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Rare life threatening reactions to both propofol and sevoflurane in a patient with an undiagnosed myopathy: a case report

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Keypoints

1. Myosin heavy chain (MYH7)-related myopathies are emerging as an important group of muscle diseases of childhood and adulthood. Patients with myopathies are a challenge for anesthesiologists because of possible life-threatening reactions to anesthetic agents. The majority of complications occur in patients with undiagnosed myopathies.
2. Propofol is traditionally considered a safe drug for patients with suspected myopathic disease and total intravenous anesthesia (TIVA) with propofol is usually the anesthetic of choice. Conversely, patients with a known adverse response to propofol would receive an inhaled anesthetic for their procedure.
3. This case report details life-threatening rhabdomyolysis to both agents necessitating the avoidance of both with subsequent anesthetic use. Care must be taken when using either inhalational anesthesia or TIVA with propofol. Short term use of propofol may in fact be safe as our patient demonstrated severe rhabdomyolysis after a prolonged and high dose infusion. Risk factor analysis for the development of propofol infusion syndrome should guide the use of propofol in myopathic patients.

Abstract

Propofol infusion syndrome (PRIS) and anesthesia-induced rigidity (AIR) are both rare complications reported in the literature. This report describes a patient with a previously undiagnosed myopathy (MYH7) that had severe adverse reactions, although different in nature, to both propofol and sevoflurane. The patient was a 4 month old caucasian female with prenatally diagnosed DORV, a subaortic VSD, and a secundum ASD who presented for complete repair of her CHD. This report details her hospital course and outcomes with a brief review of the literature that is pertinent to her case. Myosin heavy chain (MYH7)-related myopathies are emerging as an important group of muscle diseases of childhood and adulthood. Precautions must be taken when using either inhalational anesthesia or TIVA (total intravenous anesthesia) with propofol.

Keywords

Propofol Infusion Syndrome (PRIS), Anesthesia-induced rigidity (AIR), myopathy, children, inhaled anesthetics, propofol.

Introduction

Propofol Infusion Syndrome (PRIS) and anesthesia-induced rigidity (AIR) in children receiving general anesthetics are rare and life-threatening occurrences. The literature suggests avoiding inhaled agents in patients with

myopathies and advises using propofol as a safe alternative. This report describes a patient with a previously undiagnosed type 1 myosin myopathy that had severe adverse reactions, although different in nature, to both propofol and sevoflurane.

Case report

BR was a 4-month-old weighing 5.4kg with prenatally diagnosed DORV, a subaortic VSD, and a secundum ASD who presented for complete repair of her CHD. She underwent inhalational induction with sevoflurane and her maintenance anesthesia consisted of fentanyl, isoflurane, propofol and rocuronium. She had a complete repair of her DORV and was admitted to the CICU post operatively on milrinone and nitroprusside with AAI pacing for a slow junctional rhythm. She was also on low dose epinephrine for the first 48 hours postoperatively. She was sedated with narcotics, dexmedetomidine, and propofol overnight in anticipation of extubation on postoperative day (POD) #1. Upon extubation, she developed stridor and upper airway obstruction and required reintubation after several hours. She was sedated with a continuous infusion of propofol thereafter, at doses ranging from 25-200 mcg/kg/min. She received two courses of dexamethasone in anticipation of extubation, but on POD#3, there was no leak around the ETT. Because of this, the decision was made to change the ETT to a smaller size and give her another 24 hours of dexamethasone prior to attempting extubation. Her propofol infusion was stopped because of the cumulative dose of propofol she had received and the duration of the propofol infusion (Table 1). Of note, laboratory values on the morning of POD#3, when propofol was stopped, showed normal electrolytes, a BUN of 20 mg/dL, serum creatinine of 0.41 mg/dL, lactate of 1.5 mmol/L and an ABG with pH 7.38, pC02 40, and pa02 89. However, her CK was noted to be elevated at 13,607 u/L, with a serum TG 130 mg/dl, AST 510 and ALT 131. Approximately 12 hours later on POD #3, she developed hypotension and cardiovascular collapse with a severe metabolic acidosis (pH 7.00 with BE of -15). She required epinephrine and vasopressin infusions for augmentation of her blood pressure.

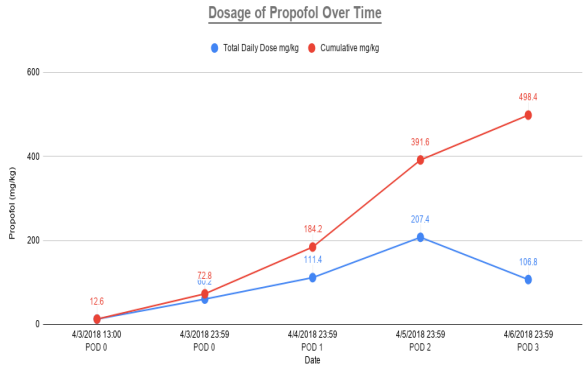

Table 1. Dosage of propofol over time

Although her lactate at this time was 1.7, her AST was 2212, ALT 521 and creatinine 0.71. She received volume, epinephrine and vasopressin infusions, and ECMO was considered for hemodynamic support.

Her cardiac rhythm demonstrated several unstable rhythms ranging from bradycardia that proved resistant to pacing via temporary epicardial wires to tachycardia that was unresponsive to medical therapy and electrical cardioversion. ECHO at this time demonstrated moderately diminished biventricular function.

She also developed generalized tonic-clonic seizures that were controlled with lorazepam and levetiracetam.

On POD#4, she remained unstable requiring amiodarone for dysrhythmia control. However, she did not progress to require ECMO support. The CK and lactate peaked on POD#3: 81,235 u/L (Table 2) and 3.4mmol/L, respectively. A continuous EEG on POD#4 demonstrated extremely low amplitude activity consistent with a severe diffuse encephalopathy.

On POD #4, her hemodynamics stabilized and she was able to wean off epinephrine and vasopressin by POD#5. However, her creatinine continued to rise and she developed oliguric renal failure requiring CRRT for the next 7 days. She was unable to be successfully weaned from mechanical ventilation and failed several extubation attempts over the ensuing four weeks due to severe weakness.

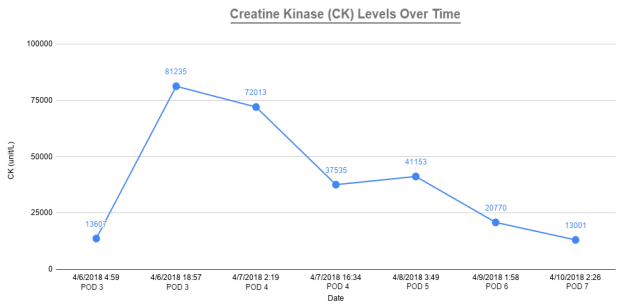

Table 2. Creatine kinase levels over time

Because of this, she was then scheduled for placement of a gastrostomy tube and a tracheostomy thirty-eight days after her initial cardiac operation. Due to the concern for PRIS, the anesthetic plan consisted of inhalational anesthesia with narcotics. The existing ETT was connected to the anesthesia circuit and sevoflurane was incrementally introduced. After 2-3 minutes, she was noted to have significant muscle rigidity. Her arms could not be lifted above her head and her abdomen was tense with protrusion of her rectus abdominus muscles. Two consecutive doses of rocuronium did not resolve the rigidity. Sevoflurane was discontinued and her ETT was connected to an oxygen supply separate from the anesthesia machine. End tidal C02 never exceeded 43 mmHg with normal ventilatory parameters and her temperature peak was 36.8 Celsuis. The operative procedure was cancelled and she returned to the cardiac ICU and recovered with complete resolution of her rigidity over several hours. Her CK prior to surgery was 1032 u/L and peaked two days later at 1486 u/L.

She was taken back to the OR four days later for another attempt at gastrostomy tube placement and tracheostomy. Her anesthesia consisted of midazolam, dexmedetomidine, and a remifentanil infusion. She tolerated the anesthesia and surgery without problems and without significant change in her CK levels. She was discharged two weeks later and continues to improve consistently on follow up.

Discussion

We report an unusual case of severe rhabdomyolysis in response to propofol and subsequently to sevoflurane in a patient that later proved to have type 1 myosin myopathy.

In 1992, Parke et al reported the death of five children as a result of myocardial failure after receiving long term, high dose propofol infusion (1). Our patient exhibited almost every reported feature of propofol infusion syndrome (PRIS); however, it was manifested after a 12-hour delay in stopping propofol. PRIS is explained by inhibition of the uptake of free fatty acids into mitochondria causing peripheral and cardiac muscle damage (3,4). The leading explanation for PRIS along with inhibition of fatty acid oxidation, is that high doses uncouple the respiratory chain by inhibiting complex IV (23,24). Propofol is also structurally similar to coenzyme Q and so inhibits electron flux from complexes I and II (23,24). Several authors have purported that PRIS may unmask a preexisting mitochondrial disorder, and any patient who manifests PRIS should be screened for mitochondrial disorders (2,10). This was done in our patient, but no defect was uncovered.

Known risk factors for PRIS include young age, critical illness, catecholamine and steroid use, >48 hours of propofol infusion, and high propofol doses (>4 mg/kg per hour or a total cumulative dose of 360mg/kg), all of which were present in our patient (2,5, 25,26). Priming and triggering factors have been proposed in the pathophysiology of PRIS. Priming factors include endogenous catecholamines, glucocorticoids, systemic inflammation, and cytokine production, all of which are routinely seen post cardiopulmonary bypass, and even more so in neonates and infants (11,12). High-dose propofol and exogenous catecholamines appear to be the triggering factors (6). Catecholamines and steroids aggravate propofol's inhibition of fatty acid metabolism, promoting rapid and irreversible peripheral and cardiac muscle injury leading to massive increases in serum creatine kinase (CK) (4,7). The two most serious manifestations of this in our patient were cardiogenic shock and renal failure, both of which are reported features of PRIS (8,9). In addition, she also exhibited acidosis, arrhythmia, liver dysfunction, and

rhabdomyolysis, which are all complications of PRIS (8,9). Approximately one month after exhibiting life-threatening features of propofol infusion syndrome, this patient presented for another anesthetic and surgery. Propofol was avoided and within minutes of receiving sevoflurane, she demonstrated features of anesthesia-induced rigidity (AIR) and rhabdomyolysis. There are scattered reports of AIR in response to inhaled anesthetics, and inherited myopathies appear to be a risk factor. This reaction appears to be idiosyncratic, and does not always manifest with every exposure (13, 14). These episodes mimic malignant hyperthermia with elevation of CK and other features and warrant genetic testing for mutations in the ryanodine receptor. (14) An extensive genetic workup was done in this patient and there were no mutations in the ryanodine receptor nor mutations consistent with mitochondrial disease. Unexpectedly, a mutation in the gene coding for the myosin heavy chain (MYH7) was discovered.

Hereditary myosin myopathies are a group of muscle diseases with variable clinical features and onset. They are caused by mutations in the skeletal muscle myosin heavy chain (MYH7 gene) (15). While mutations in the MYH7 gene have been associated with cardiomyopathies (16,17), there are only a few reports of these patients having complex congenital heart disease, and all of those reports are patients with Ebstein anomaly (18,19). Patients with myopathies are a challenge for anesthesiologists because of possible life-threatening complications (20,21). The majority of complications occur in patients with undiagnosed myopathies (as in the patient described above). With a view to preventing possible critical anesthesia-related complications in such patients, Trevisan et al have published a “Safe Anesthesia Table,” listing both the anesthetic drugs to be avoided and those considered harmless for myopathic patients, irrespective of age and type of pathology (22). Propofol is one of the “safe” drugs and total intravenous anesthesia (TIVA) with propofol is usually the anesthetic of choice for myopathic patients undergoing general anesthesia. On the other hand, patients with a known adverse response to propofol would receive an inhaled anesthetic for their procedure. Unfortunately, our patient demonstrated life-threatening rhabdomyolysis to both agents necessitating the avoidance of both with subsequent anesthetic use.

Conclusion

Myosin heavy chain (MYH7)-related myopathies are emerging as an important group of muscle diseases of childhood and adulthood. As this case report suggests, care must be taken when using either inhalational anesthesia or TIVA with propofol. Short term use of propofol may in fact be safe as our patient demonstrated severe rhabdomyolysis after a prolonged and high dose infusion. Risk factor analysis for the development of PRIS should guide the use of propofol in myopathic patients.

References

1. Parke TJ, Stevens JE, Rice AS, Greenway CL, Bray RJ, Smith PJ, et al. Metabolic acidosis and fatal myocardial failure after Propofol infusion in children: five case reports. BMJ 1992; 305(6854):613-6.
2. Finsterer J, Frank M. Propofol is a Mitochondrion-Toxin and May Unmask a Mitochondrial Disorder. Journal of Child Neurology 2016; 31(13):1489-94.
3. Stelow EB, Johari VP, Smith SA, Crosson JT, Apple FS. Propofol-associated rhabdomyolysis with cardiac involvement in adults: chemical and anatomic findings. Clin Chem 2000; 46:577-81.
4. Orsini J, Nadkarni A, Chen J, Cohen N. Propofol infusion syndrome: Case report and literature review. Am J Health Syst Pharm 2009 May 15; 66(10):908-915.
5. Cremer OL, Moons KG, Bouman EAC, Kruijswijk JE, de Smet AMG, Kalkman CJ. Long-term Propofol infusion and cardiac failure in adult head-injured patients. The Lancet 2001 Jan 13; 357(9250):117-8.

6. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of Propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med 2003; 29:1417-25.

7. Bray RJ. Propofol Infusion Syndrome in children. Paediatric Anaesth 1998; 8:491-9.

8. Culp KE, Augoustides JG, Ochroch AE, Milas BL. Clinical Management of Cardiogenic Shock Associated with Prolonged Propofol Infusion. Anes Analg 2004; 99:221-6.

9. Casserly B, O'Mahony E, Timm EG, Haqqie S, Eisele G, Urizar R. Propofol infusion syndrome: an unusual case of renal failure. American Journal of Kidney Disease 2004; 44(6):E98-E101.

10. Chidambaran V, Costandi A, D'Mello A. Propofol: A Review of Its Role in Pediatric Anesthesia and Sedation. CNS Drugs 2015; 29(7):543-63.

11. Gruber EM, Laussen P, Casta A et al. Stress Response in Infants Undergoing Cardiac Surgery. Anesth Analg 2001; 92:882-90.

12. Brix-Christensen, V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. Acta Anaesthesiol Scan 2001; 45(6):71-9.

13. Gray RM. Anesthesia-induced rhabdomyolysis or malignant hyperthermia: is defining the crisis important? Ped Anesthesia 2017; 27:490-3.

14. Cohen and Kaplan. Repeat episodes of severe muscle rigidity in a child receiving sevoflurane. Ped Anesthesia 2006; 16:1077-9.

15. Oldfors A. Hereditary myosin myopathies. Neuromuscular Disorders 2007; 17:355-367.

16. Feng X, He T, Wang J et al. Asn 391 Thr Mutation of beta-myosin heavy chain in a hypertrophic cardiomyopathy family. Int Heart J 2018; 59:596-600.

17. Adhikari AS, Koolker KB, Sarkar SS.et al. Early-onset hypertrophic cardiomyopathy mutations significantly increase the velocity, force, and actin-activated ATPase activity of human beta-cardiac myosin. Cell Reports 2016; 17:2857-64.

18. Hirono, K et al. Familial Ebstein's anomaly, left ventricular noncompaction, and ventricular septal defect associated with an MYH7 mutation. J Thorac Cardiovasc Surg. 2014; 148(5):e223-6.

19. Postma, AV et al. Mutations in the sarcomere gene MYH7 in Ebstein anomaly. Circ Cardiovasc Genet 2011; 4:43-50.

20. De Francisci G, La Sala M, Addabbo G, et al. Considerations about anesthesia in patients suffering from myopathy. Ped Anesthesia and Critical Care Journal 2013; 1(2):43-45.

21. Schieren M, Defosse J, Bohmer A, et al. Anaesthetic management of patients with myopathies. Eur J Anaesthesiol 2017; 34:1-9.

22. Trevisan CP, Accorsi A, Morandi LO. Undiagnosed myopathy before surgery and safe anaesthesia table. Acta Myologica 2013; 32:100-5.

23. Vanlander AV, Okun JG, Jaeger A, et al. Possible pathogenic mechanism of propofol infusion syndrome involves coenzyme Q. Anesthesiology 2015; 122:343-52.

24. Krajcova A, Waldauf P, Andel M, Duska F. Propofol infusion syndrome: a constructed review of experimental studies and 1530 published case reports. Crit Care 2015; 19:398.

25. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports.Br J Anaesth 2019; 122(4):448-59.

26. Krajcova A, Waldauf P, Andeel M, et al. Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. Critical Care 2015; 19:398.