Malignant Hyperthermia Following Preoperative Oral Administration of Dantrolene

Desiray C. Fitzgibbons, M.D. *

Management of a patient with malignant hyperthermia (MH) continues to challenge the anesthesiologist. The following case is that of a patient in whom symptoms of MH developed despite his having received the recommended anesthetic regimen and preoperative oral administration of dantrolene.

REPORT OF A CASE

An 11-year-old, 30-kg boy who had a diagnosis of atraumatic, noncongenital retinal detachment with secondary cataract was scheduled for cataract extraction and possible scleral buckling. Medical history was negative except for an uneventful patent ductus ligation at 3 months of age with rectal thiopental followed with halothane–nitrous oxide–oxygen anesthesia. Family history was unattainable, as the patient was adopted.

Meperidine, hydroxyzine, and glycopyrrolate were given im for premedication. Anesthesia was induced with thiopental, halothane, 0.5 per cent inspired, and d-tubocurarine, 1.5 mg. Generalized fasciculations followed the intravenous administration of succinylcholine, 50 mg. One minute later, trismus prevented laryngoscopy. The pulse rate had increased from 100 to 130 beats/min; however, body temperature was unchanged. Analysis of venous blood gases showed no abnormality. Except for the patient's complaint of generalized myalgia on the following day, the postanesthetic course was uneventful. Creatine phosphokinase (CPK) levels were obtained in the operating room (158 U/L), 18 hours later (2,118 U/L), and at one week (114 U/L). (Normal CPK is 15–19 U/L). Based on the trismus following succinylcholine administration and the elevated CPK value, the patient was considered to be susceptible to malignant hyperthermia.

Three weeks later, the patient received dantrolene sodium, 25 mg, q.i.d., orally for the 48 hours prior to operation. This dose produced complaints of muscle weakness by the patient. Preoperative electrocardiogram, CPK, and electrolytes were within normal limits. An anesthesia machine was purged with 6 l/min of oxygen for 40 hours after the halothane vaporizer had been removed. Fresh soda lime and a new anesthetic circuit, mask, and endotracheal tube were used. The patient was premedicated with pentobarbital, 60 mg, im at 6 A.M. Anesthesia was induced at 8:15 A.M. by the intravenous administration of droperidol, 5 mg, fentanyl, 0.1 mg, and thiopental, 250 mg. The inspired oxygen concentration was 100 per cent. After intravenous administration of pancuronium, 2 mg, the trachea was sprayed with 5 per cent cocaine. Intubation of the trachea was easily accomplished, and breath sounds were equal. Esophageal temperature was monitored. Droperidol, 1.5 mg, fentanyl, 0.05 mg, and thiopental, 250 mg, were given iv by 8:35 A.M. The patient was hyperventilated with oxygen, 3 l/min, and nitrous oxide, 7 l/min, at 20 l/min. Temperature during induction was 36.5°C in the esophagus; it was 37.4°C rectally. Pulse rate and arterial blood pressure (BP) were 100 beats/min and 110/70 torr, respectively, at the start of induction. Rotor transtentatively following the surgical incision, then decreased to 85 beats/min and 105/65 torr over the next 30 min.

After insertion of a radial arterial catheter, analysis of arterial blood-gas values at 8:40 A.M. showed pH 7.50, Pco2 24 torr, Po2 175 torr, and HCO3 19 meq/l. From 8:45 to 9:30 A.M. temperatures were unchanged. Between 9:00 and 9:15 A.M., fentanyl, 0.05 mg, iv, was given. From 9:15 to 9:30 A.M., pulse rate increased to 100 beats/min and BP to 120/60 torr. There was no change when thiopental 75 mg, and fentanyl, 0.05 mg, were given iv. At 9:30 A.M., the 9:15 A.M. blood-gas results were received: pH 7.23, Pco2 63 torr, Po2 67 torr, and HCO3 26 meq/l. The cataract extraction had been completed and the surgeons had just decided not to proceed with scleral buckling.

Vigorous hyperventilation was begun with 100 per cent oxygen. Pulse rate at 9:35 A.M. was 120 beats/min and BP was 140/80 torr. Drugs administered between 9:35 and 9:50 A.M. included sodium bicarbonate, 50 meq; dantrolene sodium, 30 mg; furosemide, 50 mg; procainamide, 450 mg (over 10 min); mannitol, 12.5 g; 50 per cent dextrose, 20 ml; regular insulin, 20 units. At 9:45 A.M., pulse rate had returned to 100 beats/min and BP to 120/80 torr. The patient remained afebrile. Arterial blood-gas values at 9:50 A.M. were pH 7.68, Pco2 23 torr, Po2 455 torr, and HCO3 26 meq/l. At 10:10 A.M., the nerve stimulator showed four equal twitches with train-of-four stimulation. Naloxone, 0.4 mg, iv, was given in divided doses until good respiratory effort was achieved. The trachea was then extubated and the patient taken to the recovery unit by 10:25 A.M.

The patient was sleeping and pink, with administration of 10 l/min oxygen by face mask. Blood pressure was 110/60 torr, pulse rate 122 beats/min, respiratory rate 24/min, and rectal temperature 35.9°C. At 10:30 A.M., arterial blood-gas values were pH 7.25, Pco2 67 torr, Po2 360 torr, and HCO3 28 meq/l. Pulse rate was 130 beats/min. Repeat arterial blood-gas values at 10:40

---

* Staff Anesthesiologist, Group Health Cooperative of Puget Sound Hospitals; Auxiliary Faculty, Department of Anesthesiology, University of Washington, Seattle, Washington.

Accepted for publication July 24, 1980.

Address reprint requests to Dr. Fitzgibbons: Department of Anesthesiology, Group Health Hospital, 2700—152nd Avenue, NE, Redmond, Washington 98052.

Key words: Hyperthermia; malignant pyrexia. Neuromuscular relaxants: dantrolene.
A.M. were pH 7.23, P_{CO_2} 69 torr, P_{O_2} 354 torr, and HCO_3 28 mEq/L. Pulse rate was 144 beats/min and respiratory rate was 32/min. The skin had become cyanotic and mottled. At 10:50 a.m., the patient received dantrolene sodium, 30 mg, i.v. Values for arterial blood drawn at 10:55 a.m. were pH 7.33, P_{CO_2} 49 torr, P_{O_2} 296 torr, and HCO_3 25 mEq/L. Pulse rate had decreased to 120 beats/min and respiratory rate to 24/min. Temperature remained unchanged. At 11:30 a.m., arterial blood-gas values were pH 7.36, P_{CO_2} 42 torr, P_{O_2} 341 torr, HCO_3 23 mEq/L. During the next three hours in the recovery unit, the patient's condition remained stable.

For three days, the patient received dantrolene sodium, 25 mg, orally, q.i.d. Results of analyses of serial serum samples for arterial blood-gas values, CPK, electrolytes, creatinine, calcium, and myoglobin were all within normal limits. The patient was discharged 72 hours postoperatively.

**DISCUSSION**

This case involved a phenomenon not previously reported: development of an episode of malignant hyperthermia following oral pretreatment with dantrolene and administration of an anesthetic suggested by most to be non-triggering.

After the first anesthetic administration MH was diagnosed because of the trismus, tachycardia, and elevated CPK. Skeletal muscle abnormalities were not found; however, retinal detachment has been seen in people susceptible to malignant hyperthermia.

The tachycardia, hypercarbia, and respiratory acidosis that occurred intraoperatively were considered manifestations of malignant hyperthermia, because the level of controlled ventilation had remained the same, breath sounds were unchanged, and there was no noticeable change in airway resistance. Pulse rate and BP increased despite minimal and constant surgical stimulation and a deepening of the anesthesia. A review of cases of MH shows a great variety of initial signs and magnitudes of changes from normal. Donlon et al. reported the cases of two patients anesthetized with halothane and succinylcholine. An 8-year-old child developed tachycardia, with pulse rates as high as 136/min, and analysis of arterial blood showed pH 7.13, P_{CO_2} 77 torr, and P_{O_2} 450 torr. The second patient was a 56-year-old whose pulse rate was 108 beats/min with arterial blood-gas values of pH 6.80, P_{CO_2} 180 torr, and P_{O_2} 245 torr. Bloom et al. reported the case of a 10-year-old who developed a pulse rate of 130/min after administration of halothane and succinylcholine. Faust et al. suspected a 6-month-old infant of being susceptible to MH. Despite administration of a "non-triggering" anesthetic, the patient developed metabolic acidosis and had tachycardia, with a pulse rate of 160 beats/min from a baseline of 130 beats/min. Mayhew et al. reported the case of another 6-month-old infant, who developed a fever after halothane–succinylcholine anesthesia, followed by a pulse rate increase from 110 beats/min to 160 beats/min. With an inspired oxygen concentration of 100 per cent, arterial blood-gas values were pH 7.03, P_{CO_2} 86 torr, and P_{O_2} 57 torr. The most recent case reviewed was that reported by Pan et al., in which the triggering agents were enflurane and succinylcholine. The 35-year-old patient developed slight tachycardia (from 80 to 96 beats/min) three hours after induction of anesthesia, and eventually had a temperature of 42°C.

The lack of fever, metabolic acidosis, or any elevation of serum CPK and myoglobin values could have been due to the combination of pre- and postoperative oral administration of dantrolene, the use of a "non-triggering" anesthetic regimen, and the prompt treatment with intravenously administered dantrolene once symptoms occurred. Rosenberg and Ryan feel that respiratory acidosis occurs first from an overproduction of carbon dioxide. Later, metabolic acidosis results from anaerobic metabolism. The hypermetabolism of this patient's skeletal muscle was probably blunted by the orally administered dantrolene and then stopped by the intravenously administered dantrolene in the initial stages.

The cause of the triggering is unknown. Faust et al. reported a similar case, except that the patient had not received dantrolene orally in the preoperative period. Stress has been reported to cause MH, and may have been a factor in this case despite preoperative sedation.

Oral prophylactic administration of dantrolene has been recommended for patients based on its successful prevention of porcine MH. Suggested dosage schedules vary according to individual preferences. Pandit et al. used 1.7 mg/kg, q.i.d., for three days. Reiton suggests working up to 2 mg/kg in divided doses by the second and third days. Free and Jaimon report a case of a patient given 1.4 mg/kg dantrolene four hours preoperatively. Two hours later the patient vomited. To avoid this problem, the authors suggested starting at 0.05 mg/kg to 1.0 mg/kg per dose and increasing to 2 mg/kg in one to two days. Finally, Gronert et al. reported a case in which the patient developed symptoms of MH while awake. Orally administered dantrolene was used as treatment, rather than prophylaxis. The therapeutic oral dose was 1.1 to 2.2 mg/kg total. It may be that

---

each patient's effective prophylactic and therapeutic
doses are related to the penetrance of his MH gene
and vary with the precipitating factors of each episode.

In summary, a case is presented in which the pa-
tient was diagnosed as malignant hyperthermia-
susceptible following trismus with succinylcholine and
an elevated CPK. Despite preoperative oral admin-
istration of dantrolene and neurolept-anesthesia, MH
was triggered during the second exposure to
anesthesia. Following successful treatment, the pa-
tient had a recrudescence of symptoms and was
again treated successfully, this time with intravenously
administered dantrolene only.

References

1. Relton JES: Anesthesia for elective surgery in patients
susceptible to malignant hyperthermia, International Anes-
thesiology Clinics: Malignant Hyperthermia. Edited by BA
Britt. Boston, Little, Brown, 1979, pp 141–151

2. Ryan JF: Treatment of acute hyperthermia crisis, Inter-
ational Anesthesiology Clinics: Malignant Hyperthermia.
Edited by BA Britt. Boston, Little, Brown, 1979, pp 153–168

masseter spasm after succinylcholine. ANESTHESIOLOGY
49:298–301, 1978

4. Britt BA: Preanesthetic diagnosis of malignant hyper-
thermia, International Anesthesiology Clinics: Malignant
Hyperthermia. Edited by BA Britt. Boston, Little, Brown,
1979, p 77

5. Bloom DA, Fonskalsrud EW, Reynolds RC: Malignant hyper-
pyrexia during anesthesia in childhood. J Pediatr Surg
11: 185–190, 1976

6. Faust DR, Gergis SD, Sokoll MD: Management of suspected
malignant hyperpyrexia in an infant. Anesthesiol Clin
(Clev) 5:3:3–35, 1979

7. Mayhew JF, Rudolph J, Tobey RE: Malignant hyperthermia
in a six-month-old infant: a case report. Anesth Analg
(Clev) 57:262–264, 1979

8. Pau TH, Wollack AR, De Marco JA: Malignant hyper-
thermia associated with enflurane anesthesia: a case report.
Anesth Analg (Clev) 54:47–49, 1975

9. Wingard DW: Malignant hyperthermia—acute stress syn-
drome of man? Malignant Hyperthermia: Current Con-
cepts. Edited by EO Henschel. New York, Appleton-
Century-Crafts, 1977, pp 70–95

malignant hyperthermia by oral dantrolene, The Second
International Symposium of Malignant Hyperthermia.
Edited by JA Aldrete, BA Britt. New York, Grune and
Stratton, 1978, pp 499–507

11. Pandit SK, Kothary SP, Cohen PJ: Orally administered
dantrolene for prophylaxis of malignant hyperthermia.
ANESTHESIOLOGY 50:156–158, 1979

12. Free CW, Jaimon MPC: Pre-anesthetic administration of
dantrolene sodium to a patient at risk from malignant

hyperthermia: awake episodes and correction by dantrolene.

Anesthesiology
54:75–77, 1981

Segmental Effect of Morphine Injected into the Epidural Space in Man

Haruka Asari, M.D., Kazuji Inoue, M.D., Toshinari Shibata, M.D., Takehisa Soga, M.D.

Although narcotics have injected into the epidural
and subarachnoid spaces to produce analgesia, there
is no documentation whether the narcotic
analgesics applied in that fashion exert any segmental
effect clinically, as occurs with local anesthetic-
induced epidural or spinal anesthesia. This report
presents the results of a clinical study we have
performed to clarify the segmental effect of morphine
injected into the epidural space.

* Assistant Professor of Anesthesiology.
† Clinical Associate of Anesthesiology.
‡ Assistant in Anesthesiology.

Received from the Department of Anesthesiology, Yokohama
City University, School of Medicine, Mail Code: 292, 3-46
Urafunecho, Minamiku, Yokohama, Japan. Accepted for publication July 22, 1980.

Address reprint requests to Dr. Asari.

Key words: Analgesics, narcotic; morphine. Analgesia: measure-
ment. Anesthetic technique, peridural: lumbar; thoracic.

Materials and Methods

Fifty patients undergoing upper abdominal surgical procedures, including 36 gastrectomies and 14
cholecystectomies, were selected for this study. In all cases, skin incisions were made in sixth to eleventh
thoracic segments on the sensory dermatome. Be-
fore the operation, every patient consented to receive epidural injection for pain relief immediately after
termination of the operative procedure. Premedica-
tion consisted of atropine sulfate and diazepam, and
anesthesia was maintained by use of halothane, nitrous oxide, and pancuronium. After conclusion of
the surgical procedure and extubation of trachea,
an experimental solution was injected epidurally.
The patients were divided into two groups. They
received the epidural injections either at the level of
the tenth to eleventh thoracic interspace (Group I, high level) or at the level of the fifth lumbar and

0003-3022/81/0100/0075 $00.65 © The American Society of Anesthesiologists, Inc.