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Intravenous Dantrolene in a Patient with Myasthenia Gravis

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Myoneuropathies such as muscular dystrophy, myotonia, and central core disease may increase susceptibility to malignant hyperthermia (MH).§[1,2] However, susceptibility to MH has not been associated with myasthenia gravis (MG). While the neuromuscular effects of dantrolene have been studied in healthy adult volunteers,[3] the effects of this drug have not been described in a patient with MG. We, therefore, report the following case to describe the effects of dantrolene on neuromuscular function in a patient with MG.

REPORT OF A CASE

A 16-year-old girl with MG was admitted for a transcervical thymectomy. The patient had been in good health until approximately 20 weeks prior to admission when she noted difficulty chewing and upper-extremity weakness. She subsequently developed lower-extremity weakness, dysphagia, diplopia, and dysarthria. A repetitive stimulus test at the ulnar nerve (electromyogram) revealed a 21% decremental pattern diagnostic of a neuromuscular transmission defect. An elevated acetylcholine receptor antibody titer and a positive edrophonium test confirmed the diagnosis of MG. On admission, the patient was receiving pyridostigmine 60 mg qid. Her past medical history was unremarkable except for a history of chronic tonsillitis. At age 9 yr, she underwent a tonsillectomy with uneventful general anesthesia. There was a strong family history for malignant hyperthermia (MH). Eight close relatives had succumbed to this disorder, while nine others had survived episodes of apparent MH. The patient had refused to be tested for malignant hyperthermia susceptibility (MHS). She was 167.6 cm and weighed 54 kg. Arterial blood pressure was 110/70 mmHg, the heart rate was 88 beats/min, and her respiratory rate was 20 breaths per min. Preoperative creatinine phosphokinase was 73 U/l (normal less than 145 U/l). Other routine preoperative laboratory values were all within normal limits as were her forced vital capacity and forced expiratory volume in 1 s. Grip strength was assessed with a Jamar Adjustable Dynamometer® (Asimov Engineering Company, Los Angeles, California), and all pyridostigmine therapy was withheld from 4:00 P.M. on the day prior to surgery. No pyridostigmine was administered on the morning of surgery. Preanesthetic medication consisted of diazepam 5 mg po 90 min prior to planned surgery. On arrival in the operating room, premedication was supplemented with droperidol 2.5 mg and fentanyl 200 μg iv. In addition to routine monitoring aids, a 20-gauge catheter was inserted in the right radial artery for continuous blood pressure monitoring. Neuromuscular function was monitored by stimulating the ulnar nerve at the wrist *via* surface electrodes and recording the force of contraction of the adductor pollicis using a force transducer (Grass FT-10®).

Trains-of-four supramaximal stimuli (2 Hz; stimulus duration 0.2 ms) were delivered to the ulnar nerve. Prior to and following commencement of a dantrolene infusion, twitch responses were recorded. Dantrolene 100 mg (1.9 mg/kg) was administered iv over 40 min prior to the induction of anesthesia. Induction was achieved with fentanyl 300 μg and thiamylal 300 mg iv. Following ventilation with 50% nitrous oxide in oxygen, the trachea was intubated easily and without use of muscle relaxants. Thereafter, anesthesia was maintained with nitrous oxide, oxygen, and fentanyl. The anesthesia machine and ventilator used had not been previously exposed to potent inhaled anesthetics. Ventilation was controlled to maintain a normal end-tidal carbon dioxide tension, measured continuously by a mass spectrometer. Multiple blood-gas determinations were within normal limits and consistent with end-tidal carbon dioxide values. ECG, arterial blood pressure, heart rate, and temperature (esophageal, axillary) did not vary significantly during the intraoperative and postoperative periods. As an additional precaution, the patient had been placed on a hypothermia blanket, and an MH treatment cart with iced solutions was immediately available.

Several changes in neuromuscular function were observed following administration of dantrolene 1.9 mg/kg. An exponential relationship was observed between the percentage of depression of twitch tension and the cumulative dantrolene dose. Maximal depression occurred 45 min after the cumulative dose of dantrolene had been administered. Following administration of dantrolene, 1.9 mg/kg, a plateau phase of twitch depression (T_1/control) was reached, which persisted through the period of neuromuscular monitoring (fig. 1). The mean twitch depression (100 − twitch height in %) was 60% (range 52–68%, n = 11) during this plateau phase. Neuromuscular recovery was not seen during the period of neuromuscular monitoring. Train-of-four fade ratio (T_4/T_1) was not significantly changed from the control value (88%) until 110 min following administration of dantrolene 1.9 mg/kg. At 150 and 155 min, fade ratios were 66% and 50%, respectively.

The transcervical thymectomy procedure was completed in 114 min. Edrophonium 10 mg iv, administered at the conclusion of surgery, caused the fade ratio to improve only slightly (from 50% to 63%). Nine minutes after skin closure, the patient was responsive to verbal commands, breathing at a normal rate and tidal volume, able to lift her head off the bed for more than 5 s, and able to generate an inspiratory force greater than −25 cm H_2O. The trachea was then extubated, and the patient was transferred to the recovery room for further close observation.

In the recovery room, vital signs remained stable, and continuous rectal temperature monitoring revealed no significant changes from preoperative values. Respiratory rate varied from 12 to 20 breaths per min, and respirations were not labored. The patient remained sleepy but responsive, and no analgesics were administered in the recovery room. Grip strength, forced vital capacity, and one-s forced expiratory volume were assessed at 30-min intervals. There was significant

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§ McPherson EW, Taylor Jr CA: The King syndrome: Malignant hyperthermia, myopathy and multiple anomalies. American Journal of Genetics 8:159–165, 1981.

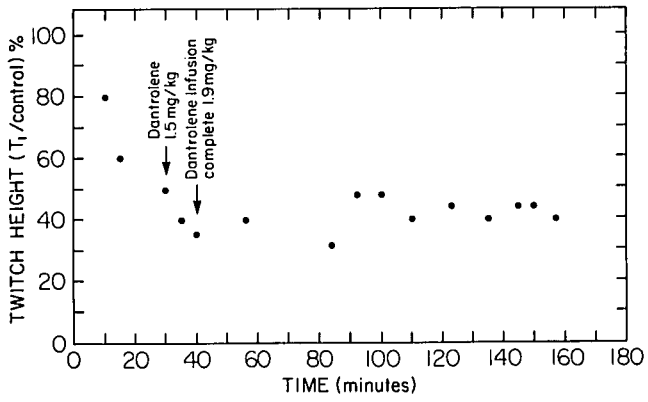

FIG. 1. Twitch height following infusion of dantrolene 1.9 mg/kg over 40 min.

depression of grip strength in the recovery room compared with control values obtained immediately prior to the administration of dantrolene (fig. 2). In the recovery room, the patient was administered 40% oxygen *via* face mask. One hour following completion of surgery, *p*H was 7.254, Pa_{CO_2} 52.8 mmHg, Pa_{O_2} 103.7 mmHg, and base excess (BE) was −4.5 mEq/l. Over the 2-h period following admission to the recovery room, grip strength steadily increased. Four hours after completion of surgery, the patient was given pyridostigmine 60 mg po with Jello®. This failed to improve neuromuscular function over the next 2 h as monitored by grip strength (fig. 2). However, head lift was performed easily, and there was no difficulty in swallowing 4 h following completion of surgery. At this time, *p*H was 7.341, Pa_{CO_2} 46.1 mmHg, Pa_{O_2} 91.5 mmHg, and BE was −0.9 mEq/l. The patient was fully responsive in the recovery room and offered no complaints of unusual weakness, disorientation, nausea, dysequilibrium, or respiratory distress. Forced vital capacity and forced expiratory volume in 1 s were 2.96 l and 2.08 l, respectively. At 280 min postinfusion of dantrolene and 160 min postcompletion of thymectomy, forced vital capacity and forced expiratory volume in 1 s were 1.50 l and 1.10 l, respectively.

Following 5 h of observation in the recovery room, the patient was transferred to the adolescent floor. The postoperative pyridostigmine

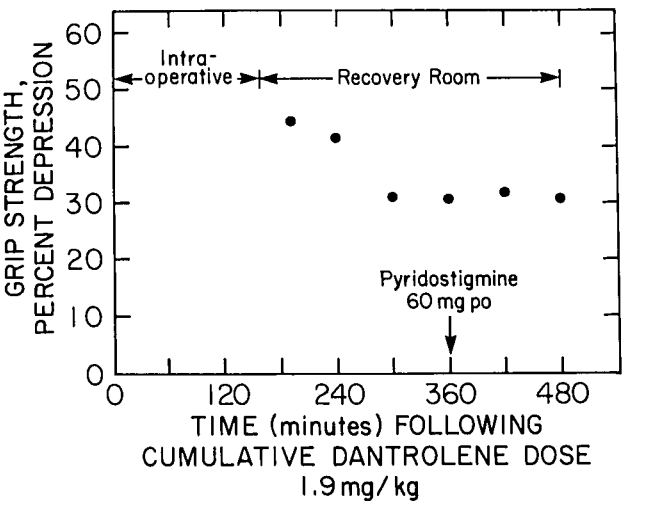

FIG. 2. Recovery of grip strength monitored by hand-held dynanometer following cumulative dose of dantrolene 1.9 mg/kg iv and lack of effect of pyridostigmine 60 mg po.

therapy was the same as the preoperative dose (60 mg qid). She had an uneventful postoperative course with no significant changes in temperature, muscle strength, respiratory function, or myasthenic condition. Creatinine phosphokinase values were 162 U/l and 139 U/l on the first and second postoperative days, respectively. There were no significant changes in SGOT, SGPT, or LDH. She was discharged on the fourth postoperative day. Eleven months following thymectomy, the patient showed considerable improvement, and her pyridostigmine dosage had been reduced to 60 mg bid.

DISCUSSION

The strong family history of MH dictated an anesthetic appropriate for an individual with MHS and documented MG. MH has not been previously described in a patient suffering from MG. A positive muscle biopsy in conjunction with histologic evidence and adenosine triphosphate (ATP) levels indicative of MHS would be necessary to confirm the coexistence of these two disease entities in this patient. Unfortunately, to date, the patient has refused to undergo a muscle biopsy. Fortunately, however, no signs of MH were manifested by this patient during the operative and perioperative periods.

This case afforded us the opportunity to evaluate the effects of dantrolene, a known muscle relaxant, in a patient with documented MG. MG is a neuromuscular disorder characterized by weakness and fatigability of voluntary muscles with improvement following rest. Studies using radioactively labeled bungarotoxin suggest that the muscle weakness is due to a marked reduction of acetylcholine receptor sites at the postsynaptic membrane. The myopathy in MH is distal to the neuromuscular junction and involves a generalized alteration in cellular and subcellular membrane permeability. This leads to an inability of the muscle cell to control calcium concentration within the muscle fiber.[4]

Dantrolene is a lipid-soluble hydantoin derivative that is thought to act within the muscle fiber.[5] Specifically, dantrolene acts on the contractile elements to attenuate calcium release without affecting uptake. It also acts on the connections between the transverse tubules and terminal cisternae of the sarcoplasmic reticulum.[6] Dantrolene 2.5 mg/kg iv causes subjective weakness and impairment of neuromuscular transmission in human volunteers,[3] therefore, we were concerned that the preoperative administration of dantrolene to a myasthenic patient might lead to profound postoperative neuromuscular dysfunction.

Acetylcholine receptor (AchR) synthesis is known to correlate with intracellular calcium concentrations.¶ Takamori *et al.* hypothesized that dantrolene may improve neuromuscular transmission in rats with experimental

¶ Birnbaum M, Reis MA, Shainberg A: Role of calcium in the regulation of acetylcholine receptor synthesis in cultured muscle cells. Pflügers Archiv European Journal of Physiology 385:37–43, 1980

autoimmune myasthenia gravis (EAMG) by altering intracellular calcium levels to effect an increase in AchR synthesis.[7] Additionally, dantrolene may have a membrane-stabilizing effect on postsynaptic membranes.[8] Dantrolene has been found to produce clinical improvement in rats with EAMG.[7] Mechanisms of this effect remain undetermined at present.

The responses to dantrolene in the MG patient reported here differ from those reported in normal, awake volunteers.[3] We found the myasthenic neuromuscular function to be somewhat resistant to the twitch depressant effect of dantrolene. The volunteers showed a mean maximal twitch depression of 75 ± SEM 1.4% achieved at a dantrolene dose of 2.4 ± SEM 0.03 mg/kg (*i.e.*, twitch was depressed to 25% of the predantrolene control twitch height). Dantrolene 1.4 mg/kg and 1.6 mg/kg iv produced 93% and 95% of maximal twitch depression, respectively.[3] Our patient received dantrolene 1.9 mg/kg; therefore, we expected twitch depression to be greater than 72% (95% of 75%). However, twitch height was depressed by only 60% (to 40% of the control height—fig. 2, plateau phase).

Awake volunteers have no apparent change in fade ratio (T_4/T_1) when administered dantrolene 2.4 mg/kg.[3] We noted a precipitous decrease in fade ratio approximately 110 min after dantrolene was administered. The difference may be attributable to the effects of general anesthesia, but this is unlikely because a N_2O–narcotic technique is believed not to affect neuromuscular transmission. Administration of edrophonium 10 mg partially antagonized this change. We are unsure as to the cause of this abrupt change in neuromuscular function. Anesthetic technique was not altered, nor were any drugs that might affect neuromuscular function (*i.e.*, anticholinesterases, muscle relaxants, or potent volatile agents) administered at this time. This change may well have been related to the patient's underlying myasthenic condition because, at this time, she had received no pyridostigmine for 19 h. In favor of this explanation is the response to edrophonium, a dose of 2–10 mg iv being that commonly used to make the diagnosis of MG.[9]

An average maximal reduction in grip strength of 42 ± SEM 4% (range 18–60%) occurred in awake volunteers after dantrolene 2.2 mg/kg was administered iv.[3] No significant recovery was noted 7 h following initial dantrolene administration.[3] In our MG patient, a 44% reduction in grip strength, as compared with that immediately before dantrolene was commenced, was noted 210 min after initiation of dantrolene prophylaxis. Four hours later, grip strength was 65% of control. Grip-strength values are characteristically low in patients with generalized MG. The change in grip strength observed in our patient recovering from general anesthesia was comparable with that seen in awake volunteers treated with dantrolene 2.4 mg/kg iv.[3] Recovery was apparently slow both in normal individuals and in this MG patient, although in the latter case, patient cooperation may have been a factor.

Respiratory variables were not affected by dantrolene 2.5 mg/kg administered to adult volunteers.[3] While our patient did not require postoperative mechanical ventilation, 3 h after completion of surgery her forced vital capacity and forced expiratory volume in 1 s were approximately 50% of preoperative control values. The effects of general anesthesia and intrathoracic surgery cannot be separated from the effects of dantrolene on postoperative respiration in the normal or myasthenic patient.

In conclusion, we report a case in which dantrolene, administered in a dose sufficient to provide prophylaxis for MH, was safely administered to a patient with generalized MG. The responses to dantrolene in our MG patient differed from those in healthy volunteers. Specifically, our patient was resistant to the twitch-depressant effects of dantrolene, but after 2–3 h demonstrated a significant decrease in fade ratio. While dantrolene may produce clinical improvement in rats with EAMG, further studies would be required to determine whether it has a similar effect in human MG.

References

1. Saidman W, Howard ES, Eger EI II: Hyperthermia during anesthesia in a patient with myotonia congenita. JAMA 190:1029–1032, 1964
2. Denborough MA, Dennet X, Anderson RM: Central core disease and malignant hyperpyrexia. Br Med J 1:272–273, 1973
3. Flewellen EH, Nelson TE, Jones NP, Arens JF, Wagner DL: Dantrolene dose response in awake man: Implications for management of malignant hyperthermia. ANESTHESIOLOGY 59:275–280, 1983
4. Gronert GA: Malignant hyperthermia. ANESTHESIOLOGY 53:395–423, 1980
5. Nelson TE, Flewellen EH: Rationale for dantrolene *versus* procainamide for treatment of malignant hyperthermia. ANESTHESIOLOGY 50:118–122, 1979
6. Morgan KG, Bryant SH: The mechanisms of actions of dantrolene sodium. J Pharmacol Exp Therap 201:138–147, 1977
7. Takamori M, Sakato S, Matsubara S, Okumura S: Therapeutic approach to experimental autoimmune myasthenia gravis by dantrolene sodium. J Neurol Sci 58:17–24, 1983
8. Campbell AK, Luzio JP: Intracellular free calcium as a pathogen in cell damage initiated by the immune system. Experientia (Basel) 37:1110–1112, 1981
9. Drachman DB: Myasthenia Gravis (second of two parts). N Engl J Med 298:186–193, 1978