orphanaesthesia

Anaesthesia recommendations for

Propionic Acidemia

Disease name: Propionic Acidemia

ICD 10: E71.121

Synonyms: Propionyl-CoA carboxylase deficiency, PCC deficiency, PA, PCCA-related propionic academia, PCCB-related propionic acidemia

Disease summary: Propionic acidemia (PA) is a rare autosomal recessive, inborn error of metabolism. PA has an estimated incidence of 1 in 20,000-250,000, depending on the geographic region. It is caused by pathogenic variants in the PCCA or PCCB genes, which code for their respective alpha and beta subunits of propionyl-CoA carboxylase, found in mitochondria. Propionyl-CoA carboxylase is expressed in every organ and is involved in the catabolism of branched-chain amino acids when proteins are degraded for cellular metabolic requirements.

Propionyl-CoA carboxylase deficiency results in the accumulation of propionic acid and related metabolites (e.g., propionyl-CoA, 2-methylcitrate, or 3-OH-propionate). Accumulation of these toxic metabolites leads to secondary mitochondrial dysfunction in turn causing progressive end-organ dysfunction. Significant genetic heterogeneity leads to varying clinical manifestations. Patients may experience severe metabolic ketoacidosis, hyperammonaemia, lactic acidosis, vomiting, gastroesophageal reflux disease (GERD), osteoporosis, acute and chronic pancreatitis, dilated cardiomyopathy, arrhythmia, hypotonia, developmental delay, intellectual disability, autism, epilepsy, and recurrent infections.

Propionic acidemia may be subdivided into early and late-onset subtypes. Early-onset propionic acidemia manifests in the first days to months of life and tends to have a more severe clinical course, punctuated by frequent hospitalizations caused by metabolic decompensations. It frequently presents with hypotonia, lethargy, vomiting, tachypnoea and feeding difficulties. Other symptoms may include seizures, hepatomegaly, diarrhoea, obstipation, coma, apnoea and hypothermia. Late-onset propionic acidemia is usually diagnosed after the first year of life, although some patients may not be diagnosed until adulthood. Patients with the late-onset subtype often present with failure to thrive, feeding difficulties, metabolic strokes, dilated cardiomyopathy, osteoporosis, and bone marrow suppression as their primary symptoms.

Management of propionic acidemia centers on the avoidance of metabolic decompensation by minimization of endogenous propionate production; avoidance of catabolic state; treatment of PA manifestations (e.g., chronic renal failure or cardiomyopathy); and treatment of secondary carnitine deficiency. Specifically, treatment strategies include avoidance of fasting or excessive physiologic stress, special protein-restricted diet to reduce propionogenic amino acids and nitrogen load, and supplementation with L-carnitine to treat secondary carnitine deficiency. Liver or liver-kidney transplants can improve clearance of propionic acid and help improve metabolic stability in severe PA patients. Although transplantation holds the promise of slowing

down end-organ decline, organ replacement in PA is not curative and patients need to adhere to protein restricted diet and carnitine supplementation in the post-transplant period.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

Recommended Medical Settings for Invasive Procedures: Surgery or invasive procedures requiring sedation on PA patients should only be carried out in centres prepared to treat acute metabolic decompensation. Procedures should not be performed in the ambulatory setting.

Common Surgical Scenarios: Although patients with propionic acidemia may present for any type of surgical need, common surgeries and procedures requiring anaesthesia include placement of feeding tubes and central venous catheters; magnetic resonance imaging; dental procedures; and liver or kidney transplantation.

Type of anaesthesia

Minimization of fasting times is of paramount when managing these patients. An infusion of intravenous dextrose should be started when the patient is made NPO.

General endotracheal anaesthesia is the most commonly described anaesthetic technique. Consider venting stomach air out if a G-tube is present. For patients experiencing nausea and vomiting, a rapid sequence induction should be considered. Several case reports describe the safe use of bolus propofol for the induction of anaesthesia, but continuous infusion should be avoided as propofol emulsion can worsen mitochondrial dysfunction. Sevoflurane, isoflurane and desflurane have been used for anaesthetic maintenance in this patient population. Non-depolarizing muscle relaxants that do not undergo ester hydrolysis such as vecuronium and rocuronium have been safely in PA patients. Anaesthesia should be maintained at a sufficient depth to avoid a stress response. Patients with propionic acidemia are prone to hypotonia and lethargy, thus they may be particularly sensitive to opioids and sedatives.

Mitochondrial dysfunction and impaired thermoregulation in severely affected PA patients can predispose them to hypothermia. Body temperature should be monitored and the use of cold IV solutions should be avoided to prevent hypothermia.

Acid base status should be closely monitored. Sodium bicarbonate infusions may be necessary to treat metabolic acidosis during complex procedures.

Drugs that induce catabolism, such as dexamethasone or other steroids, should be avoided.

Orogastric tubes and/or throat packs should be employed during any oropharyngeal procedures that may lead to swallowed blood, such as ENT or dental procedures, as, the protein load of digested swallowed blood may be sufficient to precipitate metabolic decompensation.

If a PA patient presents with metabolic crisis, an elective procedure should be postponed until the patient is stabilized. In the setting of metabolic crisis, a PA patient should be stabilized with temporary protein restriction and IV fluids containing dextrose and electrolytes. PA patients in metabolic crisis presenting with significant hyperammonaemia may also require nitrogen scavengers (e.g. sodium benzoate) and carglumic acid. Persistent hyperammonaemia will require haemodialysis.

Any anaesthetic technique should be used with caution and close postoperative monitoring is required as the stress of surgery may be sufficient to induce a metabolic crisis. General anaesthesia should be used with caution and appropriate postoperative monitoring in consultation with a clinical geneticist or metabolic physician.

Special care is needed with drugs that prolong QT interval, especially in patients with prolonged QTc intervals at baseline prior to the scheduled procedure.

Necessary additional pre-operative testing (beside standard care)

Cardiac evaluation of these patients should include a 12-lead EKG and an echocardiogram. Propionic acidemia may cause dilated cardiomyopathy, hypokinetic ventricles and/or ventricular hypertrophy. Special attention should be paid to the baseline QT interval, as propionic acidemia has also been associated with QT prolongation and sudden cardiac death.

A baseline evaluation of the patient's metabolic status should include glucose levels, electrolyte analysis, creatinine, ammonia levels, blood gas analysis, lactate, ALT, AST, and complete blood count.

Particular preparation for transfusion or administration of blood products

There are no specific recommendations or disease-related concerns when preparing for blood product transfusion in patients with propionic acidemia.

Particular preparation for anticoagulation

There are no specific recommendations or disease-related concerns regarding anticoagulation.

Particular precautions for positioning, transportation and mobilisation

Propionic acidemia may predispose patients to basal ganglia strokes, dystonia, joint contractures and osteoporosis. Special attention should be given to careful positioning in order to avoid fractures or injury.

Interactions of chronic disease and anaesthesia medications

Patients with seizures may be on chronic anti-epileptic medication therapy and may experience increased metabolism of anaesthetic medications.

Anaesthetic procedure

Anaesthetic Goals:

Any event that can precipitate metabolic acidosis should be avoided, including:

- Inadequate caloric supplementation and protein overload
- Hypoxia

- Hypo- and hyperthermia
- Dehydration
- Hypotension
- Lactic acidosis
- Cardiac arrhythmia

Preoperative:

The patient should continue L-Carnitine supplementation pre-operatively. L-Carnitine may be given intravenously if oral intake is impaired.

Metronidazole may reduce propionate metabolism by gut flora and can be continued in the perioperative period.

Patients with propionic acidemia should be scheduled as the first case of the day in order to minimise pre-operative fasting

When fasting, patients with propionic acidemia require dextrose containing maintenance IV Fluids to prevent protein catabolism

For prolonged cases, consider an insulin infusion 0.01 units/kg/hr

- In hyperglycaemic patients, insulin can facilitate cellular glucose uptake and prevent catabolism
- Caution with IV insulin is needed in patients with lactic acidosis. In patients with severe oxidative phosphorylation, insulin can lead to increased cellular uptake of glucose and lactate buildup.

Induction:

Rapid sequence induction and intubation should be considered for patients experiencing reflux or vomiting.

Maintenance:

Avoid lactate containing fluids.

Maintenance fluids should be administered at 1-1.5 times the patient's maintenance rate depending on the patient's cardiac and renal status.

Follow electrolytes, lactate, and treat as indicated: It is recommended to supplement the dextrose infusion with the daily requirements of sodium (3 mmol/kg/day) and potassium (2 mmol/kg/day). Close monitoring of electrolytes during the procedure is recommended.

Monitor body temperature as patients with propionic acidemia are prone to hypothermia. Normothermia should be maintained throughout.

Emergency:

Muscle relaxation should be fully reversed prior to extubation.

As patients with propionic acidemia are prone to hypotonia and difficulty clearing airway secretions, awake extubation should be performed.

Monitor body temperature and maintain normothermia throughout emergence as patients with propionic acidemia are prone to hypothermia.

Post-operative:

Continue dextrose-containing infusions until the patient resumes oral intake.

Avoid hypoxia and hypercarbia.

Monitor closely for signs of metabolic decompensation. Signs include:

- Anorexia
- Nausea/vomiting
- Lethargy
- Abnormal respiratory pattern
- Spasticity
- Hyper-reflexia/clonus

Drugs to avoid:

Any drug that may serve as a substrate for propionate

- Propofol contains significant polyunsaturated fats. A portion of these are metabolised to propionic acid. Some case reports describe the safe use of bolus propofol for the induction of anaesthesia, but continuous infusion should be avoided.

Drugs that are derived from propionic acid

- Ibuprofen
- Naproxen/Naproxen Sodium
- Fenoprofen
- Ketoprofen
- Flurbiprofen
- Oxaprosin

Muscle relaxants metabolised by ester hydrolysis as their metabolism generates odd-chain organic molecules:

- Succinylcholine
- Cisatracurium
- Atracurium
- Mivacurium

Drugs that prolong QT intervals should be used with caution in patients with a baseline prolonged QT interval including anti-emetic drugs, e.g. ondansetron and promethazine,

Particular or additional monitoring

Electrolytes, ammonia levels, lactate, and blood glucose should be evaluated pre-operatively. For prolonged procedures, intraoperative monitoring of arterial or venous blood gas, glucose,

lactate, electrolytes, and ammonia levels should be considered. For patients with prolonged QTc intervals, we recommend an EKG peri-operatively.

Possible complications

Patients may experience a metabolic decompensation under periods of stress, fasting and illness. If unidentified and untreated, this may progress to coma and death. Perioperative fasting and the stress of surgery or blood loss may trigger catabolic states that cause metabolic decompensation.

Post-operative care

Post-operatively, dextrose-containing maintenance IV fluids should be continued until the patient successfully resumes oral intake. If a prompt return (<6-12hours) to pre-operative enteral feeding is not possible, arrangements should be made to start parenteral nutrition.

Disease-related acute problems and effect on anaesthesia and recovery

Patients with propionic acidemia are prone to life threatening metabolic acidosis and hyperammonaemia which may progress to coma, brain damage and death within hours.

Triggers for metabolic decompensation include:

- Fasting
- Poor feeding
- Surgical stress
- Hypothermia
- Infections
- Dehydration
- Vomiting/diarrhoea
- Home medication disruption
- Corticosteroids
- Increased dietary protein burden

Metabolic crisis may present as:

- Anorexia
- Nausea/vomiting
- Lethargy or altered mental status
- New onset or changed from baseline neurological findings, e.g. hypotonia or new-onset and worsening spasticity
- Abnormal respiratory pattern
- Sudden vision or hearing changes
- Hyper-reflexia/clonus
- Seizures

- Hypothermia

A physician with expertise in metabolic diseases should be contacted immediately if signs of metabolic crisis are present.

- The workup for suspected metabolic crisis should include:
- Evaluation and treatment of triggering conditions
- STAT ammonia level
- CBC, CMP, blood gas, lactate

Emergency crisis treatment includes:

- Sedation, mechanical ventilation and vasopressor support if clinically indicated
- Temporarily restrict protein intake
- Patient should be made NPO for up to 24 hours
- Carnitine 100mg/kg/dose every 6-8 hours
- IV fluids to correct dehydration
- IV normal saline boluses
- Avoid lactated ringers
- Maintenance IVF with fluids containing D10% (or greater) at 1.5x maintenance rate
- Persistent metabolic acidosis should be corrected slowly with sodium bicarbonate
- Ammonia scavenging drugs, such as sodium benzoate and sodium phenylacetate may be utilised in the setting of hyperammonemia
- Carglumic acid can be used for acute hyperammonemia
- Critically high ammonia levels (>200 µmol/L) may require emergent dialysis. Consult with your metabolic and nephrology teams to discuss local guidelines for dialysis.

Ambulatory anaesthesia

Ambulatory surgery should not be performed in patients with propionic acidemia due to the possibility of surgical stress triggering a metabolic crisis which may not present until the post-operative period.

Obstetrical anaesthesia

Pregnancy has been reported in patients with mild forms of PA. Nutritional monitoring is important due to changes in metabolic and nutritional needs during pregnancy. Morning sickness should be treated aggressively, as nausea and vomiting can trigger catabolic states. Hospitalization, hydration, and nutritional supplementation may be required to prevent or treat decompensated states.

Metabolic demands increase further during labour and delivery. Supplementation with intravenous fluids and dextrose should be maintained, and patients should be monitored for signs of decompensation. Uterine involution can trigger catabolism, thus further monitoring is required in the postpartum period.

References

1. Rafiq M, Tobias J. Anesthetic Care of a Child With Propionic Acidemia. Journal Of Medical Cases 2015;6:420–425
2. Rodriguez LI, Tainsh EJ, Varga E, Mavarez AC. Anesthetic management for pediatric liver transplantation in a patient with propionic acidemia: A case report. J Investig Med High Imp Case Rep 2021;9:232470962110150. https://doi.org/10.1177/23247096211015025
3. Harker HE, Emhardt JD, Hainline BE. Propionic acidemia in a four-month-old male: A case study and anesthetic implications. Anesth Analg 2000;91:309–311. https://doi.org/10.1213/00000539-200008000-00014
4. Alex G, Kiss EE, Saynhalath R, et al. Anesthetic Management of Children With Propionic Acidemia Undergoing Esophagogastroduodenoscopy. Cureus 2021;13: e18168. doi:10.7759/cureus.18168
5. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis 2014;9:130. https://doi.org/10.1186/s13023-014-0130-8
6. National Organization for Rare Disorders. Propionic Acidemia. NORD guide to rare disorders. Philadelphia 2003: Lippincott Williams & Wilkins.
7. Janež J, Škapin AD. Resistance to Rocuronium in a Patient with Propionic Acidemia Undergoing Appendectomy for Acute Appendicitis: A Case Report with Literature Review. Signa Vitae 2020;16:187–191. doi:10.22514/sv.2020.16.0026.
8. Sibulo L, Kogel W, Landolt L, Seeni S, Markel J, Mlady A. Anesthetic Management of a Child With Propionic Acidemia Complicated by Bacteremia and Severe Acute Respiratory Syndrome Coronavirus 2. J medic cases 2021;12:152–156. https://doi.org/10.14740/jmc3628
9. Rajakumar A, Kaliamoorthy I, Reddy MS, Rela M. Anaesthetic considerations for liver transplantation in propionic acidemia. Indian J Anaesth 2016;60:50. https://doi.org/10.4103/0019-5049.174799.

Date last modified: **November 2022**

Authors:

Joseph M. Sisk, Anaesthesiologist, Departments of Anesthesiology and Pediatrics, The University of North Carolina at Chapel Hill, USA
Joseph_Sisk@med.unc.edu

David N. Flynn, Anaesthesiologist, Department of Anesthesiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
David_Flynn@med.unc.edu

Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

Reviewers:

Matthias Baumgartner, Department of metabolic disorders, University & Childrens' Clinic Zürich, Zürich, Switzerland

Patrick Forny, Department of metabolic disorders, University & Childrens' Clinic Zürich, Zürich, Switzerland

Oleg Shchelochkov, Clinician, Associate Investigator, Director of Residency and Fellowship Programs NIH/NHGRI, Bethesda, USA

Disclosure The reviewers have no financial or other competing interest to disclose.