native to previously described techniques for SLV in pediatric patients.

References


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Sensitivity to Mivacurium in a Patient with Mitochondrial Myopathy


THE mitochondrial myopathies are a clinically and biochemically heterogeneous group of disorders characterized by structural mitochondrial abnormalities on skeletal muscle biopsy.¹ The morphologic hallmark of mitochondrial myopathy is the ragged red fiber.² seen with the modified Gomori trichrome stain, containing peripheral and intermyofibrillar accumulations of abnormal mitochondria. In some cases, the fibers do not have a ragged appearance. Affected fibers also contain an excess of glycogen granules and increased numbers of fine neutral lipid droplets.³ Both isolated myopathies and several multisystem syndromes have been identified. The syndromes, which are defined through characteristic clinical manifestations in addition to mitochondrial myopathy, are chronic progressive external ophthalmoplegia, including Kearns-Sayre syndrome,⁴ MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes) syndrome,⁴ MERRF (myoclonus epilepsy and ragged red fibers) syndrome,⁵ MNGIE (myopathy, external ophthalmoplegia, neuropathy, and gastrointestinal encephalopathy) syndrome,⁶ and NARP (neuropathy, ataxia, and retinitis pigmentosa) syndrome.⁷

Patients with mitochondrial myopathies have been reported to be sensitive to the effects of thiopental.⁸ In addition, they are susceptible to develop atrioventricular conduction blocks, ranging from bundle-
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branch block to third-degree AV block. Intraoperative administration of 10 mg hyperbaric tetracline was reported to be safe in a patient with MELAS syndrome. There are conflicting reports on the response of mitochondrial myopathy patients to the neuromuscular blocking drugs. We report the anesthetic management of a patient with mitochondrial myopathy and the response to the nondepolarizing muscle relaxant mivacurium.

Case Report

A 16-yr-old boy, weighing 37 kg and 165 cm in height, with the diagnosis of mitochondrial myopathy was scheduled for surgical closure of tracheotomy stoma. Mitochondrial myopathy had been diagnosed 2 yr previously, at which time he was admitted to the hospital because of a 1-yr history of generalized fatigue and bilateral ptosis. At physical examination, he was slender, and neurologic examination revealed ptosis; restricted eye movements in lateral, medial, and upper directions; and mild proximal and distal muscle weakness. Nerve conduction study results were normal. Needle electromyography of tibialis anterior, quadriceps, biceps, and thorac muscles was suggestive of myopathic changes. Myasthenia gravis was suspected, but an edrophonium test was negative. Muscle biopsy from the rectus femoris muscle showed no evidence of ragged red fibers with the modified Gomori trichrome stain. ATPase reactions showed slight type II fiber predominance. Pulmonary function tests suggested a mild restrictive ventilatory impairment. The patient experienced increasing shortness of breath over a 5-wk period, which culminated in acute respiratory failure necessitating tracheal intubation and mechanical ventilation. Tracheotomy was performed 2 weeks later. Plasmafreehemoglobin was performed four times without improvement of the patient's conditions. Electron-microscopic studies confirmed the mitochondrial abnormalities in the muscle. It showed that the mitochondria were numerically increased. Usually enlarged with disorganized cristae, and contained paracrystalline structures surrounded with an abundance of glycolgen. Relevant laboratory results included negative antistriated muscle and acetylcholine receptor antibodies, normal creatine kinase, normal serum lactate acid, and normal thyroid function. Mechanical ventilation eventually was discontinued. The patient was discharged 4 months after his first admission.

Anesthesia

No premedication was given. An intravenous catheter for fluid and drug administration was inserted. The tracheotomy stoma was covered with an airtight dressing. A 20-G radial arterial cannula was inserted using local anesthesia before induction of general anesthesia. The electrocardiogram and invasive arterial pressure were monitored continuously. Hemoglobin oxygen saturation (SpO2) was monitored by pulse oximetry. Temperature was monitored by a nasopharyngeal thermistor and maintained between 35.5°C and 37.5°C. Noninvasive temporary pacemaker electrodes (Cardio Aid, SW, Medico Teknik A-S, Albertoslaund, Denmark) were applied to the patient, and an infusion of isoproterenol was prepared. Anesthesia was induced with incremental doses of propofol and maintained with 70% N2O in oxygen and a propofol infusion of 45–90 μg·kg⁻¹·min⁻¹. The patient received no sedative or opioid. Topical anesthesia of the larynx and trachea was achieved by spraying 4 ml 4% lidocaine. The concentrations of nitrous oxide, oxygen, and carbon dioxide were measured continuously by a multiple-gas analyzer (Capnomac, Datex, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal partial pressure of carbon dioxide 35–40 mmHg). The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myostest peripheral nerve stimulator (Biometer, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer). Preload tension on the thumb was maintained at 300 g throughout the procedure.

Fade was initially present in the TOF response. After stabilization of twitch height, the TOF ratio (the amplitude of the fourth evoked response as a fraction of the first evoked response; T4/T1) was noted to be 0.59. Administration of 10 mg edrophonium did not produce any measurable effect on the TOF fade or on the T1 response (the first response in TOF). Ten minutes later, 15 μg·kg⁻¹ mivacurium (10% of the commonly used dose) was administered over 5 s. The first measurable effect (lag time) and the maximum neuromuscular block (onset time) developed in 46 and 145 s, respectively. The maximum block attained was 98% inhibition of T1. Bronchoscopy was performed for evaluation of the upper airways. Thereafter, tracheal intubation was carried out, and the conditions were excellent.

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The first twitch (T1) recovered to 10% of the control tension 575 s (9.6 min) after the administration of mivacurium. Recovery of T1 to 25%, 75%, 95%, and 100% of control took 12.9, 24.6, 36.3, and 38.3 min, respectively. At 100% recovery of T1, the TOF ratio was 0.54. Monitoring of the neuromuscular was continued for another 10 min, at which time TOF ratio had recovered to 0.60. Anesthesia was discontinued, the endotracheal tube was removed, and the patient was able to sustain a head-lift for 5 s and cough effectively. No abnormalities in cardiac rhythm were noted, and there was no need to use the external pacemaker. The patient was observed for 24 h in the intensive care unit and later was discharged to the ward. Vital signs were stable throughout the perioperative period. Postoperative neurologic examination showed no significant change. The patient made uneventful recovery and was discharged home after 2 days.

Discussion

Our patient with mitochondrial myopathy demonstrated an extreme sensitivity to mivacurium, and despite appropriate dosing of the relaxant, recovery was prolonged. This finding is in marked contrast to that of D’Ambra et al., who suggested that mitochondrial myopathy does not involve the neuromuscular junction. Mivacurium sensitivity is known to occur in patients with myasthenia gravis or those with plasma cholinesterase deficiency. The facial appearance of this patient and extreme sensitivity to mivacurium are similar to those seen in myasthenic patients. In this patient, however, myasthenia gravis had been ruled out by edrophonium test (both clinically and with mechanomyographic monitoring) and by the absence of an elevated titer of acetylcholine receptor antibodies. In addition, plasma cholinesterase activity, dibucaine, and fluoride numbers were within normal limits in this patient.

Hart et al. demonstrated that administration of edrophonium during constant infusion of mivacurium (a situation different from the usual clinical practice) resulted in increase of concentrations of mivacurium’s two potent stereoisomers, cis-trans and trans-trans. However, 8 min after antagonism, edrophonium’s effect on mivacurium elimination had resolved. Plasma clearance of edrophonium in humans is rapid. Calvey et al. reported that concentrations of edrophonium in plasma decreased from 7.82 ± 2.95 nmol·ml⁻¹ (mean ± SE) to 1.75 ± 0.15 nmol·ml⁻¹ between 2 and 5 min. Edrophonium (10 mg (270 µg·kg⁻¹)) was administered 10 min before the administration of mivacurium to our patient. The prior administration of edrophonium to this patient may have influenced the quality of mivacurium-induced blockade. All patients with similar presentations who received mivacurium would not respond the same way.

Savarese et al. reported that 30 µg·kg⁻¹ mivacurium (ED₅₀) produced 9.4% (SE 4.5%) inhibition of T1 in normal patients with a mean time to 95% recovery of T1 of 12.5 min (SE 2.5 min). In contrast, after administration of 15 µg·kg⁻¹ mivacurium, which caused 98% block in our patient, the duration from injection to recovery of T1 to 95% of control force was 36.3 min. This patient was far more sensitive than previously described in myasthenics. Paterson et al. noted in myasthenic patients that 30 µg·kg⁻¹ mivacurium produced 37.5% twitch depression. We noted in myasthenic patients during nitrous oxide/oxygen/fentanyl anesthesia that the mean maximum depression of T1 after 20 µg·kg⁻¹ mivacurium was 90% from control tension. Furthermore, the nature of this patient’s recovery from mivacurium-induced neuromuscular block was more prolonged than previously described in myasthenic patients. Gitlin et al. found that a patient with myasthenia gravis who had received 0.15 mg·kg⁻¹ mivacurium had recovered two twitches in response to the TOF stimulation within 10 min after the administration of the relaxant.

The response of patients with mitochondrial myopathy to neuromuscular blocking drugs is controversial. Robertson described a 7-yr-old boy with ocular muscular dystrophy (a disorder associated with structurally and/or functionally abnormal mitochondria), who showed an extreme sensitivity to d-tubocurarine with lack of reversal by neostigmine. Others have used this sensitivity to investigate patients with ophthalmoplegia. Further, Lessell et al. reported an unusual sensitivity to succinylcholine in a 43-yr-old woman with progressive ocular myopathy. In contrast, D’Ambra et al. suggested that mitochondrial myopathy did not involve the neuromuscular junction because their patient showed normal response to both pancuronium and succinylcholine.

The existence of a myopathy should raise concerns of malignant hyperthermia. Ohtani et al. reported a case of malignant hyperthermia after succinylcholine in a patient with mitochondrial myopathy. This patient was treated promptly, but there were no details of sub-
sequent in vitro test of muscle contractility specific for malignant hyperthermia. Therefore, one may wish to avoid known triggering drugs of malignant hyperthermia. Drugs that can trigger malignant hyperthermia (such as potent volatile anesthetics and succinylcholine) were avoided in our patients. We used nitrous oxide, propofol, and mivacurium, all of which have been reported to be safe in susceptible patients.

Decreased ventilatory responses to both hypoxia and hypercapnia (not related to respiratory muscle weakness) have been recognized as a part of spectrum of mitochondrial myopathy. The decreased ventilatory response is of special significance to anesthesiologists because it may become apparent with opioids or other drugs that may impair regulation of breathing after surgical procedures. Therefore, we avoided sedatives and opioids in our patient.

Mitochondrial myopathies are a group of disorders with variable clinical manifestations and an underlying mitochondrial defect. We have described anesthetic management of a patient with mitochondrial myopathy who demonstrated an increased sensitivity to mivacurium. This sensitivity was not due to decreased plasma cholinesterase activity or myasthenia gravis. With reduced dosage and adequate monitoring of neuromuscular function, mivacurium can be used safely in the patient with mitochondrial myopathy. However, it is premature to make any generalizations from this report.

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