



## Kennedy Krieger Institute

### **Information for Anesthesiologists and Surgeons for Operative and Perioperative Care of Patients with Mitochondrial Diseases**

#### **I. Introduction**

Patients with primary disorders of mitochondrial energy metabolism usually undergo general anesthesia for muscle biopsies, gastrostomies, and other elective operative procedures without anesthetic reactions or worsening of their medical condition. Nevertheless, general anesthesia is a known risk factor for disease-related injury due to direct impairment of mitochondrial function by anesthetics, excessive perioperative fasting, and the stress of the operative procedure itself. Although general anesthesia may present unpredictable risks for certain mitochondrial disease patients, most operative and perioperative complications that have occurred have been both predictable and preventable. Furthermore, whereas most injuries have occurred in patients who are substantially medically compromised, it is important to recognize that even a brief procedure, such as a gastrostomy or myringotomy, can lead to injury if simple but important precautions are not taken. The following discussion addresses most of the recognized operative risks for mitochondrial diseases and describes simple preventative measures that can be taken.

#### **II. Preoperative Evaluation**

Most patients with mitochondrial diseases have clinical problems that are limited to the tissues that have the highest rates of oxidative metabolism, namely the heart, skeletal musculature, and the nervous system. However, almost any organ can be compromised in a patient with a mitochondrial disease. Other common sites of involvement of special interest to surgeons and anesthesiologists include the liver, kidneys, and, to a lesser extent, exocrine pancreas, bone marrow, and endocrine system.

Prior to anesthesia, the patient should have a complete physical examination and laboratory testing pertinent to known and potential medical problems. Baseline laboratory testing at the time of admission or in the previous week for outpatient procedures should include a comprehensive metabolic profile, magnesium, CBC and differential, creatine kinase, amylase, and ammonia. While many patients will have mild chronic elevations of AST, ALT, creatine kinase, and ammonia, a substantially greater elevation of these markers of mitochondrial dysfunction and tissue injury could indicate an unsuspected viral process or other unsuspected change in the medical or metabolic status of the patient. Special attention should also be paid to serum electrolytes, because mild to moderate renal tubular dysfunction is common in mitochondrial disease, and the stress of surgery can lead to a worsening hyperchloremic metabolic acidosis or acute hyponatremia. The intraoperative or postoperative development of acute severe hyponatremia can cause sudden and irreversible injury of the brainstem and pons, such as pontine myelinolysis. Hypomagnesemia due to increased renal losses and/or poor absorption in more severely affected patients is an uncommon but important abnormality to identify preoperatively, especially because of its association with an increased risk for cardiac arrhythmia.

Specific System Problems The specialist involved in the care of any significant organ problem, such as cardiomyopathy, liver disease, or seizure disorder, as well as the neurologist, geneticist, or metabolic specialist responsible for the overall direction of the patient's care should be informed of the planned surgery or other procedure requiring anesthesia at least several weeks in advance. Such specialists should affirm that the patient is medically prepared for the procedure and should specify in detail how medications they have prescribed should be handled in the operative and perioperative periods. If relevant, the results of a recent EKG and echocardiogram should be reviewed, and specific recommendations for cardiac medications on the day of the procedure should be made and the risk of arrhythmia assessed. In general, the risks for cardiac arrhythmia in patients with mitochondrial disease are determined more by the type and status of the cardiomyopathy than by the specific mitochondrial diagnosis or associated biochemical abnormalities.

### **III. Preoperative fasting and perioperative nutrition**

Most complications of anesthesia and surgery that have occurred in children with mitochondrial disorders have not been caused by malignant hyperthermia or metabolic acidosis but by a failure to modify and monitor nutrition and appropriately in the perioperative and postoperative periods. The following aspects of nutrition are the most important to consider.

#### General nutrition

Because many patients with mitochondrial diseases have skeletal muscle hypoplasia or atrophy, they often have a substantially reduced ability to mobilize protein amino acid reserves for gluconeogenesis during periods of fasting or reduced caloric intake. In addition, some patients with mitochondrial diseases that affect substrate transport can develop a more severe metabolic acidosis with extended fasting than they do after meals or with high carbohydrate intake. Therefore, the common preoperative directive of "NPO after midnight" cannot be given. For otherwise well patients who are scheduled for an outpatient procedure, surgery should be scheduled for the early morning—preferably the first case in the day—and the patient should be awakened early enough on the day of surgery to give approximately 10 to 20% of daily calories as carbohydrate-rich clear fluids up to 3 hours before the procedure. On arrival at the hospital, an appropriate intravenous fluid containing 10% dextrose should be administered at 150% of the calculated fluid maintenance rate. For children with unstable cardiac function who are at risk for congestive failure, a more concentrated glucose solution may need to be given by central catheter to provide full calories on a restricted fluid intake. Because patients with mitochondrial disease often have a chronic or intermittent lactic acidosis and a limited ability to metabolize lactate, lactated Ringer's should not be used. The selected IV fluids should provide 5 to 6 mg/kg/min glucose and should be continued throughout the operation and postoperative period until the patient is able to resume at least full enteral caloric intake if not a normal diet. Parents should be provided with specific nutritional guidelines for the next several days to be certain that partial nutrition for several days does not lead to the fasting state.

#### Amino Acid Nutrition

If it is anticipated that the patient will require exclusively or predominantly intravenous nutrition for more than 24 hours, full parenteral nutrition including at least 1 g/kg/d of amino acids should be started within the first 24 hours. Amino acids are required to provide sufficient

substrate for anaplerotic function of the citric acid cycle and, thereby, both decrease the risk for postoperative hypoglycemia and facilitate wound healing. Ideally, any patient who is not in optimal nutritional condition should be hospitalized for one or more days before surgery so that new baseline chemistries can be obtained and full parenteral nutrition given. Furthermore, because many hospitals have early ordering deadlines for peripheral alimentation solutions, orders for peripheral alimentation may need to be written before going to the operating room. Another important reason to assure adequate blood amino acid levels at all times is that cardiac muscle is much more dependent on amino acids than most other tissues for the normal anaplerotic functions of the citric acid cycle. Therefore, prolonged or excessive glucose administration, which directly depresses blood amino acid levels, should be avoided. Because fatty acids are the preferred fuel for muscle, lipids should be a component of extended parenteral nutrition at a level of at least 10% of total calories unless there is prior evidence of fat intolerance.

### Medications

Advice about perioperative medication management should be sought from the prescribing physicians and/or the coordinating specialist, such as a geneticist or neurologist. Many children with mitochondrial diseases also are treated with various combinations of carnitine, thiamine, and other B vitamins, and one or more antioxidants, such as vitamin E, alpha-lipoic acid, and coenzyme Q10. Other than carnitine, thiamine, and riboflavin, most vitamin cofactors can be withheld for one or even several doses without harm. For children with known or suspected complex I deficiency, however, a single missed dose of carnitine, thiamine, or riboflavin can precipitate clinical or biochemical worsening. Fortunately, the cofactors used for complex I deficiency can all be given intravenously, if needed. However, if such therapy is anticipated, the hospital pharmacy should be contacted in advance to ensure the availability of the required medications. For carnitine, an intravenous dose at half of the oral dose can be given, since typically, less than half of an oral dose of carnitine is absorbed. Thiamine often is available as a separate intravenous medication, and an intravenous dose of 50 mg should easily exceed the amount that can be absorbed in any 8-hour period, regardless of the oral dose. If it is necessary to assure uninterrupted treatment with riboflavin or other B vitamins, these often can be provided from an ampoule of the standard vitamin mixture for parenteral nutrition.

## **IV. Electrolyte Management**

In addition to serving as the principal source of amino acids for gluconeogenesis, the skeletal musculature constitutes the largest reservoir of potassium in the body and is the tissue most important for the regulation of the serum potassium level. For individuals with mitochondrial myopathies and substantially reduced muscle mass, the ability to buffer changes in serum potassium levels is diminished in proportion to the reduction in muscle mass. Children with especially severe muscle hypoplasia can rapidly become hypokalemic when there are on-going losses of potassium or dangerously hyperkalemic when given intravenous potassium in amounts easily handled by most children. In addition, anesthesia may further impair the ability of muscle to regulate potassium levels because of adverse effects of anesthesia on mitochondrial function and plasma membrane stability. There also is an increased risk for depression of the serum potassium level any time high carbohydrate intravenous solutions are continued for an extended period after anesthesia. Therefore, the general practice for patients with mitochondrial disease should be to avoid including potassium in intravenous fluids unless safe levels (i.e., low normal to average levels) of serum potassium have been documented within the previous 24 hours.

During the procedure and postoperative recovery period, serum potassium levels should be measured as frequently as needed for a given clinical situation to assure continued maintenance of normal serum potassium levels.

## **V. Choice of Anesthetic Agents**

### Volatile Agents

Although patients with mitochondrial diseases are often said to be at risk of malignant hyperthermia, there have been no clearly documented cases of malignant hyperthermia in a child or adult with a primary mitochondrial disease. Severe rhabdomyolysis in some mitochondrial disease patients has occurred in the post-operative period, but this is rare and the mechanism usually is metabolic decompensation from inappropriate fasting rather than the specific calcium dysregulation of malignant hyperthermia. Also of concern is that prolonged exposure to anesthesia with volatile agents causes a degree of mitochondrial dysfunction even in normal individuals, possibly because enflurane, sevoflurane, and similar agents are highly lipid soluble drugs that can alter lipid bilayers, including the mitochondrial inner membrane, and also inhibit complex II of the mitochondrial respiratory chain. In addition, there is evidence in experimental models that the same volatile agents inhibit the homolog of the 49-kDa component of human mitochondrial complex I. Although sevoflurane and other inhalation agents have been used routinely in patients with mitochondrial diseases without adverse events, consideration should be given to employing non-volatile anesthetic agents, especially for short procedures.

### Desflurane

Although we try to avoid the use of enflurane, sevoflurane, and other highly lipid-soluble inhalational anesthetics, these have been used for short periods of time without complications in some patients with mitochondrial disorder. However, desflurane, a newer halothane anesthetic, can cause acute deterioration in mitochondrial diseases sensitive to vitamin E levels, which includes most. Studies have shown that desflurane causes significant systemic oxidative stress, as measured by malondialdehyde levels as well as vitamin E depletion in operative room workers exposed to desflurane (9-11). In one adolescent with ophthalmoplegia and optic atrophy due to a mitochondrial disorder, a one-hour exposure to desflurane at end of anesthesia for scoliosis surgery caused an acute 50% depletion of vitamin E, with rapid evolution of cerebellar ataxia and other central and peripheral neurological signs of vitamin E deficiency.

### Propofol and Mitochondrial Disease

Although there is circumstantial evidence associating prolonged infusion of Propofol with the induction of a “mitochondrial” syndrome of metabolic acidosis, rhabdomyolysis, and cardiac collapse, no equivalent or related syndrome has been linked to the short-term use of Propofol for preoperative management of a patient. Rather, the risk for “propofol infusion syndrome” appears to increase with the duration of use of propofol, with possibly reduced tolerance of propofol in those with impaired mitochondrial function. Moreover, since there is evidence that the toxic effect of Propofol is caused by inhibition of mitochondrial fatty acid oxidation, appropriate attention to pre- and intraoperative nutrition designed to prevent fasting, as outlined above, should limit the increase in free fatty acids levels that likely contributes to the evolution of a Propofol-induced crisis. The greatest risk may fall to mitochondrial patients who are inappropriately fasted after midnight and arrive in the OR suite in the fasting state with high free fatty acid levels.

## Neuromuscular Blocking Agents

Succinylcholine is contraindicated in patients with mitochondrial disease. In addition, non-depolarizing neuromuscular blocking agents may exert a prolonged effect in a child with a mitochondrial myopathy.

## **VI. References**

Although in the last few years there have been several retrospective series of patients with mitochondrial disease who underwent general anesthesia and even propofol infusion anesthesia with no complications, the literature is necessarily strongly biased toward reporting of complication-free anesthesia. Anyone who specializes in the care of mitochondrial diseases knows of patients who suffered serious morbidity or mortality directly related to anesthesia. Such cases occur unexpectedly, and, unless some important management discovery is found in treating the patient, they are unlikely ever to be reported.

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