Editorial
Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child

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As pediatric anesthesiologists, it is unusual in these days of complex technology and advances in genetic research to find ourselves presented with conflicting information and continued controversy regarding anesthesia plans for a particular group of children. This still occurs, however, when presented with the task of determining the best management for the child with an undiagnosed myopathy (1–6). Drs Flick et al. (1) in this issue of Pediatric Anesthesia have taken their 13 years of experience to help guide the thought processes for this population of children. The authors reviewed the charts of all children who had undergone muscle biopsies to rule out suspected neuromuscular disorders (NMD). All of the children received volatile anesthetic agents with or without succinylcholine and no child in the review of 274 charts developed malignant hyperthermia (MH) or rhabdomyolysis from the delivered anesthetic. Seven of the patients had biopsies consistent with muscular dystrophy and three consistent with mitochondrial disorder. Although the results of this review should be comforting, no child in their population was subsequently diagnosed with Evans myopathy, King syndrome or central core disease, the only known disorders that are truly associated with malignant hyperthermia (7). Any of these diagnoses would have certainly changed the results, but not the conclusion. Appropriately, Flick et al., rather than assigning a risk of zero based on their findings, have estimated the risk of a patient with NMD to have MH or rhabdomyolysis from exposure to a volatile anesthetic at less than or equal to 1.09%. This is in comparison with the 0.46% risk in an MH-susceptible child of developing an episode of malignant hyperthermia after nontriggering anesthesia (6).

Over the years there has been great controversy as to how to manage the child with hypotonia of unknown etiology for a surgical procedure. There are essentially two families of diseases that deserve consideration, the muscular dystrophies and the mitochondrial myopathies. The incidence of neuromuscular disorders in children is as frequent as 1 in 3200 male births vs an incidence of up to 1 in 4000 children having a mitochondrial disorder of some variety (8). Being faced with a child having one of these disorders is therefore not necessarily a rare event in common pediatric practice. Knowing the differences between the management of these two disorders is imperative so that the appropriate anesthetic plan is formulated. As alluded to previously, a main concern for these children are the risks of malignant hyperthermia or rhabdomyolysis that may result in perioperative morbidity or mortality. The risk or association of malignant hyperthermia with certain muscular dystrophies has been a well-known entity and a subject of controversy in the literature and book chapters. As Flick et al. discussed, although muscular dystrophy is often considered to be associated with MH, several studies and reviews have demonstrated that NMDs other than the three disorders previously mentioned are not truly associated with MH and experienced practitioners deliver inhaled agents to children with muscular dystrophy without sequela (1,9).

It is not always easy to determine which child with neuromuscular disease may be at risk for perioperative events and muscle contracture testing may be inaccurate (10,11). Only about 50% of
patients who have muscle contracture testing indicating MH susceptibility actually have mutations in the ryanodine receptor (12). It is unclear why the other half has abnormal contracture testing. With the inability to truly determine risk of MH, it is often recommended that children with hypotonia and suspicion of NMD be anesthetized with nontriggering agents to avoid the issue all together (1,10,11,13). Additionally, knowing that MH may not be a risk does not imply that rhabdomyolysis does not present as a separate and significant risk.

To address the concerns that surround the anesthetic management in children with muscular dystrophy, a recent Editorial in Pediatric Anesthesia by Yemen and McClain revisited the issues and made recommendations in the interest of patient safety (14). These authors presented a series of patients with DMD who had undergone uneventful surgery and anesthesia but who suffered unexpected events including hyperkalemic cardiac arrest in the recovery room. To avoid the risks of malignant hyperthermia and rhabdomyolysis, these authors suggest that inhaled agents be avoided in this population of patients. Others agree with these recommendations as the availability of other agents precludes the need for volatile anesthetic use (15). In a separate editorial during the days when succinylcholine was considered to be primarily responsible for the hyperkalemic cardiac arrest that were reported, Morris suggested that succinylcholine be contraindicated in patients with DMD but went on to state that inhaled agents are not contraindicated as there was a lack of strong evidence against the volatiles (16). Several years later, Gronert reviewed the cardiac arrests associated with succinylcholine and disagreed stating that practice need not change based on these isolated case reports (17). Flick et al. suggest that their series should provide the clinician with reassurance when using volatile anesthetics in children undergoing diagnostic muscle biopsy. They also suggest that this interpretation should be made with care, particularly as the sample size is not large enough to truly capture the rare episodes of MH or rhabdomyolysis.

It seems clear from the literature that there remains some disagreement as to whether using inhaled agents is worth the risk in patients with neuromuscular diseases. It is also clear that the risk of malignant hyperthermia is extremely low in this population due to the small numbers of patients who are truly susceptible, but when the risk of rhabdomyolysis is added, there is an increased possibility of perioperative adverse events. Assuming that the recommendations to avoid triggering agents are followed for procedures on children with unknown etiology for their hypotonia, a total intravenous technique using propofol as the primary agent is a logical choice. Can it be assumed that a total intravenous anesthetic (TIVA) technique is appropriate for all children with myopathies? One must consider the anesthetic implications in patients with mitochondrial myopathies in particular.

Mitochondrial disorders are a rare set of diseases that manifest themselves through defects in electron chain transport or oxidative phosphorylation (2,5,18). There are three basic categories that constitute the mitochondrial myopathies. There are respiratory chain deficiencies, mitochondrial DNA mutations that include mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), mitochondrial neurogastrointestinal encephalopathy (MNGIE) and myoclonic epilepsy with ragged red fibers (MERRF) syndrome and mitochondrial deletions such as Kearns-Sayre syndrome. Although there is considerable overlap in these categories, it allows for some ability to organize these complex disorders. Alternatively, classification by specific enzyme activity of the different complexes in the oxidative phosphorylation system has been used to associate the clinical findings with the biochemical defect (5). A comprehensive review by Shipton and Prosser described the underlying abnormalities in the disorder and outlined the significant issues associated with mitochondrial myopathies and anesthesia (2). Central to this review and to a prior review that was published in Pediatric Anesthesia in 1998 is the notion that there is a wide range of mitochondrial diseases and there are no true recommendations for anesthesia techniques that rely on evidence-based medicine (2,5,18–22). Early in the understanding of the mitochondrial defects, these diseases were considered to be associated with malignant hyperthermia and therefore children with mitochondrial myopathies were often managed perioperatively with nontriggering anesthetics (4,5,20,23–26). A TIVA using propofol as the primary agent was once considered the preferred technique in these patients who were considered susceptible to
malignant hyperthermia. The association between mitochondrial myopathies and malignant hyperthermia has now mostly been dismissed. Although propofol has been used in children with mitochondrial myopathies without event, the choice of a TIVA anesthetic using propofol may no longer be considered the anesthetic of choice for this group of children. Within the past year it has been suggested that propofol with its lipid carrier composed of long-chain fatty acids may have an adverse effect on fatty acid oxidation and mitochondrial respiratory chain function, and therefore put patients with mitochondrial disorders and closely-related carnitine deficiency syndromes at risk for a clinical scenario similar to propofol infusion syndrome (PRIS) (27).

Propofol infusion syndrome is known as a potentially fatal reaction that may occur in children who receive high-dose propofol infusions, typically for sedation in intensive care units (28,29). This condition is characterized by bradycardia, metabolic acidosis, rhabdomyolysis, and lipidemia and may lead to cardiac failure. Early reports of propofol infusion syndrome came from the British literature and described the condition in children receiving doses of propofol at >4 mg kg\(^{-1}\) h\(^{-1}\) for greater than 48 h (28,29).

The suggested dose of >4 mg kg\(^{-1}\) h\(^{-1}\) and length of infusion >48 h that were associated with propofol infusion syndrome were described in patients who did not have underlying mitochondrial perturbation (28–30). If a child has a mitochondrial disorder, and is therefore more susceptible to the effects of an increased lipid load, the true dose that may result in PRIS is unknown and may have unpredictable results. Although the chance of propofol infusion syndrome occurring during a surgical procedure of a finite duration would be extremely rare, there remains concern that even a short-term high-dose propofol infusion may result in propofol infusion syndrome, particularly if a child has impaired fatty acid utilization (31–33).

This use of propofol in children with mitochondrial myopathies is further complicated by the fact that children who suffer from propofol infusion syndrome often have a clinical picture that is similar to malignant hyperthermia. Metabolic acidosis, rhabdomyolysis with myoglobinuria, hypotension, and cardiovascular collapse may occur with either condition (34,35). In order to differentiate these two processes, one should consider the time to onset. A malignant hyperthermia episode typically occurs within 4–5 h of the delivery of a triggering anesthetic and the arrhythmias present early from the hyperkalemia that ensues. Propofol is considered a non-triggering anesthetic and its sole use without contamination from other triggering agents should allow immediate dismissal of a diagnosis of MH. However, if there remains some question as to etiology of the presenting signs, propofol infusion syndrome typically would occur after a prolonged infusion over a day to days. Perioperative evaluation for lactate levels are deceiving as they are elevated with mitochondrial disease with or without an associated anesthetic or PRIS. In light of these considerations, it has been suggested that patients with known mitochondrial disease should not receive propofol (36).

The risks of using alternative IV anesthetics in children with mitochondrial myopathies remain under investigation. As one might expect, all anesthetics have been used for children with mitochondrial disorders without complications (5). It has been reported that these children are sensitive to thiopentone and etomidate, however reports are inconsistent (23,37–39). With the dilemma of using volatile agents versus propofol and the side effects or risks associated with each technique depending on the underlying diagnosis, other agents such as ketamine, etomidate, or dexmedetomidine should be considered.

The use of muscle relaxants in children with mitochondrial disease has presented conflicting reports. Some reports have touted no increased sensitivity or complications with atracurium, vecuronium, and pancuronium although there may be patient variability depending on severity and type of mitochondrial myopathy (18,25,40–42). Others have demonstrated increased sensitivity to atracurium, rocuronium, mivacurium, and cisatracurium (18,40,41,43–45). This is not dissimilar to the use of muscle relaxants in children with muscular dystrophy where reports of sensitivity have been inconsistent (46–49). Any child with hypotonia should be considered at risk of variable response to muscle relaxation and doses adjusted accordingly. Succinylcholine is best avoided as it has been associated with at least one case of malignant hyperthermia in a child with mitochondrial disease.
There have been no follow-up case reports of MH in this population from succinylcholine and it has been used in other children with mitochondrial disease without complication, however if succinylcholine can be avoided, nondepolarizers should be used in its place (42).

Pain management is essential in children with mitochondrial disorders as the response to pain may worsen their risk of lactic acidosis from depletion of energy stores and increased oxygen demand. Although narcotics have been used without adverse events, they should be used with caution and titrated to effect (3). Nonsteroidal adjuncts and nonopioid analgesics should be used as appropriate to decrease opioid requirements. If a regional anesthesia technique is possible, this may be a technique of choice as the increased risk of respiratory depression that may occur with opioids can lead to worsening acidosis. A straight regional technique also negates the question of MH risks as well as issues associated with potential sensitivity to muscle relaxants.

The use of sevoflurane is certainly considered acceptable based on the work of Morgan et al and is considered the agent of choice by some clinicians (3,50). Children with Complex I respiratory chain disorders are at greatest risk of sensitivity to inhaled agents and reach anesthetic depths according to bispectral index values at lower concentrations of sevoflurane than controls (50). Despite this, there is no contraindication to using inhaled agents in children with mitochondrial disorders of any known type, although arrhythmias with halothane have been reported in patients with Kearns-Sayre syndrome due to the underlying conduction defects in children with this disorder (3,51).

Whether or not one chooses inhaled or intravenous techniques in the child with a mitochondrial myopathy, other considerations must be weighed during the perioperative period (5). The preoperative fasting period should be kept to a minimum to avoid hypovolemia and depletion of glucose stores. Likewise, intravenous fluids must contain glucose and should avoid lactate that might worsen an underlying lactic acidosis. Any stress that may provoke increased energy requirements such as perioperative pain or hypothermia must be avoided. Children with Kearns-Sayre syndrome are at risk for arrhythmias and must have adequate preoperative workup and perioperative monitoring (3,19).

Children with hypotonia may present for a variety of surgical procedures. In addition to muscle biopsies for diagnosis, many will require endoscopies for gastrointestinal symptoms, gastrostomy tubes for feeding disorders, radiologic procedures or EEGs for seizures, strabismus surgery, and hearing tests. If presented with a child who has an undiagnosed myopathy, there are several clues to help provide the anesthesiologist with the best information to make an educated guess as to the etiology of the muscular disease. For example, a child who has muscular dystrophy of any variety will typically have a history of muscular dystrophy in the family. Physical exam clues include the presence of hypertrophic calves despite global hypotonia in a young child or an elevated creatine kinase (52). Without a family history of neuromuscular disease, and with a suspicion of mitochondrial disorder, the anesthetic plan may lean towards the assumption that the child may have an undiagnosed mitochondrial myopathy. A preoperative elevated serum lactate is a useful marker for the disease.

The dilemma remains. If the etiology of the myopathy is known, this information may be applied to formulate an appropriate anesthesia plan. With the knowledge of the two groups of diseases at this time, the choice of a TIVA for the patient with muscular dystrophy and the decision to use an inhaled agent for the child with mitochondrial myopathy would be most appropriate. The issue remains with the truly undiagnosed myopathic child. Administering an inhaled agent to a child with muscular dystrophy is an accepted technique and will be without incident the vast majority of the time. Based on the population statistics presented by Flick et al. (1), there should be no significant risk of rhabdomyolysis or malignant hyperthermia in nearly 99% of the anesthetics. The remaining 1.09% is the population that causes others to question the use of inhaled agents at all in children with muscular dystrophies and results in the overall recommendation that a total intravenous technique is preferred.

For many pediatric anesthesiologists who consider a 1% risk to be unacceptable, a total intravenous technique may be used in all children with undiagnosed myopathy. If propofol is used as
the primary agent in moderate doses (<4 mg·kg\(^{-1}\)·h\(^{-1}\)) and for short periods of time (<48 h), risks should remain at a minimum for malignant hyperthermia, rhabdomyolysis, or propofol infusion syndrome.

As anesthesiologists, we typically serve as consultants for patients with known disorders and provide the safest anesthesia possible based on the information that is obtained. When information is lacking, as in the case of a hypotonic child who presents for a muscle biopsy, our skills at obtaining a focused history to provide clues for our management are essential. As more knowledge is gathered regarding the true risks based on the pathophysiology of the various neuromuscular diseases, and with the additional investigation of other agents in this population of children, an educated guess will hopefully be a thing of the past. More large scale studies and reviews are needed to answer this important question that has been readressed by Flick et al.

References


Accepted 12 September 2006