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Propofol administration in patients with methylmalonic acidemia and intracellular cobalamin metabolism disorders: a review of theoretical concerns and clinical experiences in 28 patients

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Abstract

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Compliance with ethics guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent/assent was obtained from all patients/guardians for being included in the study. This article does not contain any studies with animal subjects performed by any of the authors.

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Background—Methylmalonic acidemia and intracellular cobalamin metabolism disorders represent a heterogeneous group of inborn errors of metabolism. Most patients will require diagnostic and/or therapeutic procedures frequently requiring sedation or anesthetic management due to neurological and neurocognitive impairments. It has been stated that propofol is contraindicated in this population. We report our experience with propofol administration in a large series of patients.

Methods—28 patients (14 *mut*, 7 *cblC*, 3 *cblA*, 3 *cblB*, 1 *cblG*) aged 2–35.6 years enrolled in a natural history study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00078078) identifier: NCT00078078) and required anesthetics for 39 diagnostic or therapeutic procedures. Data were collected on the anesthetic technique, perianesthetic course and adverse events related to propofol.

Results—Propofol was used as the sole induction agent in most cases (36/39) and as the primary maintenance agent in all cases. Infusion rates were 100–400 mcg.kg⁻¹.min⁻¹ (mean=214). Infusion duration was 60–325 min (mean=158) and total doses ranged between 270–3610 mg (mean=1217). Adverse events were recorded in 2 cases; neither appeared to be related to propofol administration.

Conclusions—Propofol is an effective, safe induction and maintenance agent for elective short procedures requiring anesthesia in patients with MMA and cobalamin metabolism disorders. Despite multiple comorbidities and propensity toward instability, those affected can receive anesthesia with an acceptable safety profile, if metabolically and hemodynamically stabilized prior to the event.

Introduction

Methylmalonic acidemias (MMA) and intracellular cobalamin metabolism disorders constitute a heterogeneous group of inborn errors of metabolism (Figure 1). Their phenotypes are diverse and a definitive diagnosis is made by cellular biochemical studies and molecular genetics (Adams and Venditti 1993; Manoli and Venditti 1993). Enzymatic defects can be subdivided into three groups: isolated MMA, combined MMA and hyperhomocysteinemia/homocystinuria, and isolated hyperhomocysteinemia/homocystinuria (Watkins and Rosenblatt 1986; Adams and Venditti 1993; Coelho et al. 2008; Gailus et al. 2010). Newborn screening can now detect affected infants through elevated propionylcarnitine (C3) and the secondary analyte changes of increased C3/C2 ratio and low methionine (Weisfeld-Adams et al. 2010). The multi-systemic manifestations of these disorders demand that patients often undergo diagnostic and/or therapeutic interventions under anesthesia, e.g. for gastrostomy and central venous access device placement (O'Shea et al. 2012).

Propofol (2,6-di-isopropylphenol) is a short-acting, intravenous, widely used anesthetic agent. It is metabolized mostly in the liver by conjugation to glucuronide and sulfate, with some forms first undergoing hydroxylation by cytochrome P-450 isoforms, to finally be excreted in the urine in the form of these inactive metabolites (Court et al. 2001, Guitton et al. 1998). Although the drug is rapidly cleared from the bloodstream (half-life=0.5–1 hour), terminal elimination half-life can be over 24 hours, due to the slow release of the drug from fatty tissue. Propofol has established efficacy, pharmacologic advantages (rapid onset of

action and redistribution, easy titration, anti-emetic effect) and an excellent safety profile in children even in serious illnesses; with the main adverse effects being apnea, hypoxemia, airway obstruction, hypotension, bradycardia, arrhythmias, hypertriglyceridemia, myoclonus, and hypothermia (Kiringoda et al. 2010; Tait 2010). Propofol infusion syndrome (PRIS) is a rare complication first described in pediatric patients, characterized by severe ketoacidosis, rhabdomyolysis, myocardial failure, pulmonary hypertension, and high mortality. The pathophysiology of the syndrome remains unclear, but risk factors include doses higher than $70 \text{ mcg.kg}^{-1}.\text{min}^{-1}$ for prolonged infusions ($>48\text{hr}$), critically ill patients, and inborn errors of fatty acid oxidation (Parke et al. 1992; Schenkman and Yan 2000; Cannon et al. 2001; Vasile et al. 2003; Fernandez and Fernandez 2010). In comparison to pentobarbital and inhalation anesthetics, such as sevoflurane, propofol was found to be equally effective, with shorter recovery times, and similar adverse events profile (Bryan et al. 2009; Mallory et al. 2009). Propofol also has the added benefit of excellent safety even in severe renal insufficiency, which many MMA patients are afflicted with (Ickx et al. 1998).

At least two major anesthesiology textbooks state that propofol is contraindicated in MMA and related disorders (Bissonnette 2006; Holzman 2008). These statements are accompanied neither by physiologic hypotheses nor by supporting data. The existing literature on the anesthetic management of MMA and cobalamin disorder patients is scarce and focuses on transplantation procedures (Sharar et al. 1991; Ho et al. 2000; Nagarajan et al. 2005; Kasahara et al. 2006; Manzoni et al. 2006; Chao et al. 2012). None of the available reports involve the use of propofol, and Kasahara et al review 18 cases of liver transplantation but do not include the anesthetic regimen. As a result, guidelines for routine anesthetic management are lacking.

We describe the clinical safety profile of propofol in a population of patients with MMA and cobalamin metabolism defects, review the theoretical concerns, and provide general anticipatory guidance.

Methods

Data were retrospectively collected from patient studies that were conducted through National Institutes of Health (NIH) natural history study “Clinical and Basic Investigations of Methylmalonic Acidemia and Related Disorders” ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00078078) identifier: NCT00078078). In all patients, the diagnosis and subtype was assigned via cellular biochemical studies, complementation analysis (David S. Rosenblatt, Division of Medical Genetics, McGill University), and/or molecular genetic testing (GeneDx, Gaithersburg, MD). Consent/assent was obtained from guardians and/or patients. A separate consent for each anesthetic procedure was obtained.

During each admission, all procedures were performed under the same anesthetic. The patients underwent a thorough pre-anesthesia evaluation, where the history of previous drug reactions and anesthesia complications were reviewed, neuromuscular and neurocognitive status was evaluated, and a history of seizures or stroke-like episodes was noted. Laboratory tests included: CBC, electrolytes, blood glucose, urinalysis, coagulation studies, renal and liver function tests, and an ECG. Ammonia levels were not monitored, unless patients were

acutely ill. A peripheral IV was placed prior to the sedated procedure in most cases. Patients were maintained *nil per os* 3–6 hours prior and received maintenance infusions of 5–10% dextrose in 0.9 or 0.45% normal saline, to prevent dehydration, hypoglycemia, and acidosis.

Demographics, clinical characteristics, laboratory findings, and anesthetic parameters, including length of anesthesia, technique, and medications, were compiled by reviewing charts and perianesthetic records of all patients who received propofol for study procedures between 2005–2012. Any complications, during the anesthetic event and the remainder of the admission, were examined.

Results

Medical records of 28 patients, ages 2–35.6 years, with MMA and cobalamin disorders (14 *mut*, 7 *cblC*, 3 *cblA*, 3 *cblB*, 1 *cblG*), who received propofol for sedation or induction/maintenance of general anesthesia on 39 separate occasions during their initial and follow-up visits to the NIH, were analyzed. Demographic and selected characteristics of the cohort are presented in Table 1.

Most patients had been diagnosed in the infantile period (n=24, 86%), 2 by newborn screening. Almost half (n=13, 46%) had basal ganglia injury (globus pallidus lesions on MRI and/or the presence of a movement disorder). Many of the patients (n=12, 43%) also had a history of seizures and/or were on anti-epileptic medication during their admission. At the time of their anesthetic event, 5 patients (18%) had impaired renal function (elevated blood urea nitrogen to creatinine ratio and cystatin C levels), 2 patients had abnormal liver function testing, and 2 had previously undergone a combined kidney and liver transplantation at other institutions.

Most patients (n=20, 71%) underwent a single anesthetic event, 5 patients underwent anesthesia 2 times, and 3 patients 3 times. Each event occurred at a separate visit. The majority of patients underwent anesthesia for MR imaging studies (n=29); in some, the MRI studies were performed in combination with another procedure (n=8), such as lumbar puncture (n=1), gastrostomy tube replacement (n=1), ophthalmologic, electroretinograms and/or dental evaluations (n=6). The studies performed were brain and/or spine MR imaging and spectroscopy, without contrast. On 2 occasions, anesthesia was necessary for the removal of an infected central catheter.

Table 2 lists the perianesthetic course and care, and anesthetic premedication regimen for each anesthetic event. Propofol was used either as the sole induction agent (n=36) or in a combination (n=3), and as the primary maintenance agent in all cases (n=39). In the majority of cases, induction was achieved with intravenous agent. In five cases where intravenous access was not available prior to the procedure, induction was achieved with the use of sevoflurane until a peripheral IV was placed. Maintenance was achieved with the infusion of propofol in all 39 occasions; the mean infusion rate was 214 mcg.kg⁻¹.min⁻¹ (100–400 mcg.kg⁻¹.min⁻¹) and the mean total dose 1217 mg (270–3610 mg). Infusion duration was 60–325 min (mean=158). The standard recommended dose for maintenance of anesthesia is

125–300 mcg.kg⁻¹.min⁻¹, with higher doses frequently required in patients under 5 years old (Lexicomp Online®, 2015).

One patient had a history of a previous anesthetic complication; this patient had developed metabolic acidosis during orthopedic surgery for a tibial fracture at another institution. Most patients were transferred to the post-anesthesia care unit for recovery following the procedure(s). In 2 cases, the patients were considered medically fragile and were pre-emptively transferred to the intensive care unit (ICU) for the recovery period, since anesthesia was performed to remove an implantable catheter in the context of febrile bacteremia. In a third case, a patient with severe neurocognitive deficits was transferred to the ICU for monitoring. All recovered uneventfully.

Adverse events were noted in 2/39 cases. The first patient (*mut⁰*) developed central line related septicemia and mild metabolic decompensation (pH 7.33, bicarbonate 14 mEq/L, and moderate ketones) during the admission. The catheter was removed and the patient was transferred to the ICU. A chest radiograph and subsequent chest CT revealed a right upper lobe consolidation, presumably due to aspiration pneumonitis. The administration of anesthesia did not worsen the patient's metabolic acidosis or lactate levels based on follow-up blood gases; recovery was uneventful and the patient was discharged from the ICU 5 days later. The second patient (*cbfC* deficiency and neuromuscular symptoms) underwent anesthesia for a brain MRI, spectroscopy, and an electroretinogram. Due to the prolonged duration of the studies, intubation was performed prior to the electroretinogram, and the procedure was completed without adverse events. The same evening the patient developed fever, rigors, cough, and leukocytosis. Blood gas, lactate, CPK levels, and liver function tests were normal. A chest radiograph was negative, although based the clinical symptomatology the episode was considered a subclinical aspiration pneumonitis. The patient was placed on empiric antibiotics, defervesced, and remained clinically stable thereafter.

Discussion

This is the first report describing the anesthetic care of a large series of patients with MMA and intracellular cobalamin metabolism disorders and provides important information for clinicians in the fields of biochemical genetics and anesthesia. The patients received anesthesia for routine procedures, and most (37/39) were in the well state.

Conventional teaching advises against using propofol in patients with these inborn errors of metabolism (Bissonnette 2006; Holzman 2008). A number of theoretical concerns surround the use of propofol in MMA but have not been previously discussed. Several studies (both *in vitro* and *in vivo*, from rat, guinea pig, and human tissues) document a propofol-induced inhibition of mitochondrial respiratory chain complexes, such as Complex IV, in combination with uncoupling effects, raising concerns for its use in mitochondrial disorders (Rigoulet et al. 1996; Cray et al. 1998; Schenkman and Yan 2000; Shao et al. 2008). In support of genetic susceptibility underlying propofol toxicity, mice lacking *Ndufs4*, a Complex I subunit, are twice as sensitive to propofol when compared to wild type littermates, and three times as sensitive to isoflurane and halothane (Quintana et al. 2012). However, a retrospective study of 122 patients with mitochondrial diseases, where 24

received propofol for induction and 15 for maintenance, revealed no severe anesthesia-related morbidity or mortality (Driessen et al. 2007). Moreover, though propofol may increase the risk of lactic acidosis in patients undergoing intracranial surgery, and, prolonged propofol infusion was not found to cause lactate elevations in patients undergoing spine surgery (Rozet et al. 2009). Similarly, propofol had no effect on oxidative stress or on lactate and pyruvate levels in children undergoing elective cardiac surgery for congenital heart disease (Bonhomme et al. 2009; Rozet et al. 2009; Dumaresq et al. 2011). Mitochondrial effects of propofol could be of importance in our patients because *mut* MMA, and likely other forms of isolated MMA as well as *cbfC* deficiency (Ben-Omran et al. 2007), features a distinct mitochondriopathy, which is characterized by formation of megamitochondria and decreased Complex IV activity, in human and mice hepatocytes (Brusque et al. 2002; Chandler et al. 2009). Our clinical experience suggests that effects of propofol on mitochondrial function in this population may represent a largely theoretical concern, or bear mostly subclinical implications, perhaps because the hepatic metabolism of propofol is rapid and mostly cytosolic (Court et al. 2001; Meyer and Maurer 2011).

In MMA, odd chain fatty acids (OCFA) metabolism appears to be a significant precursor source of organic acids (Sbai et al. 1994). Though OCFA are rare in natural foods, patient tissues have higher than normal OCFA concentrations, perhaps through endogenous formation secondary to accumulation of propionyl-CoA metabolites (Wendel 1989). Sbai et al. compared 1-¹³C-propionate recovery in fasted and carbohydrate-fed patients and found differences consistent with OCFA oxidation during fasting, at rates that may even exceed the precursor amino-acid catabolism (Sbai et al. 1994). Thus, it is important to emphasize that the metabolism of propofol itself does not result in the production of OCFA, or other propionyl-CoA precursors (Court et al. 2001, Guitton et al. 1998).

The lipid emulsion in which the drug is carried also needs to be considered. Diprivan® (APP Pharmaceuticals, Illinois, USA) and the generic formulation (Hospira, Illinois, USA) consist of 1% 2,6-isopropylphenol, soybean oil (100mg/mL), glycerol (22.5mg/mL), and purified egg lecithin (12mg/mL) (Stoelting RK 2000). The lipid content of the emulsion could theoretically augment fatty acid load and increase the hepatic output of ketoacids; such a scenario would be highly unlikely if a continuous dextrose infusion was provided. Another concern is the possible content of OCFA in the soybean oil in the emulsion (Bissonnette 2006). However, naturally occurring soybean-oil and egg lecithin mostly consist of 16- and 18-carbon chain fatty acids, with minimal-to-none amounts of OCFA (Diedrich and Macholz 1989). Regardless of OCFA content, excessive lipid administration could exacerbate subclinical pancreatic disease, especially in a population at risk for pancreatitis, such as MMA (Devlin et al. 2005; Gottschling et al. 2005).

Our clinical experience of 39 anesthetics shows that propofol represents an acceptable agent for the induction and maintenance of anesthesia in MMA and cobalamin disorder patients. The adverse events that were noted (n=2) were likely not related to propofol. None of our patients became clinically unstable during the anesthesia or the remainder of their admission, with the exception of the patient that decompensated prior to anesthesia, caused by catheter-related septicemia.

It must be noted that our data is clinical and that metabolic parameters, including blood gases and levels of organic acids, were not monitored while the patients were under sedation during our studies. It is possible that our patients may have had mild subclinical metabolic acidosis which was alleviated by dextrose administration. Our results only pertain to MMA and related disorder patients, in a group of international patients that underwent mostly elective procedures in the well-state at a single US center, and should not be extended to other mitochondrial disorders or inborn errors of metabolism without further study. The results should also be interpreted individually due to the genetic heterogeneity within this patient population.

Before any anesthesiologic intervention, a neurologic examination must be performed, and the presence of strokes or seizures in the patient's history should be documented (Baum VC 2007). Baseline laboratory investigations should include a CBC, coagulation studies, blood glucose, electrolytes, urinalysis, blood gas analysis, renal function assessment and liver function tests. All of these are clinically relevant as patients can have cytopenias, kidney, and liver dysfunction. Hypotension, hypoxia, dehydration or low caloric intake can prompt a metabolic crisis. Adequate hydration and caloric intake with dextrose enriched fluids, and avoiding prolonged fasting to minimize protein catabolism is important. In terms of intra-operative fluids, part of our cohort had received lactated Ringer's solution; however we advise caution as there are *in vivo* and *in vitro* evidence that suggest that MMA patients can have difficulties in metabolizing lactate (Cray et al. 1998; Stoelting RK 2002; Saad et al. 2006). Patient positioning must be done carefully as these patients can suffer from osteoporosis. The use of nitrous oxide should be avoided, especially in cobalamin metabolism defects, because it inhibits B12-dependent enzymes and has been shown to increase methylmalonic acid levels even in normal individuals (Baum 2007).

In summary, the perianesthetic records of 28 MMA and cobalamin disorder patients who underwent propofol anesthesia on 39 occasions, with duration up to 5 hours, revealed no clinical signs of metabolic decompensation related to propofol. We studied outcomes of predominantly elective procedures and were able to carefully manage hydration and acid base status. In the two emergent interventions, propofol did not cause further deterioration; however the prediction of anesthetic risks and outcomes in the emergency setting will require further study. Our experience suggests that in the setting of metabolic stability, propofol anesthesia can be administered uneventfully and safely to patients afflicted by MMA and cobalamin metabolic disorders.

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Details of contributing authors

Dr. Ktena collected data, analyzed results, wrote and edited the manuscript, and approved the final manuscript as submitted. Dr. Ramstad provided clinical care, assisted in writing and editing of the manuscript, and approved the final manuscript as submitted. Dr. Baker provided clinical care, assisted in writing and editing of the manuscript, and approved the final manuscript as submitted. Dr. Sloan recruited patient subjects, collected clinical and laboratory data, assisted in writing and editing of the manuscript, and approved the final manuscript as submitted. Dr. Mannes provided clinical care, assisted in writing and editing of the manuscript, and approved the final manuscript as submitted. Dr. Manoli provided clinical care, participated in data analysis, assisted in writing and

editing of the manuscript, and approved the final manuscript as submitted. Dr. Venditti directed the clinical research protocol, provided clinical care, supervised the study, participated in data analysis, assisted in writing and editing the manuscript, and approved the final manuscript as submitted.

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Synopsis: A review of the perianesthetic records of 28 patients with isolated MMA and intracellular cobalamin metabolism disorders suggests that propofol anesthesia can be administered safely to these patients, in the setting of metabolic stability.

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Figure 1. Schematic representation of methylmalonic acidemias (MMA) and intracellular cobalamin metabolism disorders

OH-Cbl=hydroxocobalamin, CN-Cbl=cyano-cobalamin, Ado-Cbl=adenosyl-cobalamin, Me-Cbl=methylcobalamin

Schematic representation of the pathway that converts propionyl-CoA into succinyl-CoA.

The solid line boxes refer to the defects involved in combined methylmalonic acidemia and hyperhomocysteinemia/homocystinuria, the dashed line boxes to isolated methylmalonic acidemia and the dotted line boxes to isolated hyperhomocysteinemia/homocystinuria. Figure adapted from GeneReviews™ - Methylmalonic Acidemia.

Table 1
Patient Demographics and Clinical Characteristics

The MMA or cobalamin disorder subtype was designated via cellular biochemical studies, complementation analysis, and/or molecular genetic testing. Basal ganglia injury was identified through neurological examination and confirmed with brain MRI. Seizure disorder was defined as the presence of seizures in the patient's history, whether or not the patient was currently on anti-epileptic medication.

Sex, n (%)	
Male	15 (54%)
Female	14 (50%)
Age at diagnosis, months	
Mean	8.7
Median	2.5
Range	0–72
Subtype, n (%)	
<i>Mut</i>	14 (50%)
<i>cblC</i>	7 (25%)
<i>cblA</i>	3 (11%)
<i>cblB</i>	3 (11%)
<i>cblG</i>	1 (4%)
Age at anesthesia, years	
Mean	18.3
Median	19.3
Range	2–35.6
Clinical findings, n (%)	
Basal ganglia injury	13 (46%)
Seizure disorder	12 (43%)
Impaired renal function	5 (18%)
Elevated liver enzymes	2 (7%)
Kidney and liver transplant	2 (7%)

Table 2
Perianesthetic course and anesthetic premedication regimen

Most patients were transferred to the post anesthesia care unit for recovery. Lactated Ringer's solution was used in a small number of cases, per routine anesthesia practice, though discouraged by the primary team. In two cases, the patients were considered medically fragile and were pre-emptively transferred to the intensive care unit (ICU) for the recovery period, since anesthesia was performed to remove an implantable catheter due to septicemia, and in a third case a patient with severe neurocognitive deficits was transferred to the ICU as a measure of caution; all recovered uneventfully.

Procedure	n		
MRI+MRS	28		
MRI+MRS+Other *	8		
Implantable catheter removal	2		
Airway management	n		
Nasal Cannula	37		
Laryngeal Mask	1		
Endotracheal Tube	1		
Induction	n, (%)	Dose, mean (range)	Units
<i>Intravenous Agents</i>			
Propofol, Bolus	36 (92%)	60 (20–150)	mg
Midazolam	12 (31%)	2 (1–5)	mg
Fentanyl	3 (8%)	50 (20–100)	mcg
Ketamine	1 (3%)	50	mg
<i>Inhalational Agents</i>			
Sevoflurane	5 (13%)	2.9 (2.3–4)	%
Maintenance			
Propofol	39 (100%)		
Infusion Rate		214 (100–400)	mcg.kg ⁻¹ .min ⁻¹
Total Dose		1217 (270–3610)	mg
Fluids Administered			
Dextrose-Normal Saline	31 (79%)	256 (100–500)	ml
Ringer's Lactate	8 (21%)	294 (150–500)	ml
Premedication/Other Medication Administered			
Lidocaine	5 (13%)	40 (20–80)	mg
Glycopyrrolate	5 (13%)	0.2 (0.1–0.2)	mg.ml ⁻¹
Cisatracurium	1 (3%)	4	mg
Neostigmine	1 (3%)	1	mg

Ondasentron	1 (3%)	4	mg
Ephedrine	1 (3%)	5	mg
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Average Duration of Anesthesia, min	158 (60–325)		
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Recovery Location	n		
PACU	36		
ICU	3		

MRI=magnetic resonance imaging, MRS=magnetic resonance spectroscopy, PACU=post-anesthesia care unit, ICU=intensive care unit

* Other = ophthalmological or dental evaluations (n=3), electroretinograms (n=3), lumbar puncture (n=1), gastrostomy tube replacement (n=1).