The Use of High-Dose Hydroxocobalamin for Vasoplegic Syndrome

Joseph D. Roderique, MA, MS, Kofi VanDyck, MD, Brita Holman, MD, Daniel Tang, MD, Betty Chui, CCP, RN, and Bruce D. Spiess, MD, FAHA

Department of Anesthesiology, Virginia Commonwealth University Medical Center, Richmond, Virginia

We describe a case of hypotension on cardiopulmonary bypass for coronary artery bypass grafting, double valve repairs, and patent foramen ovale closure. The patient experienced vasoplegic syndrome while on cardiopulmonary bypass. He was treated with high-dose hydroxocobalamin (vitamin B12). His blood pressure responded rapidly, obviating any further vasopressor requirements. (Ann Thorac Surg 2014;97:1785–6) © 2014 by The Society of Thoracic Surgeons

Vasoplegic syndrome is a complication of cardiopulmonary bypass that occurs in 8% to 12% of all cases [1–3]. Although the precise cause of vasoplegic syndrome has yet to be defined, it is related to a dysregulation of nitric oxide release, nitric oxide production, or nitric oxide signaling. Risk factors for vasoplegic syndrome include preoperative use of angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and β-blockers. Levin and colleagues [2] found that the duration of cardiopulmonary bypass increased the risk for vasoplegic syndrome by 38% for every 30 minutes spent on bypass. Catecholamine-resistant vasoplegic syndrome has a mortality rate as high as 25% [2–4]. The use of methylene blue is gaining acceptance in treating catecholamine-resistant vasoplegic syndrome [1]. Side effects of methylene blue include interference with oximetry measurements, serotonin syndrome, and in some cases methemoglobinemia. Because of the development of serotonin syndrome, methylene blue is contraindicated in patients taking serotonergic antidepressants, and an alternative is needed. This is the first report on the use of high-dose hydroxocobalamin (Cyanokit; Meridian Medical Technologies, Columbia, MD) to resolve catecholamine-resistant vasoplegic syndrome as an alternative to methylene blue.

A 71-year-old man with a past medical history of coronary artery disease, cardiomyopathy, heart failure, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, depression, and gout presented with progressive dyspnea on exertion, increasing over a 3-week period. His medical history included an ejection fraction of 0.25 with left anterior descending coronary artery thrombosis. Medications included lisinopril, carvedilol, cilostarzid, simvastatin, budesonide/formoterol fumarate dihydrate, allopurinol, and colchicine. He was a former 50-pack-year smoker and alcoholic, now abstinent for 6 years. A transesophageal echocardiography study after admission showed severe mitral regurgitation, moderate tricuspid regurgitation, a dilated hypertrophied left ventricle with reduced systolic function (ejection fraction, 0.25), a dilated right ventricle, dilated left atrium, elevation of right ventricular systolic pressure, and a patent foramen ovale. He was taken to the operating room for coronary artery bypass grafting of one vessel (the left anterior descending coronary artery), two-avalve annuloplasty or repair, and patent foramen ovale closure.

Immediately after anesthesia induction, he became hypotensive, leading to the use of a norepinephrine drip at 0.05 to 0.1 μg · kg⁻¹ · min⁻¹, which was decreased to 0.07 μg · kg⁻¹ · min⁻¹ on starting surgery. When cardiopulmonary bypass was initiated, the mean arterial blood pressure (MAP) was 30 to 40 mm Hg with 6.5 L/min of systemic cardiopulmonary bypass pump flow. Norepinephrine was increased to 0.1 μg · kg⁻¹ · min⁻¹ and a vasopressin drip was added at 2 U/h. Each dose of cardiopedia was followed by a decline in MAP to 20 mm Hg or less. Perfusion was delivering numerous high-dose boluses of phenylephrine and norepinephrine with minimal response. Seventy minutes after cardiopulmonary bypass initiation, 5 g of intravenous hydroxocobalamin (Cyanokit) was infused for 10 minutes. After infusion, the MAP increased to 70 to 80 mm Hg. The norepinephrine drip was titrated down to 0.05 μg · kg⁻¹ · min⁻¹, and the vasopressin drip was stopped, and MAP remained greater than 60 mm Hg. Cardiopedia administration produced less-profound hypotension, and no further bolus doses of vasoconstricting agents were required. After weaning from cardiopulmonary bypass, the patient was transferred to the intensive care unit. At the time of transport he was on epinephrine at 0.08 μg · kg⁻¹ · min⁻¹, norepinephrine at 0.05 μg · kg⁻¹ · min⁻¹, vasopressin at 2 U/h, and inhaled epoprostenol at 50 μg · kg⁻¹ · min⁻¹ with an MAP of 80 to 90 mm Hg (systolic pressures of 120 to 145 mm Hg). He received no donor blood products. He was given back 445 mL from a cell-saving device, and 3.3 L were ultrafiltered on cardiopulmonary bypass.

On postoperative day 1, the patient was extubated and was receiving only epinephrine at 0.07 μg · kg⁻¹ · min⁻¹ for pressure support, which was discontinued later that day. Total chest tube output during the first 24 hours was only 340 mL, and the chest tube was discontinued on postoperative day 2 (total output, 520 mL). The urine became pinkish-purple during administration of hydroxocobalamin, and continued until discharge (reaction typically lasts from 2 to 5 weeks). There was no noticeable decline in renal function. In this patient the urinalysis results were not reportable because of interference, and the hemoglobin was falsely elevated. These interferences did not affect our management. The patient did well and was discharged home on postoperative day 11.
Comment

At present, there is no universally accepted definition for vasoplegic syndrome [1, 3]. From a survey of trials using methylene blue for vasoplegic syndrome, accepted parameters for defining vasoplegic syndrome are a systemic vascular resistance of less than 800 dyne s cm$^{-5}$, an MAP of less than 60 to 65 mm Hg, a cardiac index of greater than 2.5 to 3 L m$^{-1}$ min$^{-1}$, and a requirement for at least one or more high-dose pressors (ie, norepinephrine >0.05 µg kg$^{-1}$ min!$^{-1}$). If one or more of these conditions are met either during cardiopulmonary bypass or within 24 hours after cardiopulmonary bypass, then it is generally accepted that this constitutes vasoplegic syndrome [1].

The most widely accepted theories on the mechanism of vasoplegic syndrome involve dysregulation of nitric oxide homeostasis [1, 3]. It has been demonstrated that methylene blue is capable of binding nitric oxide (a reactive oxygen species), inhibiting both constitutive and inducible nitric oxide synthase, and inhibiting soluble guanylate cyclase [2, 3]. Unfortunately, methylene blue has now been shown to precipitate serotonin syndrome when administered to patients taking a serotonergic antidepressant as a result of a direct inhibitory effect of methylene blue or its metabolite on monoamine oxidase activity [2, 4].

Clinically, serotonin syndrome is characterized by the triad of altered mental status, neuromuscular hyperactivity, and autonomic instability [5]. Many patients with heart failure are also taking an antidepressant. Switching antidepressants or stopping them altogether for several days before undergoing cardiopulmonary bypass can decrease the risk of serotonin syndrome. Our patient was taking citalopram. An alternative therapy for the treatment of vasoplegic syndrome was, therefore, needed.

Hydroxocobalamin is one of four forms of vitamin B$_{12}$ found in the body. High-dose hydroxocobalamin has been used for more than 40 years in Europe for the treatment of cyanide poisoning. No significant adverse events have been reported, even with doses as high as 30 g within 24 hours [6]. In recent years hydroxocobalamin has been approved for use in the United States for the same indication (cyanide poisoning) and is currently marketed under the trade name Cyanokit. Cyanokit is supplied as a kit, typically containing a single 5-g vial of powdered hydroxocobalamin, which is then reconstituted with 200 mL of a diluent (not included in the kit). This may be either normal saline solution, lactated Ringer’s solution, or dextrose 5% in water for a final concentration of 25 mg/mL. This may be infused during a period of 15 minutes to 2 hours, and may be immediately followed by a second 5-g dose if necessary. There are currently no contraindications to its use, and it is not known to interact with methylene blue.

A side effect of Cyanokit administration is a rapid, sustained, and significant increase in blood pressure. It has been demonstrated that this is caused by direct binding of nitric oxide and direct inhibitory effects on nitric oxide synthase and soluble guanylate cyclase [7, 8]. Unlike methylene blue, hydroxocobalamin is not known to have any direct effects on the serotonergic pathway and has not been associated with an increased risk of serotonin syndrome.

This case is important because it represents the first report on the use of high-dose hydroxocobalamin for vasoplegic syndrome. More importantly, it also represents a viable alternative to methylene blue for the treatment of vasoplegic syndrome in patients taking a serotonergic antidepressant. The use of hydroxocobalamin in this patient population presents a novel solution to this problem, and may have additional clinical benefits beyond its effects on blood pressure, which will require further evaluation.

References


Thoracoabdominal Aortic Repair in a Patient With Ehlers-Danlos Syndrome

Toshihiro Fukui, MD, Daisuke Hiraoka, MD, Tomoya Uchimuro, MD, Tomoki Shimokawa, MD, Shuichiro Takanashi, MD, and Yukihiro Takahashi, MD

Departments of Cardiovascular Surgery and Pediatric Cardiac Surgery, Sakakibara Heart Institute, Tokyo, Japan

Type IV Ehlers-Danlos syndrome is a life-threatening inherited disorder of connective tissue associated with multiple aneurysm formation. Thoracoabdominal aortic repair in these patients has rarely been performed.

Accepted for publication Aug 7, 2013.

Address correspondence to Dr Fukui, Department of Cardiovascular Surgery, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu, Tokyo 183-0003, Japan; e-mail: tfukui.cs@gmail.com.