Brugada-type electrocardiogram changes associated with nitroprusside toxicity

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Introduction

Nitroprusside toxicity is a known potential complication of the use of nitroprusside for the control of accelerated hypertension. Toxicity is manifested as both cyanide intoxication and thiocyanate intoxication. Nitroprusside contains 5 cyanide molecules bound to an iron core, and these cyanide...
KEY TEACHING POINTS

- Nitroprusside toxicity is marked early by tachyphylaxis, or by the rapid requirement of increasing doses to achieve the desired effect. It can be followed by signs of cyanide and thiocyanate toxicity to include lactic acidosis, arrhythmias, altered mental status, and miosis.
- The first-line treatment for cyanide toxicity is hydroxocobalamin. Thiocarbonate may be effective if renal function is normal, but in the setting of kidney failure thiocyanate can accumulate, leading to a separate toxicity, which requires hemodialysis for clearance.
- Brugada pattern can be elicited by numerous drugs and under conditions of significant metabolic stress. Cyanide poisoning may directly affect heart muscle and electrical currents to mimic Brugada pattern or may uncover an underlying pathology secondary to the severe metabolic demands placed on the heart.

Nitroprusside molecules are released as nitroprusside breaks down to release nitric oxide, which leads to vasodilation. The body removes the cyanide by forming methemoglobin or thiocyanate, which can then be cleared by the kidneys. Clearance of thiocyanate is the primary method of cyanide clearance. Healthy adults can detoxify between 50 and 68 mg of nitroprusside, but this capacity has been shown to be limited in smokers and postoperative patients.1,2

Nitroprusside tachyphylaxis is one of the earliest signs of cyanide accumulation and is characterized by increasing nitroprusside requirements in order to maintain the same level of antihypertensive effects. Elevated lactic acid can be seen as well, but may not manifest until much later. Other findings of cyanide toxicity include tachycardia, altered mental status, and increased venous oxygen content. Classically, the odor of almonds may be appreciated. When renal function is impaired, thiocyanate toxicity can develop, manifested by altered mental status, miosis, hallucinations, and seizures.1

Several case reports exist outlining atypical presentations of nitroprusside toxicity; however, to our knowledge, no reports exist of Brugada-type electrocardiogram (ECG) morphology being induced by nitroprusside or cyanide toxicity in humans. We present a case that demonstrates the development of Brugada pattern after treatment for cyanide toxicity secondary to nitroprusside.

Case report

The patient is a 52-year-old woman with history of hypertension and tobacco dependence who presented to an outside hospital with right fifth toe pain and discoloration. She was found to have aortoiliac disease and was transferred to a tertiary care facility for an angiogram. During the procedure, she was noted to have sustained systolic blood pressures in the 180s, so a nitroprusside infusion was started. Although there was a brief period of hypotension, her blood pressures soon rose and peaked at 240 mm Hg systolic. The infusion rate was increased to treat these rising pressures. The patient subsequently noted difficulty breathing and became tachypneic and hypoxic. She was intubated and transferred to the intensive care unit (ICU), where the nitroprusside was transitioned to nicardipine and her blood pressures rapidly normalized. Physical examination was notable for constricted pupils and mottling of the skin that improved with heated blankets.

Computed tomography scans of the head and chest, bronchoscopy, and echocardiogram were negative for any acute pathology. Laboratory tests showed a pH of 7.33 with an arterial pO2 of 84 mm Hg despite receiving 100% FiO2. Additional blood work was repeatedly hemolyzed. Approximately 4 hours after the nitroprusside infusion had been started, treatment for cyanide poisoning was initiated with hydroxocobalamin. Cyanide and thiocyanate levels were then collected, although results were not available for several days.

When nonhemolyzed laboratory results were able to be obtained several hours later, they showed a normal lactate. Troponin rose to 0.37 and her creatinine peaked at 3.70 from a preprocedure baseline of 0.95. Her methemoglobin peaked at 5.7% approximately 10 hours after the hydroxocobalamin was administered. The patient’s course was complicated by labile blood pressures requiring either norepinephrine or nicardipine, as well as pneumonia, for which she was given meropenem.

On ICU day 3, her ECG showed significant changes consistent with a type 1 Brugada pattern (Figure 1). Electrolytes at the time were within normal limits. Cardiology attributed the changes to the patient’s metabolic derangements and recommended initiation of hemodialysis for toxin clearance. No further testing, such as cardiac magnetic resonance imaging or electrophysiology testing with flecainide, was felt to be indicated at that time. Hemodialysis was performed daily for several days, with gradual improvement in her clinical status. She was weaned from the ventilator, extubated on ICU day 6, transferred to the floor the following day, and discharged home on hospital day 14.

Available cyanide levels were less than 0.1 mg/L on 2 separate measurements; however, neither were collected prior to hydroxocobalamin administration owing to the problems with hemolysis. A thiocyanate level was collected the day following hydroxocobalamin administration and was 12.6 μG/mL, with the upper level of normal being 12.0 μG/mL. Follow-up ECGs never showed full resolution of the repolarization abnormalities prior to discharge. The patient had follow-up appointments with nephrology and she was no longer receiving hemodialysis as of 2 months post-discharge.

Discussion

Nitroprusside toxicity is thought to be rare, but it may be under-recognized and therefore underdiagnosed.3 Our
patient’s tachyphylaxis was an early sign of developing nitroprusside toxicity and her profound hypoxia cannot be explained by any other etiology. One atypical case in the literature describes lactic acidosis with multiorgan failure in a cardiac surgery patient 12 hours after the nitroprusside infusion was discontinued. In that case, cyanide and thiocyanate levels were low but the patient was treated with hydroxocobalamin and recovered shortly thereafter. The reason for normal toxin levels in our case may be related to the timing of sample collection and the lack of a lactic acidosis may be attributed to repeatedly hemolyzed laboratory results. Additionally, our patient’s thiocyanate level was elevated despite being measured 15 hours after receiving hydroxocobalamin. This result can be partially attributed to her history of smoking, but not likely to the level of 12.6 μG/mL. In fact, her history of smoking likely impaired her ability to clear the cyanide, making her more susceptible to its toxic effects.

Numerous medications and toxins are known to expose underlying Brugada pattern, including flecainide, procainamide, and cocaine, among others. There have also been reports of nitroglycerin causing adverse effects in patients with known Brugada syndrome, although these data are not well supported. Nitroprusside and cyanide have no previously established relationship with Brugada syndrome.

The effects of cyanide on the electrophysiology of the heart are not well understood. An early study in rats showed direct changes to heart muscle in response to cyanide, which may explain some of the ECG changes seen by Wexler and colleagues. The electrical changes demonstrated by Wexler and colleagues consisted of P-wave suppression and bradycardia, eventually culminating in ventricular arrhythmias. A more recent modeling study shows similarities between the electrical properties of the heart of cyanide-poisoned tissue and Brugada syndrome. This study by Zoltani and colleagues shows that modifications of sodium, potassium, and calcium currents directly caused by cyanide on the epicardium results in ST changes and the appearance of a J wave that closely resembles the ECG in Brugada. They suggest that restoring the depolarizing sodium current and maintaining calcium hemostasis are the most effective ways to reverse these effects. Our patient underwent hemodialysis in order to regulate any metabolic disturbances and as a method of thiocyanate clearance.

In conclusion, the presented case of cyanide toxicity secondary to nitroprusside infusion is unique because of the development of Brugada pattern on ECG. It is difficult to determine if the ECG changes were a direct result of cyanide poisoning or secondary to the severe metabolic stress placed on the patient from the nitroprusside toxicity. Regardless, it is important to recognize that nitroprusside has the potential to impact multiple organ systems, including the electrical system of the heart, through both direct and indirect pathways. Although further research into this subject would be difficult, clinicians should be on high alert for nitroprusside toxicity and all of the potential sequelae whenever it is used.

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