

MITO 101 –Anesthesia

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I. Key points

- There have been no clinical trials investigating the effects of various anesthetic agents in patients with mitochondrial diseases (MD)
- Pre-operative consultation with the anesthesiologist is appropriate in most cases
- Patients with MD may have myopathy and may show exaggerated sensitivity to neuromuscular blockade
- Patients with MD may have cardiomyopathy and conduction disturbances, which may require intraoperative monitoring
- Patients with MD may have impairment in the beta oxidation of fat, leading to ketosis, which can be avoided by the provision of calories in the form of dextrose infusion when the patient is placed NPO
- In theory, some anesthetic agents may have more risk of toxicity than others.

II. Background

All clinical manifestations of MD, including seizures, arrhythmias, cardiac dysfunction, myopathy, and endocrinopathies, can be worsened by trauma, illness, or surgical stress. Although the prevalence of MD is high (Skladal et al 2003), the heterogeneity of disease phenotypes makes clinical trials difficult. No controlled trials of different anesthetic agents or techniques have been conducted in patients with MD. Adverse effects on mitochondrial function of many agents used in anesthesia have been documented *in vitro*, but there are few reports of adverse events *in vivo*. Even agents like propofol, for which adverse effects have been reported both *in vitro* and *in vivo*, have been used successfully in isolated cases. Thus, the theoretical effects of any agent need to be considered in the general context of any one patient's medical history. It is important to realize that the absence of published reports of adverse effects with any given agent does not mean that the agent is safe to use but may simply reflect a publication bias.

III. Supportive care

Patients with MD often have significant myopathy, resulting in increased sensitivity to the effects of many drugs used in anesthesia and increased risk of pulmonary complications. Patients with myopathy may require lower doses of anesthetic and neuromuscular blocking agents than normal individuals, and monitoring techniques to titrate the dose (rather than using a weight-based dosing nomogram) may be appropriate. Close postoperative monitoring is also appropriate to ensure that patients return to their baseline level of function and can protect their airway. Patients with MD may also have cardiomyopathy, predisposing them to arrhythmias. Intraoperative ECG monitoring may be appropriate. In addition, these patients may have metabolic abnormalities, including diabetes mellitus or baseline lactic acidosis, which may worsen with surgical stress and lead to electrolyte imbalances.

Fasting before surgery shifts metabolism towards fat utilization as an energy source. As beta-oxidation of fatty acids occurs in the mitochondria, patients with

MD may be limited in their ability to metabolize fat, and fasting should be avoided by scheduling the surgery first thing in the morning and providing a dextrose infusion when the patient is NPO. This does not mean that the patient has to be admitted to hospital overnight, as the dextrose infusion can be started when the patient is admitted to the preoperative area. Blood sugar monitoring is advisable to avoid hyperglycemia. A list of potential metabolic stressors and their suggested management is included in Table 1.

IV. Type of anesthesia and choice of agent

The choice of local, regional, or general anesthesia requires consideration of both patient characteristics (ability to tolerate a procedure if awake, pre-existing peripheral neuropathy or spinal cord disease etc) and type of surgery (need for muscle relaxation, degree of post-operative pain control etc). Adverse outcomes have been reported in patients with MD, who underwent procedures under both local (Finsterer et al 2005) and regional (Cooper and Fox, 2003) anesthesia, showing that these techniques are not necessarily safer than general anesthesia. Reassuring data have been provided by Driessen et al (2007) in a series of 122 children with confirmed MD who underwent minor surgical procedures: 119 of them had normal anesthesia-related outcomes. These data suggest that, with appropriate preoperative assessment and monitoring, anesthesia can be carried out safely in patients with MD.

Choice of the best anesthetic can be difficult because most anesthetic agents have been shown to have negative effects on mitochondrial function in vitro as shown in Table 2 (Muravchick and Levy 2006). In vitro risk for malignant hyperthermia (MH) has been associated with mitochondrial myopathy (Fricker et al 2002) although the actual prevalence of this complication is unknown. In a large series of children with various muscle diseases including mitochondrial myopathies (Flick et al 2007), the risk of MH was very low, even with routine use of inhalational agents that are known to be associated with MH. However, in that series, only 3 patients received succinylcholine, a known trigger of MH. As patients with myopathies are known to be at increased risk for MH, it seems reasonable to recommend that known triggers of that condition, such as succinylcholine, be avoided.

IV. Recommendations

- Pre-op anesthetic assessment is recommended to document degree of organ system involvement and co-morbidities
- These patients may have involvement of respiratory muscles like other patients with myopathy. This can increase the risk of pulmonary complications
- Mitochondrial dysfunction can lead to ketosis and this may be worsened by trauma, illness, general anesthetic or surgical stress. Measurement of serum electrolytes and anion gap will help to identify ketosis if present.
- Avoid Ringer's lactate as patients may have pre-existing lactic acidosis
- Try to schedule surgery first thing in the morning to minimize time spent NPO
- For minor surgery - have patient arrive early in the morning for dextrose infusion

- For major surgery – start dextrose containing fluids when patient placed NPO
- Intraoperative monitoring of temperature, heart rhythm, glucose and electrolytes may be indicated
- Post-operatively, careful observation prior to extubation is required as prolonged effects of neuromuscular blockade may be present

Table 1. Metabolic stressors that can lead to decompensation in patients with mitochondrial disease

Stressor	Suggested action
fasting	Perform surgery first thing in the morning if possible; run D10 W when NPO
hypoglycemia	Intraoperative glucose monitoring
hyperglycemia	Intraoperative glucose monitoring and use of insulin infusion if glucose >8 mmol/L
hypotension	Support with fluids; avoid lactate-containing intravenous solutions
sepsis	Standard management
hypothermia	Intraoperative temperature monitoring, warm fluids prior to infusion

Table 2. Effects of drugs used in anesthesia on mitochondrial function¹

Class	Possibly contraindicated in mitochondrial disease	Rationale	Recommended alternative*
local anesthetics	bupivacaine	Inhibit mitochondrial bioenergetics and disrupt oxidative phosphorylation	No reports of adverse effects with lidocaine or ropivacaine but in vitro, lidocaine also affects mitochondrial function
induction agents	propofol	Has been shown to impair mitochondrial function (uncouples oxidative phosphorylation, inhibits electron flow along electron transport chain, antagonizes beta receptor binding, acts directly on Ca channel proteins diminishing contractility) to a greater degree than other anesthetics	Propofol has been used successfully in some patients with mitochondrial disease for induction (Driessen et al 2007). Prolonged infusions of propofol should be avoided given the effects on mitochondrial function. Adverse events with other induction agents such as ketamine, thiopental and etidomate have not been reported to date

inhalational agents	nitrous oxide	May exacerbate complex 1 inhibition induced by inhalational agents such as halothane	
	halothane, isoflurane, sevoflurane	Inhibit complex 1 activity; this effect is less marked in vitro with sevoflurane than with halothane or isoflurane	Sevoflurane has been reported in reported in more cases than any other inhalational agent with successful outcomes (Driessen et al 2007).
barbiturates	pentobarbital	Inhibit complex 1 activity and uncouple oxidative phosphorylation	No reports of adverse events reported in literature with pentobarbital so this is a theoretical consideration only
benzodiazepines	valium, midazolam	inhibit adenosine nucleotide translocase	No adverse events reported in literature with lorazepam; midazolam has been used successfully in isolated case reports
non-depolarizing muscle relaxants	rocuronium, cisatracurium, mivacurium	increased sensitivity to the paralytic effects and prolonged responses reported as in patients with other types of neuromuscular diseases.	Closely monitor neuromuscular block and use drugs with shorter duration of relaxation when possible
depolarizing muscle relaxants	succinylcholine	Patients with mitochondrial diseases may be predisposed to malignant hyperthermia as with other myopathy patients	Nondepolarizing muscle relaxants are likely preferable; however, there are no data comparing outcomes with depolarizing or nondepolarizing muscle relaxants in patients with mitochondrial diseases
opioids	No information on contraindicated opioids		Ultra short acting narcotics, i.e. a remifentanil infusion likely would be reasonable choice in these patients for maintenance of anesthesia

¹ Data summarized in references from Maslow and Lisbon (1993), Cohen et al (1998), Sharma et al (2001), Shipton and Prosser (2004) and Muravchick and Levy (2006)

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