

Anesthesia and Mitochondrial Cytopathies

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Introduction

This article will outline some basic aspects of anesthesia and address the issue of the special risks of anesthesia in patients with mitochondrial cytopathies. *The applicability of these recommendations to a particular patient is complex and should be individualized by your physician.* Considerations include whether the patient is undiagnosed (i.e. receiving their first evaluation to determine whether a mitochondrial disease is present), whether the patient carries the diagnosis of a mitochondrial disease, and what criteria were used in making the diagnosis. The clinical condition of the patient is probably the most important aspect of the pre-operative evaluation. Some patients have minimal disease manifestations and are at low risk for complications, whereas, other patients have significant disease manifestations such as respiratory muscle weakness, swallowing difficulties, liver disease, and heart disease, and are at high risk for complications.

Anesthesia, often referred to as *general anesthesia*, is the medical procedure that renders patients unconscious, insensible to pain and provides muscle relaxation. With *local anesthesia*, or regional anesthesia, patients are awake or sedated, but do not feel pain because the pain pathways are “blocked” by the local anesthetics. *Spinal* anesthesia involves the use of local anesthetics or narcotics injected around the spinal cord, causing loss of sensation below the level that the medication is injected.

Intravenous Anesthetics

In ancient times orally administered extracts of poppy seeds (opium and morphine), extracts of the deadly night shade (hyoscyne and belladonna), and extracts of fermentations (alcohol) were used for “anesthesia”. All of these drugs decrease consciousness and the awareness of pain. At present, most of these drugs or their modern counterparts are administered intravenously. Thiopental is a rapidly acting barbiturate used for induction (the first part of anesthesia when the awake patient is put to sleep) of anesthesia. Propofol and etomidate are new rapidly acting induction agents. Diazepam (Valium) and midazolam (Versed) are drugs in the benzodiazepine category, which are potent hypnotics (induce a sleep-like state). Morphine, meperidine (Demerol) and fentanyl are examples of potent narcotic pain relievers (analgesics) that are used as part of some anesthetics.

Inhalation Anesthetics

The earliest modern inhalation anesthetics were the gas nitrous oxide (also referred to as laughing gas), and ether, a *potent inhalational anesthetic*. Potent inhalational anesthetics are vapors produced from a liquid that evaporates easily. Nitrous oxide is still a basic in modern anesthesia; however, the modern potent inhalational anesthetics include halothane, enflurane, isoflurane, sevoflurane, and desflurane. The potent inhalational anesthetic agents provide all the modalities of general anesthesia; which include unconsciousness, analgesia and mild muscle relaxation.

Muscle Relaxants

In addition to the drugs that induce the sleep-like state, a group of drugs that provides muscle relaxation are often part of a modern anesthetic. These drugs interfere with the communication between nerves and muscles, and induce a paralyzed state so that the patient does not unconsciously move during surgery. There are of two types of muscle relaxants; the depolarizing muscle relaxants (succinylcholine), which causes the patient's muscles to move before paralysis occurs and is relatively short acting, and the non-depolarizing muscle relaxants which do not cause such movements. When patients are paralyzed with these drugs, the anesthesiologist or anesthetist must breathe for the patient by either hooking the breathing tube to a machine or manually squeezing a "bag" often containing a mixture of oxygen, laughing gas and a potent inhalational anesthetic.

Issues of Anesthesia in Mitochondrial Cytopathies

Modern general anesthesia consists of induction with intravenous agent and maintenance with inhalational agents and/or with intravenous agents. Muscle relaxants may or may not be used. Concerns about the side effects and possible complications associated with surgery and anesthesia are shared by patients with mitochondrial cytopathies, their families and their physicians.

The vast majority of patients with mitochondrial cytopathies have an uneventful surgery and anesthesia. Patients rarely experience a complication with a simple elective surgical procedure such as a muscle biopsy or gastrostomy tube placement. Patients with preoperative respiratory problems are at greater risk for worse problems after surgery. Similarly, those with seizures may experience post-operative seizures.

There are a limited number of reports describing adverse events and outcomes in patients with mitochondrial diseases following surgery and anesthesia. Our knowledge about these potential complications are based on these anecdotal reports. It is not possible to draw conclusions about the safety of a particular anesthetic agent based on the outcome of these cases. Although it is possible to test a particular anesthetic in a laboratory setting to see how it affects mitochondrial function, this work is based on animal experiments. How these animal studies relate to humans in a clinical (not laboratory) setting is impossible to determine. In reviewing these reports, a number of inferences can be made:

- Patients with mitochondrial cytopathies, on average, are "sicker" than the unaffected patient undergoing surgery and are having an operative procedure for potentially more serious reasons than the unaffected patient.
- As a general rule, patients with mitochondrial cytopathies are at greater risk than unaffected people for side effects of some medications. Although some medications may interfere with energy metabolism to some degree, complications are usually related to the clinical condition of the patient prior to surgery.
- The adverse events reported include new neurologic problems such a strokes, worsening of the overall neurologic status, respiratory difficulties, seizures, cardiac arrhythmias, prolonged coma and death.

- Hypotonia (low muscle tone), bulbar dysfunction (weakness of the muscles that protect the airway) and relatively poor ventilatory function (decreased ability to breathe deeply and cough) are common in patients with mitochondrial diseases and pose an increased risk for perioperative pneumonia. In one study of patients with typical Leigh syndrome (which generally represents one of the more severe forms of mitochondrial cytopathies), respiratory difficulties prior to anesthesia and surgery were a predictor of postoperative respiratory failure and death. In the cases reported, the patients awakened from anesthesia but deteriorated within a day. There did not seem to be any specific anesthetic agent or technique that triggered these adverse events. It is not clear from this study whether the deterioration was a direct result of the surgical procedure, the anesthetic drugs, or as a result of mitochondrial failure due to inadequate oxygen, which resulted form an unrecognized pneumonia or respiratory failure. Understanding these factors may make anesthesia safer, but will not avoid all risks. (J Child Neurol 1990;5:137-41)
- Malignant Hyperthermia (MH) is a life threatening, inherited syndrome triggered by potent inhalational anesthetic agents and/or depolarizing muscle relaxants. It is caused by abnormal increases in muscle calcium concentrations leading to uncontrolled muscle metabolism, subsequent metabolic acidosis, muscle damage, and elevated potassium levels. Without treatment, MH will often result in death. Patients at risk for MH may develop the disorder with their first anesthetic, or may have a dozen or more anesthetics without a problem, only to develop MH with the next anesthetic. There are specific treatments available for MH if it should develop, but the best approach is to identify patients at risk and use anesthetics that do not trigger MH. Risk factors for MH include 1) prior MH episode in the patient, 2) a family history of MH and 3) muscle disease. Many patients with mitochondrial cytopathies sometimes have an associated myopathy (muscle disease), which places them at a potential risk for MH. There are anesthetics that are “safe” for those with or at risk for MH, but these anesthetics may adversely affect mitochondrial function in some patients.
- The risk of respiratory failure and worsening of neurologic function is often noted in patients with mitochondrial cytopathies after “stressful” illnesses, including infections such as viral or pneumonia. Infections may be associated with surgical procedures, either as a complication of surgery or as the need for surgery, as in the case of a ruptured appendix. Infections, such as the common cold, can also occur randomly around the time of surgery. Certainly surgery itself, even if for a non-emergency condition, is a major stress. The following discussion is quite complicated but necessary in order to understand that anesthetic drugs alone should not be considered the only element in leading to these adverse outcomes. During infections, the body responds by making chemicals known as *cytokines*. Cytokines help the body fight infection, and are also responsible for the fever, aches, chills and the overall “rotten” feeling we get when we are ill. Cytokines induce the formation of nitric oxide. Nitric oxide (the chemical formula is NO•) is a powerful oxidant with many useful purposes in our bodies, some of which seem quite unrelated, such as forming new memories and killing bacteria. However, nitric oxide inhibits cis-acotinase (a citric acid cycle enzyme) and the iron-containing cytochromes of the respiratory chain. Therefore, NO• in high amounts may decrease energy production, which is ill-afforded in patients who already have an impaired ability to generate energy. Nitric oxide can also interact with other chemicals in the body that result in damage to the mitochondrial DNA and mitochondrial structure itself. One cytokine

known as tumor necrosis factor (TNF), is known to be released by the body during surgery, and is also known to be a potent inhibitor of complex III. TNF has many essential functions, and serves as a natural defense against infections and cancer. In otherwise healthy people, the inhibitory effect on complex III is obviously not harmful, but may play some role in people with mitochondrial diseases, who are not able to tolerate any small decrement in mitochondrial function. Therefore, anesthetic agents may not be responsible, at least without additional factors, for causing neurologic deterioration. Both the stress of surgery as well as any associated infections may trigger the events leading to a deterioration in susceptible patients. (Anesthesiology 1997;87:420-5)

- Some patients have heart rhythm problems, such as those with Kearns-Sayres, that are at risk for severe heart electrical conduction blocks, which can lead to death. Isoflurane may be a preferred inhalational agent as opposed to Halothane, because Isoflurane causes less disturbances in heart rhythms. (Anesthesiology 1994;49:876-878)
- Although spinal anesthesia is safe, it should be used with extra caution in patients with neuropathies or myopathies, because of the possible deleterious effects on blood pressure and respiratory function.

Recommendations

There is no doubt that patients with mitochondrial disease can undergo general anesthesia safely, as demonstrated by untold thousands of uneventful surgeries and anesthetic exposures. The question that patients and their physicians wish to know is how to further decrease the risk. The following recommendations are made with the understanding that there are little data suggesting that any specific precautions can lower the risk of neurologic events. However, these recommendations seem to be prudent given what is known about the effects of surgical stress, infections and anesthetic agents in patients with mitochondrial cytopathies:

1. Strict attention should be made to respiratory function before, during and after surgery, especially in patients with abnormal preoperative respiratory signs and symptoms. Vigorous respiratory physiotherapy should be standard postoperative care in any patient with pulmonary difficulties. Early use of artificial ventilation, maintaining normal oxygenation, CO₂ elimination, and vigorous respiratory physiotherapy are recommended at the first sign of respiratory deterioration.
2. There should be a heightened level of suspicion for infections such as pneumonia, which should be promptly treated.
3. Lactated Ringer's solution (also known as Ringer's Lactate) should be avoided as an intravenous fluid, as it contains lactic acid.
4. Normal blood glucose, body temperature, and acid-base balance should be maintained during surgery. Low blood glucose should be avoided. However, a high blood glucose may indicate an acute disturbance in pyruvate metabolism or oxidative phosphorylation. In this situation, the lactic acid levels may also be elevated.

5. Avoid depolarizing muscle relaxants, although these have been used safely in many patients with mitochondrial diseases. *Anesthesiology* 1979;51:343-345.
6. Delay elective surgery if there is any evidence of infection.
7. Potent inhalational anesthetic agents appear to be safe in the majority of people with mitochondrial diseases. In patients at risk for MH, such as those patients with myopathies that are often associated with their mitochondrial disease, the risks and alternative methods of anesthesia must be considered by the physician. Certainly if there has been a previous adverse reaction in the patient or family member, these agents should be avoided. (Table 1)
8. Anesthesia with combinations of barbiturates, narcotics, benzodiazepines, and nitrous oxide also pose a theoretical risk for patients with disorders of oxidative phosphorylation. (Table 2) This risk should be considered only as a potential risk unless a patient has experienced a bad reaction to any of the medications. This apparent paradox between the two methods of general anesthesia must be addressed with each patient, and the anesthesiologist must determine what is the safest route.
9. Animal studies indicate that propofol, a new intravenous anesthetic, impairs mitochondrial function to a greater degree than other anesthetics. However, this drug has been used safely as an anesthetic in many patients with mitochondrial cytopathies. There have been observations that prolonged continuous use (days) at high dosages to treat frequent seizures causes a syndrome similar to mitochondrial failure, and therefore prolonged use in a patient with a mitochondrial cytopathy may not be safe.

Conclusion

An increased awareness is needed whenever a person with a mitochondrial cytopathy is contemplating or undergoing a surgical procedure. By virtue of the illness itself, there are greater risks involved with every medical intervention. The safest anesthetic is not known and the choice of anesthetic must be individualized to the patient's particular needs. Although anesthetic agents may play a contributing factor in causing an adverse event associated with surgery, the illness, the stress of that illness, the surgical procedure and concurrent infections may play a larger role in causing neurologic deterioration. With additional research, more will be learned about these problems.

Table 1: Malignant Hyperthermia (MH) Precautions

Factor	Treatment
History	Acknowledge the potential for problems in patients with muscle disease, those with a past history or a family history of MH.
Muscle Relaxants	Avoid depolarizing drugs such as succinylcholine; and use non-depolarizing agents such as pancuronium instead.
Anesthetic Agent	-Avoid the potent inhalational agents such as halothane and enflurane -Use agents such as nitrous oxide, barbiturates, benzodiazepines, and narcotics.
Preparation for MH	Have adequate amounts of Dantrolene® available and use it as soon as the first signs of MH occur.

Table 2: Effects of Anesthetic Agents on Mitochondrial Function

Medication	Biochemical and Clinical Effects on Mitochondrial Function
Barbiturates	Inhibits Complex I activity at high levels
Benzodiazepines	Inhibits adenosine nucleotide translocase
Propofol and/or lipid carrier	Inhibits mitochondrial function
Halothane	Increased risk for heart rhythm disturbance
Nitrous Oxide (chemical formula is N ₂ O)	Neurotoxic, possibly by increasing nitric oxide production, which inhibits cis-acotinase and iron-containing electron transport enzymes; affecting energy production
Non-depolarizing Agents	Increased sensitivity to the paralytic effects and prolonged responses reported
Local Anesthetics	Bupivacaine uncouples oxidation and phosphorylation