 2 h, temperature rose to 39.2°, 38.2° and 38.3°C. Recovered.
Category B: Unequivocal MH-Primary Presenting Sign—Rigidity, Fever, Dysrhythmia or Tachycardia Patient 5 Female White 21 yr Weight 43 kg Intermaxillary fixation osteotomy Induction: thiopental, sch Maintenance: halothane, N ₂ O · O ₂ , enflurane	85 min after induction PVCs noted and continued intermittently for next hour. Temperature 37 → 38.9 → 40°C despite cooling, HR 118 → 200/min, rigidity of extremities, cyanosis and skin mottling.	pH = 7.10 P _{CO₂} = 88 mmHg BE = -5.7 mEq/l	NaHCO ₃ , 3.5 mEq/kg Furosemide, 50 mg Fentanyl, 3 ml Fentanyl + droperidol, 1 ml Dantrolene, iv, 1.1 mg/kg	HR 200 → 150 → 103/min NSR Temperature 40 → 39.1 → 37.2°C pH = 7.33 P _{CO₂} = 56 mmHg BE = +1.8 mEq/l Normal skin color. Normal muscle tone.	↑ CPK, 300 units Oral dantrolene given 3 days postoperatively. Recovered.
Patient 6 Male White 25 yr Weight 68 kg Open reduction-acromioclavicular separation Induction: thiopental, d-tubocurarine, sch Maintenance: halothane, N ₂ O · O ₂	No untoward effects observed during surgery of 55 min duration. Shortly after transfer to recovery room, patient was breathing shallowly and became cyanotic despite breathing 100 per cent O ₂ . Apnea-IPPV started with bag. During the next hour temperature ↑ from 36 → 38.3°C, HR from 85 → 190/min with hypertension. Became extremely restless and rigid. Pupils were dilated.	pH = 7.34 P _{CO₂} = 30 mmHg BE = -8.5 mEq/l	Naloxone, 0.4 mg Hydrocorisone, 16 mg NaHCO ₃ , 0.7 mEq/kg Furosemide, 20 mg Cold Ringer's lactate Dantrolene, iv, 3.8 mg/kg	HR 190 → 1115/min Temperature 38.3 → 36.9°C BP 190/125 → 120/65 mmHg pH = 7.42 P _{CO₂} = 37 mmHg BE = -0.2 mEq/l Normal skin color. Normal muscle tone.	

TABLE 1. (Continued)

History	Early Signs of MH	Confirmatory Signs	Treatment*	Results Within 30 min	Comments
Patient 7 Male White 18 yr Weight 69 kg Recurrent patellar dislocation Induction: thiopental Maintenance: halothane, $N_2O \cdot O_2$	About 50 min after induction. HR from 80 → 170/min, Temperature 1.37 → 39.5 → 42.3°C. Moderately severe rigor. Diffuse muscular swelling.	$pH = 7.27$ $P_{CO_2} = 57$ mmHg $BE = -2.7$ mEq/l Myoglobinuria.	Procainamide Chlorpromazine, 10 mg Cooled iv fluids Lidocaine, 100 mg Dantrolene, iv, 2 mg/kg (3 h after first symptoms)	↓ HR ↓ Temp Normal muscle tone. Normal skin color.	Mitral insufficiency documented by echocardiography. Cardiac isoenzymes markedly ↑ for several days. Remained comatose for 12 h. Recovered.
Patient 8 Female White 26 yr Weight 77 kg Endolymphatic sac compression and drainage. Emplacement of ear valve. Induction: thiopental, sc Maintenance: enflurane, $N_2O \cdot O_2$	Surgery lasted about 3.5 h. Anesthesia was uneventful with vital signs in normal range. Transferred from RR to ward about 3 h after surg. Shortly after temperature ↓ to 39 → 40°C despite vigorous cooling. HR 1 from 80 → 105/min. Shivering, rigor, cyanosis of extremities.	$pH = 7.33$ $P_{CO_2} = 36$ mmHg $BE = -6$ mEq/l	Morphine, 2 mg Dantrolene, iv, 2.6 mg/kg	HR 105 → 75/min Temperature 40 → 37.9°C Normal skin color.	
Patient 9 Female White 3 yr Weight 12 kg Diagnostic biopsy for MH Induction: droperidol + fentanyl Maintenance: $N_2O \cdot O_2$, diazepam				First Episode: Metabolic acidosis reported but first ABG were done 20 min after dantrolene iv admin. $pH = 7.36$ $P_{CO_2} = 39$ mmHg $BE = -2.5$ mEq/l	First Episode: HR = 165 → 100/min NSR Temperature = 38 → 36.5°C Normal muscle tone.
				Second Episode: $pH = 7.37$ $P_{CO_2} = 36$ mmHg $BE = -5.3$ mEq/l	Second Episode: Recovered.
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TABLE 1. (Continued)

History	Early Signs of MH	Confirmatory Signs		Treatment*	Results Within 30 min	Comments
		Positive muscle biopsy	Patient Control			
Patient 10 Male White 14 yr Weight 66 kg Appendectomy Induction: thiopental, sch, d-tubocurarine Maintenance: enflurane, N ₂ O · O ₂	all vital signs stabilized. 90 min later temperature ↑ to 38.6° and over next 50 min to 39°C. RF 1.30 → 56/min. Moderate rigidity and severe respiratory distress.	Caffeine 3.5 mM ≥ 4.1 mM Caffeine + 1 percent halo-halothane 0.52 mM ≥ 1.2 mM	Iced Ringer's lactate Dantrolene, iv, 1.8 mg/kg	Dantrolene, iv, 1.3 mg/kg	HR = 120 → 85/min Stabilization of BP Temperature ↓ to 37.9°C ρ H = 7.33 P_{CO_2} = 39 mmHg BE = +5 mEq/l	Normal muscle tone. Minimally abnormal EMG. Blood cultures: negative. Recovered.
Patient 11 Female White 3 yr Weight 15 kg Chiari Pelvic osteotomy Induction and maintenance: halothane, N ₂ O · O ₂	During intubation, patient was described as "bucking," 15 min after induction temperature was 38.5°C. Despite vigorous cooling, temperature ↑ over next 15 min to 39.2°C. HR ↑ to 135/min, hypertension, and RF 20 → 40/min.	ρ H = 7.30 P_{CO_2} = 42 mmHg BE = -6.5 mEq/l Myoglobinemia.	Dantrolene, iv, 2 mg/kg	ρ H = 7.3 P_{CO_2} = 39 mmHg BE = -6 mEq/l	HR = 190 → 160/min Temperature 39 → 37.4°C ρ H = 7.38 P_{CO_2} = 34 mmHg BE = -2.30 mEq/l	1 CPK, 328 units Recovered.

* Symptomatic treatment—Surface cooling and hyperventilation used in addition to Rx listed.
HR = heart rate; RF = respiratory frequency; PVC = premature ventricular contractions;

NSR = normal sinus rhythm; IPPV = intermittent positive pressure ventilation; and RR = post anesthesia recovery room.

TABLE 2. Unequivocal MH-Delayed Treatment with Dantrolene

History	Signs of MH	Confirmatory Signs	Treatment	Results	Comments
Patient 12 Female White 34 yr Weight: 63 kg Forefoot reconstruction, Bunionectomy. Induction: thiopental. Maintenance: halothane, $\text{N}_2\text{O} \cdot \text{O}_2$	Throughout the first 45 min of anesthesia HR and BP ↑ to 140/min and 160 mmHg. At 75 min there was apnea. (Intubated with sch. Taken to recovery room. Ventilation supported with a Bird respirator). 100 min after induction temperature was 40.5°C. with rigidity of extremities and opisthotonus. Excessive sweating and coma. 1 h later EKG showed ST segment depression. 2.5 h later urine output was 0. The next morning patient was deeply comatose with decerebrate rigidity. Urine formation resumed. 28 h after first symptoms of MH, patient transferred from ICU to Respiratory Failure Unit. Was comatose with rigid skeletal muscles, decerebrate posturing, fixed and moderately dilated pupils, temperature 39°C, HR 180/min, multifocal ventricular arrhythmias, syst. BP 45 mmHg, profuse intermittent sweats, violent ineffectual respiratory efforts >40/min, P_{CO_2} 38 mmHg, BE -2.5 mEq/l, dark brown urine.	$\text{pH} = 7.29$ $\text{P}_{\text{CO}_2} = 42 \text{ mmHg}$ $\text{BE} = -6 \text{ mEq/l}$	Mannitol 20 per cent Dopamine drip (only treatment reported until transfer) After transfer: Procainamide, 700 mg Propranolol, 10 mg Chlorpromazine, 50 mg Hydrocortisone, 2000 mg Dantrolene, iv, given for 21 days in doses ranging from 50–100 mg q4h	Alleviation of rigidity ↓ Temperature to 36°C ↑ BP to 105 mmHg ↓ HR to <100/min Attempts to reduce dantrolene dose resulted on each occasion in ↑ temperature.	↑ CPK, 3,096 units never regained consciousness. Survived for 44 days with massive brain damage. Expired-massive pneumonia.
Patient 13 Female White 15 yr Weight: 67 kg Arthroscopy-right knee Induction: thiopental. Maintenance: halothane, $\text{N}_2\text{O} \cdot \text{O}_2$	2 h anesthesia without incident. 10 h after surgery: temperature 38.2°C. First day: Edema and discoloration of right leg. Third day: temperature 39.9°C, HR 140/min, anuria. Fourth day: temperature 39.5°C, HR 160/min, BP not detectable. Fifth day: temperature 42°C, HR 166/min, hyperkalemia, CPK 63,-850; markedly ↑ prothrombin time. Sixth day: temperature 39.8°C, RF 40–50/min, ↑ BUN and serum creatinine. Dialysis started. Lactate level 12.5 mEq/l (N = 0.2–2.2 mEq/l), CPK 131, 700 units, SGOT 1800 U/l.	$\text{pH} = 7.24$ $\text{P}_{\text{CO}_2} = 36 \text{ mmHg}$ $\text{BE} = -16 \text{ mEq/l}$	Antibiotics Antipyretics Dopamine Mannitol NaHCO_3 , Furosemide Nitroprusside Seventh day: Dantrolene, iv, 1.5 mg/kg	With administration of 1 mg/kg of dantrolene, Temperature ↓ from 39.5 → 37.2°C and remained down for 12 h without cooling or antipyretics. BP and HR stabilized. Mild acidosis persisted for 10 h. 24 h later additional dantrolene was given when temperature ↑ to 39°C. Again there	↑ CPK, 156,900 units Urine, sputum, blood cultures: negative. Australia Antigen:negative. Had three subsequent anesthetics using $\text{N}_2\text{O} \cdot \text{O}_2$ -metocurine without difficulties. Recovered.

TABLE 2. (Continued)

History	Signs of MH	Confirmatory Signs	Treatment	Results	Comments
Patient 14 Male White 20 yr Weight 75 kg Decompression after severe head trauma (brain stem contusion and subdural hematoma) Induction: sch Maintenance: N ₂ O · O ₂ , fentanyl + droperidol	Seventh day: temperature 40°C, edema of leg I, persistent hyperkalemia and I serum creatinine. Patient diahzed, CPK 156,900 units, SGOT 2190. At the time patient was anesthetized for emergency burrholes-BP 160/85 mmHg, HR 120/min, RF 35/min, ABG normal except BE -6. Jaw rigid on intubation then developed generalized muscular rigidity. During next 1.5 h temperature ↑ to 41°C, HR 175/min, RF 40/min. Anesthesia discontinued. Despite cooling, temperature to 41.5°C. Vital signs stabilized and temperature ↓ to 36.9°C. During next 2 h temperature ↑ rapidly to 39°C, HR 160/min, BP 170/110 mmHg. After 6 h dantrolene via nasogastric tube administered. Transferred to MH Center the next day. After transfer, BP became erratic, and temperature ↑ from 37.2 to 38.9°C. Treated and vital signs stabilized. Subdural hematoma evacuated the day following transfer. Had multifocal ventricular arrhythmias attributed to MH throughout hospitalization.	pH = 7.46 P _{CO₂} = 23.5 mmHg BE = -6 mEq/l Biopsy Patient Control Caf-fine 4.2 mM 4.1 mM Caf-fine + 1 per cent halothane 0.95 mM 1.2 mM	Hydrocortisone, 100 mg q4h NaHCO ₃ , 0.6 mEq/kg Procainamide, 145 mg Pancuronium, 8 mg Dantrolene (oral), 2.7 mg/kg Diazepam, 5 mg Fentanyl + droperidol, 4 mg Cimetidine, 1500 mg Mannitol, 500 ml Dantrolene, iv, 40 mg (Administered 48 h after first signs of MH. Subsequently given in 20 to 40 mg doses q4h for 10 days)	After oral dantrolene, 3-456 units Had a strongly positive MH family history Developed leukocytosis and sputum cultures revealed the presence of klebsiella, pseudomonas sepatia and haemophilus influenza. Pulmonary complications developed 3 or 4 days before death. Survived 14 days post-MH without regaining consciousness. Expired pneumonia.	
Patient 15 ^s Male White 20 yr Weight 104 kg Reduction of closed, comminuted fracture of left tibia and fibula Induction: thiopental, sch Maintenance: halothane, N ₂ O · O ₂ , pancuronium	Vigorous fasciculations were noted with sch and intubation was difficult 10 min after induction esophageal temperature ↑ to 42.4°C. Hypotension, cyanosis, ectopic ventricular beats, generalized rigidity.	pH = 6.96 P _{CO₂} = 73 mmHg BE = -18 mEq/l Myoglobinuria.	First Episode: Cold IV saline NaHCO ₃ , 2 mEq/kg Procainamide, 300 mg Lidocaine, 100 mg Dopamine 10-20 µg/kg/min Furosemide, 100 mg Mannitol, 5 g No dantrolene	↑ CPK, 4,472 units First Episode: 12 h later patient was awake and asking for food. Cardiovascular dynamics were stable, respiratory function good and acidosis corrected. Condition remained stable for 1st 20 h except for slight muscle rigidity, ↓ fluid needed to maintain	
			First Episode: pH = 6.96 P _{CO₂} = 73 mmHg BE = -18 mEq/l Myoglobinuria.		

TABLE 2. (Continued)

History	Signs of MH	Confirmatory Signs	Treatment	Results	Comments
	Second Episode: 21 h after 1st episode there was massive edema of 1 leg and a fasciotomy was done. Pt. treated for diffuse intravascular coagulation. Profuse oozing from incision. 38 h after 1st episode, pt. became apprehensive, had masseter spasm and became cyanotic, dyspneic and tachypneic. Cardiac arrest in 20 min. Serum K 14.2 mEq/l, temp. 36°C	Second Episode: P _{CO₂} = 58 mmHg BE = -10 mEq/l Muscle biopsy demonstrated markedly diminished calcium uptake into sarcoplasmic reticulum.	Second Episode: Cardiopulmonary Bypass Dialysis Procainamide, 15 mg/kg Mannitol NaHCO ₃ , Insulin Dantrolene, iv, 11.5 mg/kg Given over 4 h period	CVP. Inadequate urinary output Second Episode: Lowering of serum K 14.2 → 8.8 → 6.6 mEq/l with spontaneous defibrillation of heart. Patient could not be weaned from cardiopulmonary bypass. 2nd cardiac arrest. Resuscitative efforts discontinued.	Expired-Pulmonary edema Heart failure

BUN = Blood Urea Nitrogen.

anesthetic agents and skeletal muscle relaxants, hyperventilation with 100 per cent O₂, cooling, Na bicarbonate, and dantrolene in repeat doses of 1 mg/kg by rapid intravenous administration until evidence for MH disappeared. Adjunctive drugs included furosemide and mannitol to maintain urinary output, insulin, and glucose to lower elevated serum potassium, KCl to correct hypokalemia, and procainamide for dysrhythmias.

The incidence of anesthetic-induced MH was thought to be extremely low. Therefore, a modified skew-restricted sequential statistical design was used.⁸ An expected mortality rate of 50 per cent⁴ was assumed. The recovery rate with dantrolene sodium would achieve statistical significance if there were seven survivors of seven confirmed MH cases. If deaths occurred, the number of survivors needed for statistical significance increased to 20 survivors of 27 confirmed cases. The design has (one-sided) significance level $\alpha = 0.025$ and power $1-\beta = 0.95$ of detecting a difference between a dantrolene survival rate of 85 per cent and the projected survival rate of 50 per cent.

Results

During a period of 18 months, 21 patients with apparent MH were treated with intravenous dantrolene by 16 anesthesiologists in the study. Eight patients had good evidence supporting the diagnosis of unequivocal MH and were treated promptly (patients 1–8, table 1). Three patients were diagnosed as probable MH and were treated promptly (patients 9–11, table 1). Four patients were diagnosed as unequivocal MH, but were treated late (table 2). These four patients therefore were excluded from the study: three of these four died. All eleven patients with unequivocal or probable MH who were treated promptly survived. In these 11 patients, the dose of dantrolene was 2.5 ± 0.5 mg/kg (mean, \pm SE). Six of the 21 patients were uncategorized as they had equivocal episodes unlikely to be MH. Since all survived, and since no adverse effects were reported after dantrolene, details on these patients are not reported. In the 11 patients retained in the study, the common early symptoms were tachycardia (four patients) and muscle rigidity (four patients). Increased temperature and cyanosis or skin mottling occurred in 11 patients and five patients, respectively. One patient (patient 5, table 1) had had nine prior exposures to triggering agents and became febrile in three of these.

Discussion

Fifteen patients with probable or unequivocal MH were identified, and eleven of these were treated promptly with iv dantrolene. Of these, eight had an unequivocal diagnosis of MH and three presented a less certain clin-

ical picture and therefore were deemed "probable" for MH. Regardless of whether one accepts eight or 11 MH patients, there were no deaths. This satisfies the statistical requirement for significance. Significant changes in clinical and biochemical signs suggestive of decreased cellular metabolism were evident in all patients within the first half hour after intravenous dantrolene administration. No sequelae from MH or adverse effects from dantrolene were reported.

In contrast, dantrolene was administered intravenously to four patients more than 24 h (more than 6 h by nasogastric tube in one patient) after the diagnosis of MH and after many measures had been used to reverse the crisis. There was some reversal of abnormal physiologic and biochemical parameters after dantrolene administration. However, the mortality rate was 75 per cent, which is comparable to that reported without dantrolene.⁷ Since dantrolene acts directly on skeletal muscle, its delivery through the vascular system to the site of action is imperative. Impairment of peripheral circulation and irreversible cellular changes were probably major factors in the poor survival rate of these patients and reinforce the need for early diagnosis and treatment. This conclusion is supported by the results in Patient 7, table 1. Administration of intravenous dantrolene was delayed three hours, and this young man was comatose for 12 h, but eventually recovered completely.

MH occurred in 13 patients exposed to recognized triggers. However, as has been reported,⁹⁻¹¹ it also occurred in two subjects not exposed to known triggers. Symptoms were delayed until after anesthesia had been discontinued in three patients, and MH recurred after an initial episode in four patients. These findings suggest that stress may be a factor in triggering or recrudescence.^{12,13}

Information provided on the six patients placed in the equivocal category was insufficient to justify a diagnosis of MH. However, all six did have multiple signs that suggested MH. In at least some of these patients, dantrolene may have been administered before clinical signs of a fulminant syndrome fully developed. In the future, early treatment of MH with dantrolene may obscure sharp lines in differential diagnosis.

Based on this study, dantrolene therapy resulted in a statistically significant lower mortality than would be expected in this group of MH patients without the use of dantrolene; this supports animal data suggesting that dantrolene is specific. There would seem to be a wide margin of safety in the dose range of approximately 1–7 mg/kg, since no adverse effects were reported.

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