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Clinically Significant Muscle Weakness Induced by Oral Dantrolene Sodium Prophylaxis for Malignant Hyperthermia

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The perioperative management of malignant-hyperthermia (MH)–susceptible patients has been controversial; however, most authorities agree that pretreatment with dantrolene sodium as a prophylactic measure is an essential and reasonably benign step in preoperative preparation.[1–6] We report a case in which dantrolene pretreatment was associated with a perioperative pulmonary complication that required a change in the anesthetic management as well as prolonged endotracheal intubation postoperatively.

REPORT OF A CASE

A 5½-yr-old girl with severe periodontal disease was admitted for evaluation and complete dental restoration. Preoperative anesthesia consultation was sought because the child could not be managed in the dental clinic and had a family history of neuromuscular disease. A sibling had had an episode compatible with MH during cleft palate surgery at another hospital. The sibling's episode had been successfully treated by withdrawal of anesthetic agents and surface cooling. Neurologic evaluation performed at that institution identified similar nonspecific neuromuscular syndromes in both siblings.

Three years prior to admission, the patient was scheduled for cleft palate repair with oral dantrolene "pretreatment" 1 day before surgery. After pretreatment, the patient became febrile and was lethargic. Surgery was postponed, and a diagnosis of otitis media was made. Seven months later, the child underwent cleft palate repair, bilateral myringotomy, and biopsy of the quadriceps muscle under general anesthesia, with no reported complications. The patient's family received copies of a muscle biopsy report describing the results as "unquestionably positive" as demonstrated by calcium uptake, adenotriphosphatase activity, and adenotriphosphatase histochemical staining.

The child was admitted to our institution 2 days preoperatively. At this time, physical examination revealed bilateral ptosis, bifacial weakness, slight lingual atrophy, poor dentition, and anterior midline palatal fistula and bifid uvula. Mild thoracic kyphosis and lumbar lordosis were noted. The patient had generalized hypotonia, distal muscle wasting of the upper extremities, and a diminished grip, biceps strength, and knee extension. She had a waddling gait and raised herself to standing by using hands-on-knees (Gower's sign). She could squat, hop, and clap her hands above her head. Preoperative laboratory evaluation, including a complete blood count and urinalysis, was normal. The serum creatinine phosphokinase (CPK) was 35 u/dl. The chest roentgenogram was unremarkable.

After a prophylactic regimen of dantrolene, 1 mg/kg, orally every 6 h for three doses had been administered prior to surgery, we planned to attempt local anesthesia with iv sedation or, failing this, general anesthesia, avoiding triggering agents. Within hours after the second dose of dantrolene, increased weakness associated with noisy respirations was noted by her family and the nursing staff. After consultation with anesthesia, the third dose of dantrolene and premedication were not given. The patient was reevaluated for anesthesia and surgery in the morning. She was afebrile. Respirations were noisy with upper airway secretions and partial soft tissue obstruction. Arterial blood pressure was 100–110/60–70 mmHg with a heart rate of 100–120 beats/min. An arterial blood gas was taken while the patient received oxygen *via* nasal prongs, 1.0 l/min. The results showed pH_a 7.31, Pa_{O_2} 99 mmHg, and Pa_{CO_2} 44 mmHg. In view of the patient's weakness and the need for dantrolene, general anesthesia with ventilatory support was planned.

Anesthesia was induced using iv increments of fentanyl and thiopental and maintained with iv fentanyl and inhalation of nitrous oxide in oxygen. Direct nasotracheal intubation was performed with no difficulty, and bilateral breath sounds were present following positioning for surgery. With a fractional inspired oxygen concentration (FI_{O_2}) of 0.33 and controlled ventilation *via* nasotracheal tube, pH_a was 7.46, Pa_{O_2} 70 mmHg, and Pa_{CO_2} 34 mmHg. The FI_{O_2} was increased to 0.4. More vigorous manual hyperinflation was attempted because diminished breath sounds were noted at the left base. After 2.5 hours of anesthesia, the temperature (37° C to 39.5° C) as well as heart rate (117 to 126 beats/min) began to increase. Arterial blood gases did not demonstrate acidosis (pH 7.45, Pa_{O_2} 142 mmHg, and Pa_{CO_2} 32 mmHg). Surface cooling was initiated with a cooling blanket and ice packs in the inguinal region and axillae. When the procedure was completed, the patient was transported to the recovery room, where the initial nasopharyngeal temperature was 36.6° C. A postoperative chest roentgenogram revealed left lower lobe atelectasis with the nasotracheal tube in good position. Copious secretions were suctioned from the tracheal tube and, with a FI_{O_2} of 1.0, pH_a was 7.36, Pa_{O_2} 471 mmHg, and Pa_{CO_2} 36 mmHg (with intermittent mandatory ventilation (IMV) = 12 mm, PEEP = 5 cmH_2O, and exhaled tidal volume of 300 ml). Recurrent low-grade fever (38.2° C) was treated with a cooling blanket and antipyretics.

Eight hours postoperatively, the patient was lethargic and weak with diminished swallow and gag reflexes despite the administration of iv naloxone. Marked hypercapnea occurred during weaning attempts. Vigorous chest physiotherapy with tracheal suctioning reexpanded the left lower lobe at 36 h after the initial dose of dantrolene. At that time the trachea was extubated. Swallow and gag reflexes were still diminished, but the patient's cough and general tone were significantly im-

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proved, in contrast with the immediate preoperative and postoperative presentation. She was transferred to the ward 12 h later. Metabolic acidosis was never observed. The serum CPK was not elevated. Urine and blood were negative for myoglobin. At 3- and 6-month follow-up visits to the dental clinic, the patient appeared active and alert.

Discussion

This child presented assessment and management problems. Local anesthesia was an unsuitable alternative for management of her dental surgery. The family was convinced that the patient was MH-susceptible on the basis of an as yet unvalidated test.[7] An earlier anesthetic episode had been uncomplicated after dantrolene pretreatment and anesthetic management avoiding known triggering agents. We do not know whether this child and her brother have MH susceptibility but, in view of their genetic heritage and the "documentation" of their susceptibility, we would consider them to be at risk. Although a more conventional muscle study might be in order for this child, the family has already had one study and is unwilling to undertake another. In this case, we believed preoperative dantrolene prophylaxis and MH precautions to be appropriate.

After two oral doses of dantrolene, the child became significantly weak. After a period of observation, we had the alternatives of either withholding anesthesia and surgery, thus returning to the operating room at a later time without dantrolene, or to proceed with anesthesia. We elected to proceed because the clinical examination and arterial blood gases were compatible with drug-induced exacerbation of clinical weakness. We suspected that therapeutic levels of dantrolene might always be associated with significant weakness in this patient.

This girl did not experience intraoperative MH. We attribute her fever either to bacteremia during manipulation of multiple carious teeth and involved gums or atelectasis due to secretion retention. Intraoperative aspiration of gastric contents is an unlikely explanation. Induction and direct endotracheal intubation were not complicated. We noted decreased breath sounds at the left base almost immediately following intubation.

Dantrolene is effective in the treatment and prevention of MH.[1–6] Prior to its introduction, it was used to control spasticity in certain neuromuscular syndromes. Dantrolene causes a dose-dependent depression of skeletal muscle contractility in many animal models and humans.[4,6,8] In our experience, patients treated with dantrolene have complained of significant weakness after taking the drug. This impression has recently been confirmed by Flewellen *et al.* in healthy volunteers.[8]

There is some disagreement regarding the most effective dantrolene pretreatment regimen for the MH-susceptible patient.[8–11] We had feared that dantrolene might cause clinically significant weakness in our patient and chose a short-term, reduced dose regimen for oral prophylaxis. We note that the dose which caused our patient's problems is less than that suggested by Wingard *et al.* in 1983.[9] An alternative approach would have been iv pretreatment in a special care area under closer surveillance. This could have decreased the time during which clinical weakness occurred, *i.e.*, shortly prior to the induction of anesthesia. Others have made the suggestion that iv administration be employed,[8,9] but uncertainty regarding safe dosage and tissue thresholds and a recent report of a "breakthrough" case of MH after oral dantrolene preoperatively has made this controversial.[10,11] We felt that oral dantrolene treatment would be tolerated because the child had undergone a similar regimen at another institution without difficulty.

Significant exacerbation of the patient's bulbar and axial myopathy preoperatively contributed to secretion retention and atelectasis, as well as a prolonged postoperative course of endotracheal intubation and ventilation. We predict that clinically important muscle weakness may occur in similar patients, and we recommend increased vigilance during "routine" dantrolene pretreatment for probable MH-susceptible patients who require urgent or semiurgent procedures. This problem may be seen in other settings because dantrolene continues to be used for managing spasticity and has recently been recommended as a useful drug in the management of heat stroke.[12–14]

In view of the recent work of Flewellen *et al.* documenting blood levels of dantrolene following iv dosing[8] and our experience with this patient, we propose that patients with clinical myopathy who require dantrolene pretreatment might best be managed with an iv loading dose and perioperative drip infusion under direct supervision in the operating room or a special care area. We also suggest a cautious approach to such patients postoperatively, because the effect of dantrolene on the bulbar and chest wall musculature persists and may present a reason for failed tracheal extubation and/or cause aspiration of gastric contents.

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A New Technique of Scavenging Exhaled Nitrous Oxide

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Sedative–hypnotics are frequently used to provide patient comfort and augment the analgesia of a regional anesthetic. Nitrous oxide is particularly valuable for such sedation due to its predictability and rapid elimination. A concentration of 50% N_2O applied through nasal prongs enhances the sedation of modest doses of parenterally administered analgesics.[1] This N_2O-based sedation provides gentle sleep with minimal postsedation intoxication. However, without a means of scavenging exhaled N_2O, significant pollution of the operating room occurs. Therefore, an effective, inexpensive, and comfortable means of scavenging exhaled N_2O is described.

METHODS

This study was conducted on 20 nonpremedicated adult patients who were to receive regional or local anesthesia for surgical procedures. Patient entry into the study was not restricted on the basis of age, sex, or physical status. All studies were approved by our Institutional Research Committees.

On arrival in the operating room and after placement of ECG electrodes and blood pressure cuff, each patient was given iv doses of droperidol (1.25 mg) as an antiemetic; nalbuphine (10–20 mg/70 kg) as an analgesic; and low doses of diazepam (0–5 mg) as needed for sedation. The regional or local anesthetic was then performed and the patient positioned in the supine position for surgery. Nitrous oxide, 50% in oxygen, was introduced through nasal prongs at a 4 l/min flow rate. The ambient air N_2O level was continuously determined with an infrared spectrophotometer at a point within the anesthetist's breathing zone (approximately 0.5 m from the patient's nose and level with the operating table). At St. Vincent Hospital and Medical Center, a Foregger 410® N_2O monitor (Puritan-Bennett Corp., Kansas City, MO) with continuous strip-chart recording of the measured N_2O level was used. At Maricopa Medical Center, an Ohio Trace Gas Analyzer for N_2O® (Ohio Medical Products, Madison, WI) was employed, with observations recorded every 5 min. Scavenging of the exhaled N_2O was achieved by the placement of a Hudson® soft-vinyl, disposable face tent (Hudson Oxygen Therapy Sales Company, Temecula, CA) securely under and against the patient's chin. A length of disposable suction tubing connected to the regulated central vacuum source was attached to the face tent *via* a 9 mm, 90% angled, metal endotracheal tube connector. Vacuum flows of between 10–30 l/min (corresponding to suction pressures of 100–200 mmHg) were then applied and the effect on ambient air N_2O levels determined.

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