Review

Mitochondrial Disease and Anesthesia

Journal of Inborn Errors of Metabolism & Screening
2017, Volume 5: 1–5

DOI: 10.1177/2326409817707770
journals.sagepub.com/home/iem
SAGE

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Abstract

It is increasingly common for children with mitochondrial disease to undergo surgery and anesthesia. Although many different anesthetics have been used successfully for these patients, serious, unexpected complications have occurred during and following anesthetic exposure. This has led to the widespread opinion among anesthesiologists that mitochondrial patients are at increased risk from the stress of surgery and anesthesia. Defects in function of the mitochondrial electron transport chain can lead to striking hypersensitivity to volatile anesthetics in children. Despite this striking finding, the connection between mitochondrial function and response to anesthetics is unknown. We review here the anesthetic considerations for patients with mitochondrial defects. In addition, we present an approach to anesthetic care of these patients at our institutions.

Keywords

anesthetics, genetics, biochemistry, mitochondria, perioperative

Introduction

Mitochondrial disease (MD) is recognized as an important cause of a wide range of physiologic changes that affect the perioperative period.[1-3] Organ systems with high metabolic requirements are uniquely dependent on the energy delivered by mitochondria, and therefore logically should have the lowest threshold for displaying symptoms of MD. Thus, mitochondrial dysfunction most commonly affects the function of the central nervous system, the heart, the gastrointestinal (GI) tract, and the muscular system.[3-5] These same systems are strongly affected by anesthetics.

As diagnosis and treatment improve for children with MDs, it has also become increasingly common for children with MD to undergo surgical procedures for their long-term care. One published case series of 122 patients with muscle biopsy–confirmed MD, and another smaller series of 38 pediatric patients show that patients with MD may undergo brief general anesthetics using volatile anesthetics or propofol without serious anesthesia-related adverse events.[6] Recently, an additional report of 26 patients with genetically confirmed MD found no correlation between anesthetic chosen and complication.[7] However, 4of 26 patients did have a hemodynamic complication in the perioperative period. In each report, the large diversity in molecular causes for MD limits the ability to generalize the results to all mitochondrial patients. Kinder Ross, in an editorial in *Pediatric Anesthesia*, pointed out that patients with myopathies and MD *usually* do well regardless of the specific anesthetic approach that is chosen,[8] a conclusion supported by more recent case reports.[9,10] However, on theoretical grounds and based upon several case reports in which adverse outcomes were observed,[11-16] many anesthesiologists believe that patients with MD are at an increased risk for perioperative complications including organ damage or death. Given the relatively small published experience of this vulnerable population, the following management principles are designed to minimize risk when a diagnosis of mitochondrial myopathy is known or suspected.

General Concerns

Surgical procedures for pediatric patients with MD usually require general anesthesia. Patients with advanced sequela

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Received November 11, 2016, and in revised form February 07, 2017.
Accepted for publication February 20, 2017.

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of MD may present with respiratory failure, cardiac depression, conduction defects, or dysphagia.[2,3] Several reports document that patients with MD may face an increased risk of perioperative complications such as respiratory depression, worsened cardiac function and arrhythmias, metabolic disturbances, or severe neurologic injury. Respiratory depression may occur simply from the combination of anesthetic drugs and preexisting muscle weakness seen in any myopathic state.

Since most of the medications used for general anesthesia are depressants of one or more of these systems, great care must be exercised in managing their use.[17] Mitochondrial patients often require smaller doses of general anesthetics, local anesthetics, sedatives, analgesics, and neuromuscular blockers (paralytics) to achieve the desired end points. Furthermore, it is important to avoid increasing the metabolic burden of patients with MD by not requiring prolonged fasting, and preventing hypoglycemia, postoperative nausea and vomiting, hypothermia (with resulting shivering), prolonged orthopedic tourniquet application, acidosis, and hypovolemia.[18,19] Obviously, anesthesiologists try to avoid these complications in all patients, but the consequences can be greater in patients with mitochondrial defects. Finally, some patients with MD do not metabolize lactate normally; therefore, lactate-containing intravenous fluids (eg, lactated Ringer's solution) should not be administered.[17]

It is worth reminding the reader that MD is not 1 disorder but represents hundreds of different enzymatic mitochondrial defects, both genetic and environmental in origin. And yet there are few reports of remarkably small numbers of mitochondrial patients that conclude that the use of anesthetics is uniformly safe.[11-13] It is therefore incorrect and inaccurate to generalize from limited case series. Furthermore, these few case series with limited observation periods do not rule out delayed postoperative complications or _metabolic decompensation that may indeed result from a biochemically stressed state exacerbated by a combination of anesthetics, preoperative fasting, catabolism, or prolonged exposure to pain.

Hypersensitivity to Anesthetics

Most MDs fall broadly into 2 categories: respiratory chain defects and fatty acid metabolism defects.[2] Of the 5 complexes of the respiratory chain, complex I is inhibited by all inhaled halogenated anesthetics (but not nitrous oxide) and many parenteral drugs as well.[20-22] In a small series of children with MD, several patients with complex I defects showed an exquisite hypersensitivity to the inhaled halogentated agent sevoflurane, observed when monitoring the depth of anesthesia using a processed electroenceohalogram (EEG), such as the bispectral index (BIS).[23]

But essentially, every general anesthetic and ancillary anesthetic drug studied depresses mitochondrial function in vitro, although some ancillary medications seem to be clinically well tolerated. Fatty acid metabolism defects do not appear to alter sensitivity to volatile anesthetics, but defects in acylcarnitine transferase may increase the cardiotoxicity of bupivacaine.[24] In addition, at least on theoretical grounds, defects in acylcarnitine transferase may increase the toxicity of propofol, which also inhibits this enzyme.[17,25,26] Defects in the tricarboxylic acid cycle, substrate transport, and many unknown defects can also lead to MD. The precise interaction of most of these other mitochondrial defects with anesthetics and surgical stress is not known at this time. We discuss specific interactions below.

Table 1. Listed below are Common Anesthetic Agents and the Sites Affected by Each. The References Match those in the Manuscript.

Medication	Mitochondrial Effects	References
Barbiturates	Complex I inhibition	33
Etomidate	Complex I inhibition, mild inhibition complex III	32
Propofol	Acylcarnitine transferase, complexes I/II/IV inhibition	25,37,38
Benzodiazepines	Complex I/II/III inhibition	34
Ketamine	Increase energy consumption +/− reports of complex I	35,36
Dexmedetomidine	None reported	None
Fentanyl/remifentanil	Minimal	39
Morphine	Mild complex I inhibition	39,40
Volatile Anesthetics	Complex I inhibition	20,21,27
Bupivacaine (Etidocaine)	Acylcarnitine translocase Mild complex I	24

Volatile Anesthetics

Volatile anesthetics (isoflurane, sevoflurane, and desflurane) suppress oxidative phosphorylation, particularly at complex I, coenzyme Q, and to a lesser extent complex V[20,21,27] (Table 1). Studies in model organisms (*Caenorhabditis elegans* and mice) with selective mutations in multiple mitochondrial proteins in complex I have shown markedly increased sensitivities to volatile anesthetics.[28-30] The increased sensitivities are well tolerated provided there is careful monitoring of the anesthetic depth of patients and the anesthetic dose is titrated to the appropriate anesthetic depth.[17] It is also worth noting that volatile anesthetics in common use today are minimally metabolized. They are predominantly excreted unchanged by the lungs within minutes of turning off the anesthetic vaporizer. Their rapid elimination allows return of mitochondrial function after their discontinuation, a benefit compared with most parenteral anesthetic agents, which undergo extensive hepatic metabolism and excretion for their offset.

Parenteral Anesthetics

Parenteral drugs commonly used during a general anesthetic (propofol, etomidate, ketamine, barbiturates, midazolam, etc.) exert the majority of their effects via ligand-gated ion channels in the central nervous system[31] (Table 1). However, all of these

drugs also have an additional effect in mitochondria: either direct or indirect inhibition of oxidative phosphorylation. In the cases of midazolam, etomidate, and barbiturates, the effect is primarily an inhibition of complex I although each has minor effects at other sites.[32-34] Some reports indicate that ketamine may also have an effect on complex I, although the work is inconclusive at this time.[35,36] Propofol strongly inhibits complex I, other sites of oxidative phosphorylation and utilization of fatty acids.[37,38] Yet, each of these anesthetic drugs has been reported to have been used successfully in a small number of patients with MD by anesthesiologists familiar with the care of patients with myopathy.[6,8,17]

Propofol is unique among parenteral anesthetics in that it is known to affect mitochondrial metabolism by at least 4 separate mechanisms. In vitro, propofol has been shown to uncouple oxidative phosphorylation and inhibit complexes I, II, and IV.[25,37,38] The strongest effect of propofol is that it inhibits the transport of long-chain acylcarnitine esters via an inhibition of acylcarnitine transferase (specifically carnitine palmitoyl transferase 1).[25] The latter effect has been implicated as the mechanism behind propofol infusion syndrome, a potentially fatal complication of long-term propofol infusions used in intensive care. Given the multiple mitochondrial effect sites of propofol, it is prudent not to use propofol-based anesthetic techniques (ie, continuous infusions of propofol, or total intravenous anesthesia) to patients with known or suspected MD. As discussed later, however, limited boluses of propofol for anesthetic induction seem generally well tolerated.[6,17]

Local Anesthetics

Regional anesthetic techniques and wound infiltration with local anesthetics provide analgesia without the inhibitory effect of parenteral opioids on respiratory drive and upper airway tone. There is a single report of ventricular dysrhythmia after a patient with carnitine deficiency received a small dose of bupivacaine (an amide local anesthetic), which may have been caused by the inhibition of carnitine–acylcarnitine translocase that occurs with that particular local anesthetic in vitro. It should be noted that other clinically useful amide local anesthetics (ropivacaine and lidocaine) inhibit carnitine–acylcarnitine translocase to a lesser degree and therefore have less of a deleterious effect on carnitine-stimulated pyruvate oxidation than does bupivacaine.[24] They should therefore be chosen over bupivacaine when nerve blocks are performed in children with MD. Chlorprocaine and tetracaine (ester class local anesthetics) have not been studied to our knowledge.

Anesthetic Medications With Minimal Mitochondrial Effects

At present, several adjuvant drugs used with a general anesthetic have *not* been shown to affect mitochondrial function in vitro. These include most opioids with the exception of morphine (which has been reported to mildly inhibit complex I and alter the mitochondrial transmembrane potential).[39,40] Given that postoperative respiratory depression is a concern in this population, the use of remifentanil, an opioid with a fast offset because it is rapidly metabolized by serum cholinesterases, has proven extremely useful in many cases. Nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used safely; many neurologists advise against using repeated doses of acetaminophen due to the energy demands on the liver for metabolism. The sedative benzodiazepines as well as the central nervous system (CNS) alpha-adrenergic agonist dexmedetomidine have also proven useful, although their clearance may be slowed and effects prolonged. Finally, although the in vitro literature is not definitive, analgesic doses of ketamine have been well tolerated by the report.

Our Approach

The following represents the evidence-based approaches of the Seattle Children's Hospital and Stanford Children's Hospital. The first point of importance is to maintain the ongoing treatment for the patient's with MD for as long as possible in the preoperative period. Some patients with MD may be taking medications such as vitamins, coenzyme Q, L-Carnitine, EPI-743 (a novel medication presently in trial for MD therapy [41,42]) as well as other medications. As a rule, we continue these medications until nil per os (nothing by mouth) (NPO) requirements necessitate their discontinuation and often add L-Carnitine to their IV fluids in patients who have shown a strong clinical response to the drug.

Anesthetic management of patients with MD requires meticulous attention to cardiorespiratory physiology and specific attention to mitochondrial function. Patients with hypotonia and generalized myopathy may be prone to intra and postoperative upper airway obstruction, hypoventilation, hypercarbia, and therefore acidosis. They benefit therefore from opioid-sparing techniques such as the use of local anesthetics, regional anesthesia, NSAIDs as well as avoidance of nondepolarizing neuromuscular blocking drugs to which patients with MD may have exaggerated sensitivity. The depolarizing muscle relaxant succinylcholine should not be administered in any patient with myopathy out of concern for their upregulation of nicotinic acetylcholine receptors in skeletal muscle, resulting in potentially lethal acute hyperkalemia and acute myolysis after succinylcholine administration.

In the perioperative setting, several measures are taken to minimize physiologic changes and therefore stress on impaired mitochondrial function. A complete anesthetic assessment should be performed to establish baseline comorbidities and the degree of organ system involvement. In particular, the history and physical should seek signs and symptoms of MD including cardiomyopathy, the history or presence of cardiac arrhythmias, respiratory weakness or insufficiency, obstructive sleep apnea, seizures, and lactic acidosis. Classical patterns of maternal inheritance of undiagnosed symptoms should also alert the anesthetist to the possibility of MD. Preoperative fasting is minimized (limited to 2 hours if possible) in order to prevent hypovolemia, hypoglycemia, and increased reliance on

fatty acid metabolism (in the setting of impaired β-oxidation of fatty acids that may be seen in MD), and dextrose-containing maintenance fluids should be initiated for all fasting inpatients with the following exception. Many patients with MD are managed with ketogenic diets for control of seizure.[43] A ketogenic diet contraindicates the administration of glucose and theoretically complicates the use of propofol due to its effect on fatty acid metabolism. When patients receive dextrose, they should be monitored to ensure that they do not develop either hyperglycemia or lactic acidosis.[44]

Outpatient surgery should be scheduled as the first case in the morning to minimize fasting intervals. Continuous temperature monitoring is used to prevent both hypo- and hyperthermia, with the use of active patient warming or cooling devices, and intravenous fluid warmers to maintain euthermia. Continuous intraoperative electrocardiogram, blood pressure, and end-tidal gas monitoring are routine for all patients undergoing anesthetics, of course. Application of surgical tourniquets should be minimized as much as possible to avoid tissue hypoperfusion and ischemia.

Maintenance anesthetics (volatile agents or intravenous drugs) should be titrated incrementally, slowly, and carefully, while monitoring anesthetic depth clinically or ideally with the BIS or other processed electroencephalography system if available. It is important to remember that some patients with MD, particularly those with disorders affecting complex I, have shown exquisite sensitivity to anesthetic agents.[23] Although induction of general anesthesia with either propofol bolus or volatile anesthetics has been used in patients with MD,[6,8] it is advised to not administer propofol by continuous infusion after induction of anesthesia out of concern for propofol infusion syndrome in this vulnerable population. However, both we and others[17,25] are of the opinion that boluses of propofol are generally well tolerated unless the patient is metabolically compromised.[16]

The following have been safely, but anecdotally, used to provide anesthesia without causing recognizable mitochondrial or physiologic decompensation:

- small intravenous boluses of propofol, benzodiazepines, or ketamine;
- continuous infusion of dexmedetomidine;
- inhalation of sevoflurane; and
- bolus dosing or continuous infusion of short- or ultrashort-acting opioids such as fentanyl, sufentanil, alfentanil, or remifentanil.

Volume resuscitation with a physiological electrolyte solution without lactate is preferable to lactated Ringer solution, since patients with MD may have impaired lactate metabolism, and serum lactate levels would be artifactually high if measured to determine the degree of metabolic decompensation, if it were suspected.

The question of how long to keep a patient with MD under observation postoperatively usually hinges on how long the patient is likely to remain in a catabolic state. Close postoperative monitoring is essential to ensure that patients return to their baseline level of function prior to discharge from the postanesthesia care unit.

Summary

Meticulous attention to the same parameters that are important for all children forms the foundation of care for patients with MD. In addition, the anesthesiologist must recognize that patients with MD have heightened sensitivity or even untoward responses to many medications routinely used in anesthesiology. Intravascular volume and hydration status require close attention, with no administration of lactate and, when appropriate, addition of intravenous glucose. Central nervous system monitoring with processed EEG has proven helpful in small case series, primarily to prevent excessive dosing of inhaled anesthetics.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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