The Risk of Malignant Hyperthermia in Children With Suspected Myopathy

Randall P. Flick, M.D.,M.P.H., F.A.A.P.

Despite continuing controversy, it is widely assumed that children with known or suspected myopathies are at increased risk for malignant hyperthermia (MH) (1). Previous reports have suggested a relationship between MH risk and a variety of neuromuscular disorders including Duchenne type muscular dystrophy (DMD), osteogenesis imperfecta, myotonia congenita, the Schwartz-Jampel syndrome, and others (2). Additionally, Kearns-Sayre syndrome and other mitochondrial myopathies have also been associated with an increased risk for MH (3,4). Others have failed to demonstrate an association between mitochondrial disorders and MH (5). There are currently only two disorders for which a clear link to MH has been established; they are central core disease and King syndrome. Both are quite rare, well defined clinically, autosomal dominant, and frequently diagnosed without muscle biopsy (6).

Malignant hyperthermia is a rare disorder of calcium metabolism in skeletal muscle. The reported incidence of MH is between 1 in 4,200 and 1 in 250,000 anesthetics depending primarily on the age of the patient, setting, and presentation (7). Malignant hyperthermia is characterized by evidence of a hypermetabolic state within the skeletal muscle. It is manifested by muscular rigidity, fever, hypercarbia, tachycardia, acidosis and, if untreated, death. In most cases the triggering event for the development of MH

symptoms is exposure to volatile anesthetic agents and/or succinylcholine, both of which are frequently used to induce or maintain general anesthesia.

Since it was first described in 1960 by Denborough *et al.* (8), MH has been associated with a variety of risk factors including exposure to many commonly used anesthetic agents and the presence of coexisting disorders, particularly myopathies. Subsequent evidence has shown that the only anesthetic agents known to trigger the onset of MH are volatile agents such as halothane and the depolarizing muscle relaxant succinylcholine.

It remains unclear, however, whether an association exists between MH and dystrophies such as DMD, channelopathies other than central core disease, and any or all of the mitochondrial disorders (9). There is a substantial body of literature consisting primarily of case reports and small series suggesting an increased risk of MH in patients with myopathies (10-13). However, no large study has, as yet, examined the question.

In a small study, Wappler *et al.* (14) sought to determine whether an increased risk of MH existed for 24 patients with a variety of known NMD. Although they found a high incidence of positive CHCT among those with NMD, the authors expressed uncertainty as to the accuracy of the CHCT in patients with neuromuscular disorders. The specificity of CHCT in patients with dystrophies and myopathies has been questioned by others as well (15). Wappler *et al.* (14) concluded, however, that patients with known NMD should be treated as MH susceptible and therefore should not be exposed to triggering anesthetic agents.

In a 1992 study of CHCT results in patients with NMDs, Heytens *et al.* (16) found that of the 60 patients biopsied only 2 were found to be MH susceptible, 10 equivocal and 48 were negative. Like Wappler *et al.* (14), Heytens *et al.* (16) speculated that the large number of equivocal biopsies was the result of a lack of specificity of the test in patients with NMD.

Of particular concern are patients with DMD. Several authors and most major texts of pediatric anesthesia suggest that patients with DMD are at increased risk for MH (17,18). In the animal model of DMD, muscle samples from mdx mice, deficient in dystrophin, have been found to have both normal and abnormal results when exposed to halothane and caffeine (19,20).

In the Wappler *et al.* (14) study, two of three patients with DMD were found to be MH susceptible according to the European protocol. However, in a study of 47 procedures in 23 patients later diagnosed with DMD, Herr *et al.* (21) found that no child developed evidence of MH despite 93% having received volatile anesthetic agents and 4% having received succinylcholine.

Much of the difficulty associated with defining the relationship between MH and DMD is related to the phenomenon of acute rhabdomyolysis. Acute rhabdomyolysis leading to hyperkalemic cardiac arrest has been reported in association with DMD and has been understandably confused with MH. Like MH, most reported cases of rhabdomyolysis have been associated with the use of succinylcholine although several have occurred in its absence (22). A decade ago the clear association between succinylcholine and rhabdomyolysis led to the United States Food and Drug

Administration to advise against the use of succinylcholine in children. Despite this, reports of hyperkalemic cardiac arrest in DMD patients continue to occur (23).

In those cases where succinylcholine was not used, volatile anesthetic agents have been implicated although the mechanism by which this occurs remains, to a large extent, unexplained.

In 2006 we undertook to describe, retrospectively, the anesthetic outcomes of 274 children in our anesthesia database with suspected myopathy exposed to volatile anesthetics and to determine whether they are at substantially increased risk for the development of signs and symptoms consistent with the diagnosis of MH.

Among our 274 patients, two were known or later found to have DMD. Five others had dystrophies of other types. None developed signs or symptoms consistent with either MH or rhabdomyolysis despite all having received volatile anesthetic agents. Although the relationship between succinylcholine and rhabdomyolysis appears evident, it is less clear whether volatile agents can be implicated in these events.

Given the rarity of both MH and rhabdomyolysis, a study of this size cannot, by any means, demonstrate clearly the safety of volatile anesthetics in the setting of suspected myopathy. At best one can presume that the likelihood, with 95% confidence, of encountering either of these rare conditions is less than 1.09% (3/274) (24). This risk can be viewed against the background risk of triggering among patients with known MH managed with a non-triggering anesthetic.

Carr and colleagues (25) in Toronto reported that in patients known to be MH susceptible, the incidence of triggering after exposure to a non-triggering anesthetic is not zero. In their study of 2,214 patients undergoing muscle biopsy to rule out MH, 1,082 had a positive CHCT. Of those patients found to be positive, five developed MH in the perioperative period yielding an incidence rate of 0.46%. It can then be concluded that the excess risk of exposure to a volatile anesthetic agent in this population is approximately 0.63%.

Furthermore, if one assumes an incidence of triggering in MH susceptible patients of 0.46% despite the use of a non-triggering anesthetic and, as has been suggested, that those with myopathies are more susceptible, in our sample of 274 patients we should have expected that, even in the absence of exposure to a triggering agent, at least one patient would have triggered. Given that all of our patients had or were suspected of having a myopathy and were exposed to a triggering anesthetic, the incidence would certainly be expected to increase.

Obviously our patient population was diverse and included a variety of myopathies or suspected myopathies and, as a consequence, one must be careful in interpreting these results especially given the knowledge that of patients with known MH many had triggering anesthetics without the development of MH prior to diagnosis.

The most commonly mentioned alternative to the use of volatile anesthetics in this population is propofol. However, the use of propofol in undiagnosed myopathic patients is likewise controversial given reports of rhabdomyolysis, unrelenting acidosis, and death, mostly in sedated pediatric patients (26,27). Among myopathic patients, it has

been recommended that those caring for children that have or may have mitochondrial disorders consider avoiding the use of propofol due to concerns that this group may be at particular risk for the propofol infusion syndrome (28,29).

Of our 274 patients, at least three were found to have a mitochondrial disorder, although it was suspected in at least 39 others. Clearly the clinician caring for undiagnosed myopathic patients inevitably finds him or herself in a position of uncertainty given the real or potential risks associated with the use of either volatile anesthetics or propofol.

One can conclude from this series that in a diverse population of children undergoing muscle biopsy for known or suspected myopathy, the excess risk of MH and of rhabdomyolysis is less than 0.63%. Each clinician must decide, based on these results, whether a risk of 0.63% or less is sufficient to justify the use of an alternative anesthetic agent such as propofol or some other approach such as the use of etomidate, ketamine, or a regional technique.

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TABLE 1. Demographics of 274 patients undergoing muscle biopsy for undiagnosed myopathy between the years 1992 and 2005.

	Mean	SD	Male	Female
Age N = 274	6.6 yrs	5.7		
Weight N = 273	26.6 kg	20.3		
Gender (%) N = 274			149 (54)	125 (46)
ASA (%) N = 271	I, 6 (2.2)	II, 126 (46.3)	III, 135 (49.6)	IV, 4 (1.5)

TABLE 2. Anesthetic agents used for induction and maintenance among 274 children undergoing muscle biopsy for undiagnosed myopathy.

Agent	Induction (%) N = 274		Maintenance (%) N = 274	
Halothane	45	(16.4)	14	(5.1)
Sevoflurane	128	(46.7)	138	(50.4)
Isoflurane	0	(0)	150	(54.7)
Desflurane	0	(0)	4	(1.5)
Sodium thiopental	30	(10.9)	0	(0)
Ketamine	4	(1.5)	4	(1.5)
Propofol	54	(19.7)	59	(21.5)
Other	4	(1.5)	0	(0)
Missing	9	(3.3)	1	(0.4)