Anaesthetic implications of cystinosis

Joseph D. Tobias MD

The author presents and discusses the anaesthetic care of a 12-yr-old boy with cystinosis. Cystinosis is a recessively inherited disorder of amino acid metabolism resulting in the abnormal intracellular accumulation of cystine. Anaesthetic care may be affected by variable end-organ involvement, most notably progressive renal deterioration beginning with the development of Fanconi syndrome and progressing to overt renal failure during the first decade of life. Additional organ system involvement may lead to cirrhosis with portal hypertension, diabetes mellitus, and hypothyroidism. Identification of the extent of end-organ involvement during the preoperative evaluation will help in the provision of safe anaesthetic care for such patients.

L'auteur présente et discute la conduite anesthésique d'un enfant de 12 ans atteint de cystinose. La cystinose consiste en une anomalie congénitale récessive du métabolisme de la cystine avec accumulation intra-cellulaire anormale de cet acide aminé. La conduite de l'anesthésie peut être influencée par des atteintes viscérales variées dont la principale est une détérioration rénale progressive. Celle-ci commence avec un syndrome de Fanconi et évolue vers une insuffisance rénale franche au cours de la première décennie. L'atteinte peut aussi se manifester au foie par une cirrhose avec hypertension portale. Il faut aussi suspecter le diabète et l'hypothyroïdie. L'identification de l'importance de l'atteinte viscérale lors de l'évaluation préopératoire permettra d'administrer en toute sécurité une anesthésie à ces patients.

Key words

ANAESTHESIA: paediatric;

KIDNEY: failure;

METABOLISM: cystini;

SYNDROMES: cystinosis, Fanconi.

From the Division of Pediatric Anesthesiology/Critical Care Medicine, Vanderbilt University, Nashville, Tennessee.

Address correspondence to: Dr. Joseph D. Tobias, Department of Pediatrics, Division of Pediatric Anesthesiology/Critical Care Medicine, Vanderbilt University, Medical Center North T-0118, Nashville, Tennessee 37232, Phone: (615) 343-0000, Fax: (615) 343-6249.

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Cystinosis is a recessively inherited disorder of amino acid metabolism resulting in the abnormal intracellular accumulation of cystine leading to progressive renal dysfunction with the development of renal failure and the Fanconi syndrome (proximal renal tubular defect with urinary losses of amino acids, glucose, potassium, bicarbonate, and phosphate). Progressive renal dysfunction and urinary losses of calcium and phosphorous lead to bony abnormalities which may require orthopaedic surgical intervention. We present a 12-yr-old boy with cystinosis who required anaesthesia during open reduction and internal fixation of a hip fracture.

Case report

The patient was a 12-yr-old, 32 kg, boy scheduled for open reduction and internal fixation of a hip fracture. The diagnosis of cystinosis had been made in infancy following a work-up for failure to thrive. His past medical history was remarkable for chronic renal failure requiring haemodialysis until he underwent a living related donor renal transplant at age eight. He had excellent graft function for the initial three years after transplantation but it had deteriorated over the past year with the development of chronic renal failure and hypertension. Current therapy included a combination of propranolol and furosemide. Other medications included calcium and magnesium supplementation, thyroid replacement therapy (synthroid 0.1 mg every day) and a graft rejection regimen of cyclosporin and alternate day steroid therapy. Preoperative physical examination revealed a small-for-age child with multiple bony abnormalities. His preoperative systolic blood pressure ranged from 100 to 120 mmHg with a diastolic of 70 to 90 mmHg. The remainder of the physical examination was unremarkable. Preoperative laboratory examination revealed normal electrolytes except for a serum bicarbonate of $16 \text{ mEq} \cdot \text{L}^{-1}$, blood urea nitrogen $68 \text{ mg} \cdot \text{dl}^{-1}$, creatinine $2.4 \text{ mg} \cdot \text{dl}^{-1}$, phosphorous $3.8 \text{ mg} \cdot \text{dl}^{-1}$, calcium $8.8 \text{ mg} \cdot \text{dl}^{-1}$, magnesium $1.8 \text{ mg} \cdot \text{dl}^{-1}$, and haemoglobin $7.8 \text{ gm} \cdot \text{dl}^{-1}$. On the morning of surgery, an iv infusion of normal saline was started. The patient was given his usual morning dose of cyclosporin, propranolol, and thyroid supplement. In addition, hydrocortisone $5 \text{ mg} \cdot \text{kg}^{-1}$ was administered. Anaesthesia was induced with thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$ and fentanyl $5 \text{ mg} \cdot \text{kg}^{-1}$. Tracheal intubation was facilitated with atracurium $0.5 \text{ mg} \cdot \text{kg}^{-1}$. Maintenance anaes-

thetia consisted of isoflurane, expired concentration 0.5 to 1.2%, and 50% nitrous oxide in oxygen. The patient's intraoperative course was uneventful. Estimated blood loss was 100 ml. Following the surgical procedure, residual neuromuscular blockade was reversed and the patient's trachea was extubated. Postoperative analgesia was achieved with intravenous morphine delivered by PCA.

Discussion

Three clinical patterns have been described in patients with cystinosis including the infantile or nephropathic form, an adolescent form, and an adult form.¹ Infantile cystinosis, as in our patient, presents with progressive renal dysfunction appearing in infancy. Renal dysfunction is initially manifested by the Fanconi syndrome followed by progressive glomerular dysfunction and renal failure. The "adolescent" form presents with renal dysfunction during the second decade of life while normal renal function is seen in the "adult" form of the disease. Despite repeated investigations, the exact defect accounting for the disorder has not been identified. However, there appears to be abnormal function of the transport system responsible for the efflux of cystine from lysosomes.¹ The defect in this system leads to the intracellular accumulation of cystine and progressive end-organ dysfunction of several systems including the kidney, liver, pancreas, and thyroid gland. Proper preoperative identification of the end-organ dysfunction is necessary to allow safe anaesthesia care.

Of prime importance in these patients is the invariable renal involvement. Early on this is manifested by the development of Fanconi's syndrome with excessive urinary losses of several anions and cations that are normally reabsorbed in the renal tubules. The Fanconi syndrome is a non-specific defect of the renal tubule leading to defective transport and impaired reabsorption of glucose, phosphate, amino acids, bicarbonate, uric acid and potassium. The excessive urinary losses of calcium and phosphorous leads to growth failure, osteomalacia, rickets, and progressive orthopaedic deformities. Renal tubular dysfunction also leads to polyuria, metabolic acidosis due to urinary loss of bicarbonate, hypokalaemia, and hypomagnesaemia.

A small subset of children with cystinosis may also develop Bartter's syndrome.² Their course is complicated by a hypochloremic metabolic alkalosis, hyponatraemia, and hypokalaemia. Such patients may have partial amelioration of their symptoms with indomethacin administration since Bartter's syndrome is thought to be the result of altered renal concentrations of prostaglandin E.

Preoperative measurement of serum electrolytes, calcium, phosphorous, and magnesium is suggested. This

is particularly relevant in patients at risk for perioperative arrhythmias, since recent reports have documented the importance not only of serum potassium, but also of serum magnesium in the prevention of cardiac arrhythmias.³ For brief surgical procedures, the patient's usual supplemental doses of calcium, magnesium, phosphorus, and potassium can be administered orally. This was the approach taken in our patient. However, for more involved procedures or when oral administration is not feasible, intravenous replacement will be required.

In addition to urinary losses of anions and cations, tubular dysfunction may lead to polyuria and isosthenuria which may further complicate perioperative fluid administration. In such patients, urine output and specific gravity may be relatively poor indicators of the patient's volume status. Invasive haemodynamic monitoring may be required in cases involving large fluid shifts/blood loss in order to accurately judge the patient's volume status. Joel *et al.* have further reviewed the perioperative implications of the Fanconi syndrome.⁴

Aside from its effects on renal tubular function, cystinosis leads to progressive renal insufficiency and failure. Azotaemia and deterioration of renal function occur early in patients with infantile cystinosis. Renal failure generally becomes manifest during the first decade of life with the need for either dialysis or kidney transplantation. Preoperative measurements of blood urea nitrogen and creatinine are indicated with attention to the obvious implications of altered renal function on the pharmacokinetics of anaesthetic agents such as neuromuscular blocking agents. Due to these concerns we chose to use atracurium to provide intraoperative neuromuscular blockade since its duration of action should not be altered by decreased renal function.

Variable involvement of other organ systems may also occur including liver cirrhosis leading to portal hypertension with oesophageal varices, pancreatic involvement with diabetes mellitus, and hypothyroidism.⁵ Preoperative evaluation of serum glucose as well as thyroid and hepatic function (liver enzymes, prothrombin time) are recommended. Our patient was already receiving thyroid supplementation while evidence of other end-organ involvement was lacking.

While young patients have normal intelligence, central nervous system involvement may occur as the disease progresses. This involvement may be manifested by a decline in school performance, cerebral atrophy, seizures, and pyramidal syndrome. Slow virus infections have been seen in patients with end-stage disease. Disturbances in sweating (normal sweat electrolyte concentrations with decreased volume) may also occur, leading to heat intolerance, hyperthermia, and flushing especially during exercise.

Progressive orthopaedic involvement and growth failure may also affect perioperative care. Poor nutrition and bony abnormalities may make these patients prone to develop pressure sores. As such, careful padding of bony prominences is suggested. In addition, the general cachectic nature of these patients may place them at risk for intraoperative hypothermia. Warming of infused fluids, regulation of the operating room temperature, and humidification of inhaled gases will help prevent considerable decreases in body temperature. One additional issue of patient comfort is the deposition of cystine crystals in the cornea and conjunctiva leading to photophobia.¹

In summary, the anaesthetic management of a patient with cystinosis is presented. Of concern to the anaesthetist is the variable end-organ involvement seen in these patients, most notably progressive renal deterioration beginning with the development of Fanconi syndrome and progressing to overt renal failure during the first decade of life. Additional involvement may lead to cirrhosis, diabetes mellitus, and hypothyroidism. Preoperative laboratory screening is indicated to identify end-organ pathology.

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