A Child with Propionic Acidemia Undergoing Dental Restorations: A Case Report

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Propionic acidemia is an autosomal recessive disease in which there is a deficiency of propionyl-CoA carboxylase, an enzyme necessary near the end of the catabolic pathway to metabolize several essential amino acids. Clinical features of propionic acidemia affect many body systems and prompt specific anesthetic care. Some of these features include gastroesophageal reflux, hypotonia of the airway, impaired gag reflex, mental delay, and seizure disorder. Long-term treatment of propionic acidemia consists of dietary supplementation and protein restriction. In times of stress, as can occur during surgery, acute decompensation may occur in patients with propionic acidemia. This is a life-threatening condition resulting in severe ketoacidosis.

This case report describes the anesthetic management of a child with propionic acidemia undergoing dental restorations. Specific anesthetic rationales are explained related to propionic acidemia for the entire intraoperative period. In addition, the signs and symptoms and treatments of an acute decompensation are discussed.

Keywords: Ketoacidosis, metabolic disorders, propionic acidemia.

Propionic acidemia is an autosomal recessive disease that occurs most often in individuals of Amish decent. In propionic acidemia, there is a gene defect for the mitochondrial enzyme propionyl-CoA carboxylase. This enzyme is necessary near the end of the catabolic pathway to metabolize several essential amino acids. Leucine, isoleucine, valine, and 3-carbon fatty acids are metabolized by this pathway (Figure). Propionyl-CoA carboxylase is encoded for by genes located on chromosomes 13 and 3. In propionic acidemia, there is a deficiency of propionyl-CoA carboxylase, which leads to an accumulation of propionyl-CoA.1

Propionyl-CoA inhibits the synthesis of N-acetylglutamate, which converts ammonia to urea. This ultimately leads to an accumulation of ammonia in patients with propionic acidemia. Propionic acid also accumulates in patients with this disease as a breakdown product of propionyl-CoA. Severe ketoacidosis results from the accumulation of propionic acid. Exacerbations of this disease are associated with excessive dietary protein intake or infection. Usually propionic acidemia is diagnosed in infancy, with a presentation of ketoacidosis and high ammonia levels. Symptoms typically appear when infants wean from breast milk. This results because formula is high in protein, whereas breast milk is relatively low in protein.1 As infants switch to a higher protein diet, manifestations of propionic acidemia present. Rarely, and for unknown reasons, late onset of propionic acidemia occurs in adulthood.2

Manifestations of propionic acidemia affect many body systems (Table 1). Early clinical features may include failure to thrive, neutropenia, anemia, and thrombocy-
topenia. Long-term outcomes of propionic acidemia may affect the central nervous system, presenting as developmental delay. This can be minimized or completely avoided with dietary protein restriction. Hypotonia is a clinical feature that may lead to respiratory insufficiency, an impaired gag reflex, and low tone of the upper airway. Untreated anorexia can progress to lethargy, seizures, coma, and death. Cardiomyopathy, gastroesophageal reflux, and optic nerve atrophy may develop. Other clinical features include episodic vomiting, pancreatitis, hyperammonemia, and metabolic acidosis.

Table 1. Clinical Manifestations of Propionic Acidemia
Abbreviation: GERD, gastroesophageal reflux disease.

<table>
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<th>Early</th>
<th>Late</th>
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<td>Failure to thrive</td>
<td>Developmental delay</td>
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<td>Neutropenia</td>
<td>Respiratory insufficiency</td>
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<td>Anemia</td>
<td>Impaired gag reflex</td>
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<td>Thrombocytopenia</td>
<td>Low tone of upper airway</td>
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<td>Anorexia</td>
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<td>Lethargy</td>
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<td>Seizures</td>
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<td>Cardiomyopathy</td>
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<td>GERD</td>
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<td>Optic nerve atrophy</td>
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<td>Pancreatitis</td>
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<td>Metabolic decompensation</td>
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<td>Hyperammonemia</td>
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<td>Hypoglycemia</td>
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<td>Ketoadidosis</td>
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<td>Lactic acidosis</td>
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Treatment of propionic acidemia can be divided into long-term management and management of acute exacerbations. Long-term management consists of dietary control and supplement replacement. Most patients are on a protein-restricted diet and take carnitine supplementation and biotin supplementation, and receive alkaline therapy for chronic acidosis. During periods of acute exacerbations, the focus is on management of acidosis and hyperammonemia. This is accomplished by treating the precipitating event and hydration with fluids containing glucose and bicarbonate.

The intraoperative period is a very stressful time for any patient. In a patient with propionic acidemia, the stress from the surgical and anesthetic management may induce an acute exacerbation of the disease, resulting in acidosis and a hypercatabolic state. The anesthesia provider must be familiar with the pathology of propionic acidemia, signs and symptoms of acute exacerbations of propionic acidemia, and the clinical management of any complications resulting from this disorder. Reference material related to the anesthetic care of a patient with propionic acidemia is minimal. This case report describes the anesthetic management of a child with propionic acidemia undergoing dental restorations.

Case Summary
A 4-year-old male child of Amish heritage presented for dental rehabilitation surgery. The child weighed 16 kg and had no known allergies to medications or to environmental substances. Medical history included a diagnosis of propionic acidemia as a newborn, slight developmental delay, and gastroesophageal reflux. Surgical history was for a cleft palate repair at 8 months of age. According to the child’s mother, there were no anesthetic-related problems from the cleft palate repair. Several extended family members also had a history of propionic acidemia.

The child has been under the care of a pediatrician who specializes in metabolic disorders since diagnosis. He underwent early genetic testing and continues to have yearly laboratory studies for serial monitoring. The treatment regimen includes a protein restriction of 15 g/d and dietary supplements. Daily medications for the child included l-carnitine, biotin, creatinine, a multivitamin, coenzyme Q10, pantothenic acid, and lansoprazole (Prevacid). He had a cardiac workup approximately 6 months before surgery to rule out cardiomyopathy. The results of the cardiac workup were within normal limits for his age and showed no evidence of cardiomyopathy.

The anesthesia care team was notified several weeks in advance that a child with propionic acidemia would be coming in for dental restorations. This permitted the anesthesia team ample time to prepare an anesthetic plan and appropriate alternatives before the day of surgery. The child’s mother was contacted, and a thorough health history was obtained. A few weeks before surgery, the Certified Registered Nurse Anesthetist caring for this patient contacted the metabolic specialist who was regularly following up the patient. From the metabolic specialist, it was discovered that this child has a metabolically benign variant of propionic acidemia. Recommendations from the physician included avoiding prolonged periods of fasting, starting a dextrose infusion preoperatively, avoiding lactated Ringer’s solution, monitoring blood glucose levels perioperatively, and monitoring the patient postoperatively until he was able to tolerate oral intake.

The day before surgery, the child’s mother was contacted to discuss the anesthetic plan for surgery. She was instructed to give the child apple juice in the morning, 3 to 4 hours before surgery, to help prevent hypoglycemia. She was also instructed to arrive early so that a dextrose
infusion could be started 2 to 3 hours before surgery. On admission, the blood glucose level was checked and was 105 mg/dL. After intravenous (IV) access was obtained, an infusion of 10% dextrose and sodium chloride (D10NS) was started at 1.5 times the normal maintenance rate by weight. The child's weight was 16 kg, making a maintenance rate of 52 mL/kg based on the 4-2-1 rule for calculation of the pediatric fluid maintenance rate. The D10NS infusion was started at 75 mL/h (1.5 x 52 mL/kg). The patient was seen by the anesthesia providers, and informed consent was obtained from the mother. The patient remained in the preoperative area for approximately 3 hours until the scheduled surgery time.

Once in the operating room, standard monitors were applied, vital signs were noted to be appropriate for age, and the child was given 50% nitrous oxide in oxygen via mask. Intravenously, 1 mg of midazolam was given to reduce anxiety. Anesthesia was induced intravenously with 100 mg of thiopental, 30 μg of fentanyl, and 0.08 mg of glycopyrrolate. Cricoid pressure was applied during induction, and the child was not ventilated to minimize the risk of aspiration. Immediately after loss of consciousness and administration of phenylephrine nasal drops, the child was intubated with a No. 5 nasal Ring-Adair-Elwyn endotracheal tube. A soft-catheter technique was used for the nasal intubation to avoid trauma to the nasal passages. The nasal tube placement was confirmed by bilateral breath sounds and positive end-tidal carbon dioxide (ETCO₂). The tube was secured in place, and the intubation was noted to be atraumatic.

Anesthesia was maintained with sevoflurane in 2 L/min fresh gas flow of oxygen and air. The child was mechanically ventilated to maintain oxygen saturations of 99% to 100% and an ETCO₂ of 34 to 39 mm Hg. Temperature was maintained by use of a warming blanket. A throat pack was placed by the surgeon to minimize gastric accumulation of secretions and blood. Dexamethasone, 8 mg, was given intravenously. The D10NS infusion was continued during the intraoperative period via infusion pump. The blood glucose level was checked after induction of anesthesia and was noted to be 96 mg/dL. The dextrose infusion was increased slightly to 80 mL/h to prevent hypoglycemia. After 1 hour, the blood glucose level was 156 mg/dL. At this point, the dextrose infusion was returned to the original infusion rate of 75 mL/h. Vital signs, including temperature, were stable throughout the entire procedure and were appropriate for age.

At the end of the surgical procedure, ondansetron, 1.6 mg IV, was given as an antiemetic, and ketorolac, 8 mg IV, was given for postoperative pain reduction. The throat pack was removed by the surgeon. A small suction catheter was used to empty the stomach, and the oral pharynx was suctioned. The volatile anesthetic was discontinued, and 100% oxygen was given. Spontaneous respirations were renewed with adequate tidal volume and respiratory rate. After confirming full return of airway reflexes and purposeful movements, the child was extubated. He was exchanging well without airway support and was transferred to the postanesthesia care unit (PACU).

In the PACU, vital signs were stable and appropriate for age. The D10NS infusion was continued at 75 mL/kg. The blood glucose level was checked once again and noted to be 124 mg/dL. From the PACU, the child was transferred to the recovery unit. Blood glucose levels were checked and recorded every hour. Approximately 2 hours after the completion of surgery, the anesthesia care team and the surgeon were at the bedside to monitor the patient’s progress. At that time, the child was tolerating oral liquids without any nausea or vomiting. The dextrose infusion was decreased by about half to 35 mL/h. After an additional hour, the child was still tolerating oral intake and had a blood glucose level of 164 mg/dL. The dextrose infusion was discontinued at that time, and the child was ready for discharge. While waiting for their transportation, the mother and child remained in the recovery area for several hours. During this time, the child’s vital signs and blood glucose levels remained stable. No problems were noted. The child was discharged home with postoperative instructions for continued care.

### Discussion

The anesthetic management of a patient with propionic acidemia should revolve around avoiding intraoperative events that precipitate acidosis: fasting, arterial hypoxemia, dehydration, and hypotension. This care begins in the preoperative period. If indicated, a glucose level, ammonia level, and pH should be obtained. This will alert the anesthesia provider to any abnormalities before anesthesia and will also provide baseline measurements. In the case study, only a glucose level was obtained, as recommended by the metabolic specialist. Continuing protein-restricted diets and any medications for propionic acidemia also helps to avoid an exacerbation. Periods of fasting can precipitate a hypercatabolic state. For this reason, the child was instructed to consume a sugar-based clear liquid before surgery, while still staying within the recommended fasting guidelines. Intravenous fluid replacement is necessary during periods of fasting. Glucose is given in the IV fluids because it helps to suppress protein catabolism and subsequent acidosis. Lactated Ringer’s solution is avoided because lactate from the solution can contribute to acidosis. Based on these rationales, a D10NS infusion was started in the case study.

Induction of anesthesia presents additional challenges for the anesthesia provider. Patients with propionic acidemia are at high risk for pulmonary aspiration due to hypotonia or an abnormal gag reflex. A rapid sequence
induction is needed to decrease this risk, as was conducted in the case report. Another concern during the induction of anesthesia is related to medication choices. Thiopental was used because propofol, a medication often used in pediatrics for rapid sequence inductions, is relatively contraindicated because of the large amount of polyunsaturated fats in the emulsion.\(^1\,^3\) Also, muscle relaxants metabolized by ester hydrolysis should be avoided because they may precipitate ketoacidosis.\(^3\,^4\) Although succinylcholine would normally be an appropriate choice for a rapid sequence induction, it should be avoided in patients with propionic acidemia because it is metabolized by plasma cholinesterase.\(^5\) A muscle relaxant was not used for the induction of anesthesia because of the contraindication of the use of succinylcholine. If needed, rocuronium was available for muscle relaxant to facilitate intubation. Rocuronium was chosen because of its rapid onset when given in intubating doses and because of its hepatic metabolism.\(^5\)

During maintenance of anesthesia, hypoxemia, dehydration, and acidosis should be avoided. Ventilation should be adequate to prevent hypoxemia and to avoid respiratory acidosis. If there is potential for the surgery to cause oral bleeding, throat packs should be placed. Blood aspirated into the gastrointestinal tract presents as an increased protein load and may trigger an acute exacerbation.\(^1\) Throat packs were placed in the case study to prevent this. Blood glucose levels should be monitored throughout the procedure to assess effectiveness of the dextrose infusion. The dextrose infusion should be adjusted to maintain glucose levels greater than 80 mg/dL.\(^6\) Any medications that may decrease gastric motility should also be avoided during the procedure.\(^1\)

Lastly, the patient's temperature must be maintained while avoiding hyperthermia, because hyperthermia increases the metabolic rate.\(^6\)

To prepare a patient with propionic acidemia for emergence from anesthesia, antiemetics should be given, postoperative pain should be addressed, and full return of airway reflexes should be confirmed. Antiemetics are necessary to avoid vomiting postoperatively. In a patient with propionic acidemia, vomiting increases caloric requirements and makes metabolic control difficult.\(^6\) The stomach was suctioned to decrease gastric volume and ondansetron was given in an attempt to lessen postoperative nausea and vomiting. In the case study ketorolac was given for analgesia. Medications derived from propionic acid such as ibuprofen, naproxen, ketoprofen, and oxaprozin should be avoided as they add an extra propionic acid load to the body.\(^1\) Ketorolac is not derived from propionic acid and is therefore safe for use in patients with propionic acidemia. Last, it is important to ensure that all airway reflexes are intact and that the patient is awake for extubation. This is necessary because the patients are at risk of respiratory distress secondary to fatigue and hypotonia.\(^1\) An awake extubation is also necessary to prevent aspiration in these high-risk patients.\(^3\)

Although the anesthetic in the case study was uneventful, the patient was at risk of a metabolic crisis. Early signs of metabolic illness are difficult to determine when the patient is under general anesthesia. These early signs include irritability, weakness, lethargy, sweating, and paleness.\(^6\) The signs and symptoms of late metabolic decompensation include lactic acidosis, ketoacidosis, hypoglycemia, and hyperammonemia.\(^6\) If these signs and symptoms are observed, treatment includes hydration with fluids containing dextrose, bicarbonate therapy, and treatment of the precipitating event.\(^4\) The dextrose infusion should be run at a rate of 1.5 times the maintenance rate. The dextrose infusion is necessary because it allows the organs to use glucose as the primary fuel. Other treatment modalities include optimizing cardiac output, maintenance of urine output greater than 2 mL/kg per hour, maintenance of urine pH greater than 7, and maintenance of potassium concentration between 3.5 and 4.5 mEq/L. (D. Morton, MD, written communication, October, 2009). By initiating these treatments and addressing the precipitating cause, an acute metabolic event can be resolved.

The anesthetist caring for a patient with propionic acidemia will face many challenges. Adequate preparation and planning will aid in having a smooth, uneventful
anesthetic (Table 2). The anesthetist needs to be aware of the unique needs of a patient with propionic acidemia. Obtaining a thorough health history is imperative to help anticipate the anesthetic needs of the patient. Knowledge of the physiology and pharmacologic contraindications related to propionic acidemia will help the anesthetist establish a plan of care. Consultation with the managing physician is suggested in order to obtain more detailed information. Prevention of an acute metabolic decompensation is ideal when providing anesthesia. Being aware of the signs and symptoms of an acute exacerbation will allow for early diagnosis and treatment.

Summary
In this case study, a general anesthetic was given without any complications or exacerbations of propionic acidemia. With adequate planning by anesthesia providers, future patients with propionic acidemia should be able to successfully undergo general anesthesia without complications.

REFERENCES

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