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Exceptional Case

EXCEPTIONAL CASE

High-dose hydroxocobalamin for vasoplegic syndrome causing false blood leak alarm

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Abstract

Blood leak alarms are important safety features in a hemodialysis machine to protect patients from loss of blood through a rupture in the dialyzer membrane (true alarms). A false blood leak alarm can be triggered by air bubbles or detector malfunction (such as deposits of grease or scale). Hydroxocobalamin is an injectable form of vitamin B12 approved by the US Food and Drug Administration for the treatment of confirmed or suspected cyanide toxicity. Due to observations of an increase in arterial pressure after high-dose hydroxocobalamin infusion for the treatment of acute cyanide poisoning, it has recently been reported as an off-label rescue treatment for post–cardiopulmonary bypass vasoplegic syndrome. We report an 83-year-old man who received hydroxocobalamin following cardiac surgery for treatment of vasoplegic syndrome. The patient developed severe acute kidney injury with volume overload. Hydroxocobalamin interference with the blood leak detector compromised his dialysis treatment. We describe the use of continuous renal replacement therapy to overcome the hydroxocobalamin-related interference with hemodialysis. As the utility of hydroxocobalamin potentially expands, physicians must be aware of its inadvertent effect on renal replacement therapy.

Key words: blood leak; dialysis; hemodialysis; hydroxocobalamin; vitamin B12

Introduction

In the hemodialysis machine circuit, blood is separated from dialysate by a semipermeable membrane [1]. Membrane integrity is important to maintain sterility and protect patients from inadvertent blood loss. Thus modern dialysis machines have been designed to cease operations when blood is detected in the dialysate [2]. The blood leak detector is placed in the dialysis solution outflow line and uses a sensor in the dialysate effluent path [3–5]. When a blood leak develops through the dialyzer membrane, an alarm is activated and blood flow through the dialyzer stops. Blood leak alarms typically occur due to physical damage caused by mishandled dialyzers. False blood leak alarms usually result from air bubbles or hardware issues (such as deposits of grease or scale on the sensor) [3].

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Hydroxocobalamin, an injectable naturally occurring form of vitamin B12 with a favorable adverse effect profile, is approved by the US Food and Drug Administration for the treatment of cyanide toxicity [6–8]. Hydroxocobalamin binds to cyanide forming nontoxic renally excreted cyanocobalamin. Incidental observation of increased blood pressure during hydroxocobalamin infusion led to consideration of its utility as a potential therapy for vasoplegic syndrome [6, 9]. The prevailing mechanism for this effect is the sequestration and subsequent depletion of nitric oxide in vascular endothelium [9–14], an important factor in the underlying mechanism of vasoplegic syndrome [5, 15, 16]. Hence hydroxocobalamin has been utilized to treat refractory vasoplegic syndrome in the setting of cardiac surgery following cardiopulmonary bypass [10, 11].

In this article we describe the first reported case of false blood leak alarms related to hydroxocobalamin treatment for vasoplegic syndrome, in which the blood leak detector erroneously prevented us from performing an acute hemodialysis treatment after the patient received high-dose hydroxocobalamin for vasoplegic syndrome.

Case report

An 83-year-old, 75-kg man with known coronary artery disease after coronary artery bypass grafting 10 years earlier, presented to our institution with worsening shortness of breath on exertion and fatigue over the past year. His past medical history was also significant for hypertension, hyperlipidemia and chronic kidney disease (CKD) stage 3b in the setting of a solitary left kidney due to a previous nephrectomy for renal cell carcinoma [baseline serum creatinine (SCr) 2.0 mg/dL, estimated glomerular filtration rate (eGFR) 34 mL/min/1.73 m^2].

His physical exam was remarkable for a grade III/VI mid-systolic murmur at the right second intercostal space and a grade III/VI holosystolic murmur at the left parasternal border and apex. There was trace pitting edema on the bilateral lower extremities. Workup included a transthoracic echocardiogram that revealed severe mitral and tricuspid valve regurgitation with moderate to severe calcific aortic valve stenosis (mean gradient 20 mmHg and valve area 0.91 cm^2). His left ventricular ejection fraction was preserved at 53%. The evaluation was then done by the cardiovascular surgery group and plans were made to perform aortic, mitral and tricuspid valve replacements. He underwent coronary angiogram to assess his coronary arteries, which revealed diffuse coronary artery disease with patent grafts.

The patient subsequently had three-valve replacement surgery. The total bypass time was 178 min and aortic cross-clamp time was 96 min. After separation from the bypass, the patient developed severe coagulopathy, pulmonary edema and vasodilatory, hemorrhagic and cardiogenic shocks. The patient received 4.5 L crystalloid, 1 L 5% albumin, 8 units packed red blood cells, 8 units of fresh frozen plasma and 2 units of platelets. Despite fluid resuscitation and high-dose vasopressors (norepinephrine 0.2 μg/kg/min, epinephrine 0.1 μg/kg/min and vasopressin 0.06 unit/min), the patient was still persistently hypotensive. A total of 250 mg methylene blue was given without significant effect. Hydroxycobalamin [5 g intravenously (IV)] was infused with mild improvement in his blood pressure. A second dose of 5 g was given with a similar effect. Given the persistent cardiovascular and pulmonary compromise, the patient was then placed on venoarterial extracorporeal membrane oxygenation (ECMO) and transferred to the intensive care unit (ICU).

The patient made a quick recovery. Bronchoscopy revealed an organizing clot extending diffusely throughout the tracheobronchial tree that was successfully removed. In 24 h the patient was successfully decannulated from ECMO. By postoperative day 4, he was weaned off vasoactive agents. Unfortunately, the patient developed postoperative oliguric severe acute kidney injury (stage 3 CKD, SCr = 5.8 mg/dL). Otherwise, laboratory testing revealed the following values: hemoglobin 8.4 g/dL (reference range 13.5–17.5), white blood cell count 14.1×10^9/L (reference range 3.5–10.5 $\times 10^9$/L), platelet 57×10^9/L (reference range 150–450 $\times 10^9$/L), blood urea nitrogen 87 mg/dL (reference range 8–24), sodium 144 mmol/L (reference range 135–145), potassium 5.2 mmol/L (reference range 3.6–5.2), chloride 102 mmol/L (reference range 100–108) and bicarbonate 22 mmol/L (reference range 22–29). A nephrology consultation was obtained.

Due to significant diuretic-resistant (receiving IV bumetanide 2 mg/h and oral metolazone 10 mg) volume overload (12 L positive volume balance after the operation), intermittent hemodialysis (IHD) was initiated on a Fresenius 2008K machine (Fresenius, Waltham, MA, USA) with Revaclear dialyzer [a blend of the polymers polyarylethersulfone (PAES) and polyvinylpyrrolidone membranes] at day 4 following IV hydroxycobalamin. Within 3 min of starting dialysis, the blood leak detector was triggered. The internal preset blood leak alarm caused the machine to shut down automatically and did not allow hemodialysis to proceed. There was no visible blood or air noted in the dialysate fluid. Considering the potential for circuit or machine malfunction, another Fresenius 2008K machine and a new circuit was tried. Again, minutes into treatment, an error message indicating a blood leak and stopped the machine. A careful inspection did not reveal visible blood or air. Thus, given the inability to proceed with IHD, and due to the readiness and availability of continuous renal replacement therapy (CRRT) at our institution, we chose CRRT as the next logical step.

Continuous venovenous hemofiltration (CVVH), the primary mode used for CRRT at our institution, was attempted using a Prismaflex machine with PAES membranes, which successfully proceeded with a replacement fluid rate of 2.5 L/h (30 ml/kg/h), with 50% of the replacement fluid prefilter and 50% postfilter, without event. Notably, the effluent fluid removed by CVVH was red colored (day 5 after IV hydroxocobalamin) (Figure 1A). Thus it was suspected that administration of hydroxocobalamin led to the red pigmentation of body fluids, triggering the blood leak detector, which generated a false blood leak alarm from the hemodialysis machine. The patient's hemoglobin remained stable.

The patient received CVVH for 9 days until the effluent fluids had become significantly less pigmented (Figure 1B and C) and then he was transitioned to IHD on the Fresenius 2008K machine without any blood leak alarms. Serum vitamin B12 levels were measured during this time period. On CVVH day 1, it was >1400 ng/L (reference range 180–914; maximum level for the lab was 1400 ng/L). On CVVH day 9, despite visual changes in effluent color, the serum B12 level was still >1400 ng/L. For the remainder of the patient's hospitalization he continued to be persistently anuric, requiring continued IHD. He was eventually transferred to a local long-term acute care facility after 30 days of hospitalization.

Discussion

As a safety feature, all hemodialysis machines are designed with a sensor for blood penetration into the dialysate.

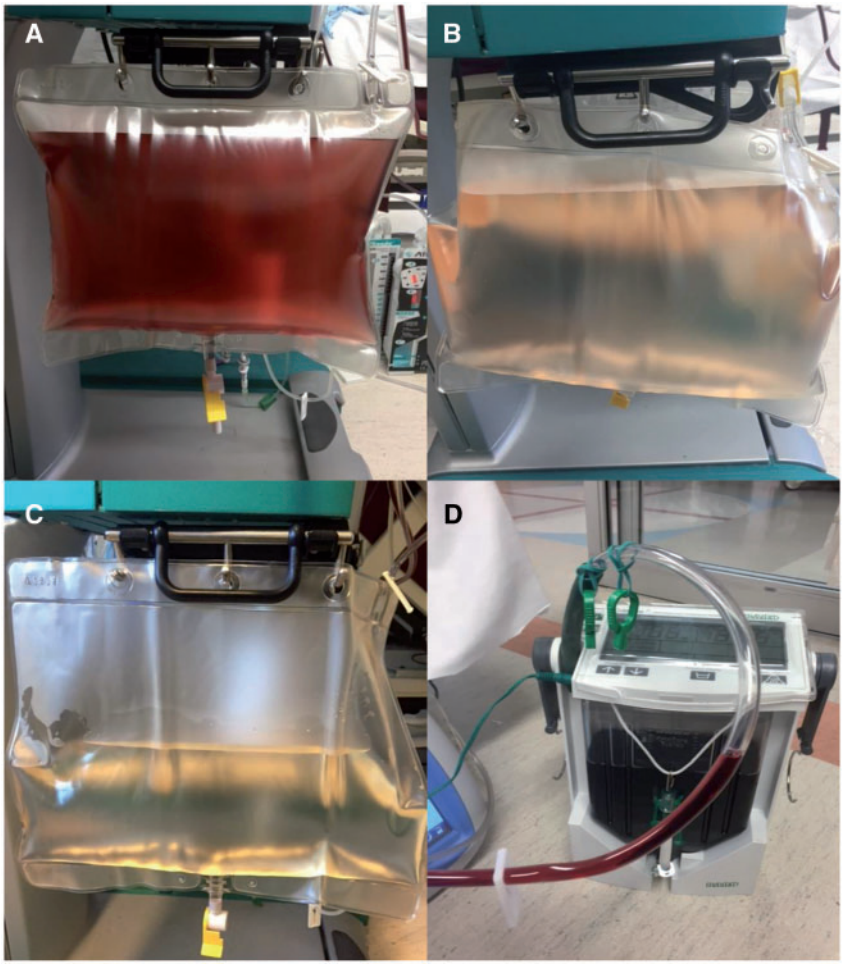

Fig. 1. (**A**) Red-pigmented effluent fluid obtained from the day of CRRT initiation (on day 5 after IV hydroxocobalamin). (**B**) On day 6 after CRRT initiation. (**C**) On day 9 after CRRT initiation. (**D**) Red urine in a different patient who received hydroxocobalamin for vasoplegic syndrome.

Depending on the manufacturer, this may be accomplished by infrared or colorimetric photodetection [1]. True blood leak culprits include dialyzer membrane compromise, heat sterilization for dialysis reprocessing [17, 18], aged dialyzer [19], dialyzer reuse [18] and hemolysis, especially when using high-flux dialyzers [3] (Table 1). Also, air bubbles or deposits of grease or scale on the detector may cause a false blood leak alarm. The case presented here shows that IV high-dose hydroxocobalamin can render hemodialysis impossible due to a false blood leak alarm.

To identify potential previously reported cases of false blood leak alarms related to hydroxocobalamin treatment, a literature search of Embase, Medline and Cochrane through September 2016 was performed using the terms 'blood leak' and 'dialysis' combined with the terms 'hydroxocobalamin' and 'vitamin B12'. Table 2 describes reported cases of hydroxocobalamin causing a false blood leak alarm. Unlike previously reported cases in which hydroxocobalamin was given for the treatment of cyanide toxicity [1, 2, 20–25], our case is the first in the setting of hydroxocobalamin infusion for cardiac surgery–related vasoplegic syndrome.

One of the few recognized adverse effects from hydroxocobalamin is a dark reddish-purple discoloration of body fluids and skin, which can lead to interference with serum and urine laboratory colorimetric assays [18, 26–30]. Chromaturia (red urine) can be observed after hydroxocobalamin treatment, lasting 7–35 days [7] and can be mistaken for hematuria [31]. Figure 1D demonstrates the red-colored urine in a different patient in our ICU who also received hydroxocobalamin for refractory post–cardiopulmonary bypass vasoplegic syndrome (this patient did not receive renal replacement therapy and urine microscopy showed no hematuria). Hydroxocobalamin has a distinct dark red color and can penetrate the dialysis filter membrane and discolor the dialysate. Machines that rely on photometric sensors for blood leak detection may then falsely signal a blood leak [20].

Table 1. Reported causes of blood leak alarm

True blood leak alarm [3, 17–19]
• Damage to the dialyzer membrane
• Heat sterilization for dialysis reprocessing
• Aged dialyzer
• Dialyzer reuse
• Hemolysis (high-flux dialyzers)
False blood leak alarm [1, 2, 20–25]
• Bubbles
• Deposits of grease or scale on the detector
• Hydroxocobalamin

Table 2. Reported cases with false blood leak alarms related to hydroxocobalamin treatment

Variable	Sutter *et al.* [1, 22]	Stellpflug *et al.* [20, 21]	Thornton *et al.* [23] and Abdelmalek *et al.* [24]	Sutter *et al.* [22] and Avila *et al.* [25]	Cheungpasitporn *et al.* (our case presentation)
Demographics	34-year-old woman	22-year-old man	33-year-old man	59-year old man	83-year old man
Indication for hydroxocobalamin treatment	Cyanide toxicity	Cyanide toxicity	Cyanide toxicity	Cyanide toxicity	Vasoplegic syndrome
Dose of hydroxocobalamin	5 g	5 g	5 g	5 g	5 g for two doses
Dialysis machine	Fresenius 2008K	NR	Fresenius 2008K	Fresenius 2008K	Fresenius 2008K
Onset of alarm after initiation of dialysis treatment	NR	During dialysis therapy initiation	Within minutes of starting dialysis	Upon initiation	Within minutes of starting dialysis
Blood leak alarm management	Attempted several hours to turn off the internal alarms to allow for hemodialysis to begin	Alarm was overridden manually, but only after treatment was delayed for >1 h During dialysis, dialysate was discolored	CRRT was successfully attempted using a Prismaflex machine Effluent was red pigmented	Dialysis treatment was successfully performed using an NxStage machine, despite the fact that the dialysate remained pink	CRRT was successfully attempted using a Prismaflex machine Effluent was red pigmented

NR, no reported data.

False blood leak alarms caused by hydroxocobalamin can adversely impact patients who urgently require hemodialysis since the blood leak alarm effectively prevents continued dialysis treatment. Delaying initiation of dialysis treatment for several hours to override blood leak alarms manually [1, 20–22] and death [20, 21] have been reported (Table 2). Also, proceeding with hemodialysis with overridden blood leak alarms carries an inherent risk to the patient in the event of a true blood leak [4, 23, 24]. On the Fresenius 2008K, a technician is required to disable the blood leak detector, as it is an internal alarm not easily accessible, and overriding blood leak alarms can potentially be a time-consuming process [1, 4, 20–22].

Blood leak alarm interference by hydroxocobalamin appears to be hemodialysis machine and circuit dependent [4]. As demonstrated in Table 2, a hydroxocobalamin-related false blood leak alarm occurred with the Fresenius 2008K dialysis machine as in our patient. The Fresenius 2008K dialysis machine contains a blood leak alarm consisting of a two-color light source transmitter and sensor (one emits red light and one emits green light) that monitor the clarity of the dialysate effluent. The photodetector is triggered when green light (wavelength 562–575 nm) is absorbed by blood [32, 33]. Avila *et al.* [2, 25] performed dialysis treatment successfully using the NxStage machine without a problem with hydroxocobalamin-related false blood leak alarms. The blood leak detector of the NxStage machine uses a single optical emitter with an 880-nm wavelength designed to detect light scatter. This method does not depend on light absorption and cannot incriminate hydroxocobalamin as possibly representing blood [2, 25].

Sutter *et al.* [4] evaluated hydroxocobalamin-related false blood leak alarms in two different dialysis machines, the Fresenius 2008K and the Gambro Phoenix X36. Hydroxocobalamin and 0.9% saline solution with food coloring (Red Dye 40) were infused into these two dialysis machines. Both triggered the blood leak alarm and the Fresenius 2008K machine shut down. Membranes of the circuits were analyzed and remained intact without blood. The findings were verified on different machines with new circuits. However, for the Gambro Phoenix X36 machine, the alarm never triggered for hydroxocobalamin or Red Dye 40. Thus the interference with the Fresenius 2008K appears colorimetric.

In our patient, we were eventually successful in providing renal replacement therapy with CVVH utilizing a Prismaflex machine. This machine can recalibrate the blood leak detector utilizing the pigmented effluent, and dialysis then proceeded without event [1, 24]. The Prismaflex blood leak detector is composed of an infrared light-emitting diode (LED) that conveys light at an angle such that it goes through the effluent line and bounces off mirrors sequentially three times before being detected by a phototransistor. Thus the transmitted light crosses over the effluent line a total of four times. The actual calibration of the blood leak detector happens during the priming sequence when the effluent line carries saline. At that point, the LED signal from the transmitter is calibrated such that the signal acquired by the phototransistor falls within a predefined satisfactory range [24]. Signals falling outside this range are sensed as a blood leak [34]. With the benefit of this information, the blood leak sensor was recalibrated against the patient's red effluent. This process is regarded as 'normalization' and this allows CRRT to proceed even though the effluent remained red tinged. As the effluent fluid displayed less red pigment, IHD was attempted again after 9 days of CVVH and was successful.

Recently, Abdelmalek *et al.* [24] and Debord *et al.* [26] also reported the successful use of CRRT in the setting of hydroxocobalamin for the treatment of cyanide toxicity, in which the

function of the CRRT machine was not impaired by hydroxocobalamin (a Prismaflex machine was used in the case described by Abdelmalek *et al.* [24]). Thus, when facing difficulties with hemodialysis after the administration of hydroxocobalamin, consider attempting dialysis with a different manufacturer's machine or model if available or contact the manufacturer directly.

Cell counts from the effluent may be considered as a safety measure to assess for an actual blood leak, which might have been missed as a consequence of the recalibration [23, 24]. In our case study, although cell counts were not performed from the red pigmented effluent fluid to confirm the absence of any red blood cells, the patient was monitored closely in the ICU and had stable serial hemoglobin and blood pressure levels despite having markedly red effluent from CVVH. Hence, this was likely a false blood leak alarm due to hydroxocobalamin administration.

Determining when to transition from CRRT to IHD can be challenging. In our case, we checked serum vitamin B12 serum levels, which were persistently elevated beyond detectable values even up to 30 days after administration. Instead, we utilized visual inspection of the effluent. Initially the effluent on CVVH was noticeably very dark red. As the days on CVVH passed, the fluid became progressively clearer such that after 6 days there was a slight pink hue. By the ninth day, the effluent fluid was visually clear and our first attempt at IHD was successful.

For the past 5 years hydroxocobalamin has been increasingly administered for the treatment of cyanide toxicity and currently >100 cases are seen annually in USA [35, 36]. High-dose hydroxocobalamin [5 g; a much higher dose than the 100–200 μg intramuscular (IM) dose used in the treatment of vitamin B12 deficiency and 1000 μg IM for Schilling test] is believed to be safe with few adverse effects [6–8]. High-dose hydroxocobalamin is becoming increasingly utilized in the treatment of post–cardiopulmonary bypass vasoplegic syndrome [9, 10], as in our case presentation. Thus it is important for clinicians to have a greater appreciation and understanding of hydroxocobalamin, the limitations on renal replacement options, and how these difficulties can be overcome with available resources in a safe and timely manner.

Based on the existing evidence, the Gambro Phoenix X36 [4] and NxStage [22, 25] machines would be suitable for hemodialysis, as their blood leak sensor response does not continually interrupt treatment due to hydroxocobalamin-related false blood leak alarms. In addition, depending on the availability of CRRT in each institution, providing CRRT with a Prismaflex machine [23, 24] is also an option to overcome the hydroxocobalamin-related interference with hemodialysis. Future studies that evaluate all of the currently existing hemodialysis machines are required.

In summary, since the utilization of hydroxocobalamin has been increasing as a treatment for cyanide toxicity and vasoplegic syndrome, awareness of hydroxocobalamin-induced false blood leak alarms is important to minimize the risk of treatment-related morbidity/mortality due to inability to provide dialysis treatment. Attempting dialysis with a different manufacturer's machine or model if available or contacting the manufacturer directly should be considered. In this case presentation, we describe the use of CRRT as an option to overcome hydroxocobalamin-related interference with hemodialysis.

Authors' contributions

All authors were involved and approved the final manuscript.

Conflicts of interest statement

None declared.

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