SODIUM NITROPRUSSIDE-INDUCED CYANIDE INTOXICATION AND PREVENTION WITH SODIUM THIOSULFATE PROPHYLAXIS

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• ***Sodium nitroprusside is an antihypertensive agent used frequently in the critical care setting. Recently, the Food and Drug Administration (FDA) published a report that led to a labeling change emphasizing the pharmacokinetics of nitroprusside with metabolism to highly toxic cyanide. Although evidence validates that cyanogenesis occurs with nitroprusside administration, prevention and treatment of cyanide poisoning is rarely instituted in clinical practice. Simultaneous infusion of thiosulfate with nitroprusside provides the sulfur donor necessary to prevent cyanide accumulation. Cyanide combines with thiosulfate to form the less toxic sodium thiocyanate, which is then excreted. A 10:1 ratio of nitroprusside to thiosulfate in the infusion eliminates the possibility of cyanide intoxication without altering the efficacy of nitroprusside. (American Journal of Critical Care. 1992;2:19-27)***

Nitroprusside is a vasodilator routinely used in the operating room and the critical care unit to control hypertension and to reduce afterload. Nitroprusside was first introduced to clinical practice in 1955,[1] was listed as an essential drug by the World Health Organization in 1974,[2] and was approved by the FDA in 1975.[3]

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Cyanide toxicity is a potentially lethal side effect of nitroprusside infusion. Although documentation of this link has been cited in the literature for more than a century,[3-9] confusion still exists regarding the relationship between nitroprusside and cyanide. Among widely held misconceptions[2,10-12] are that:

- cyanide toxicity is a threat only with long-term infusions of nitroprusside
- metabolic acidosis must exist for cyanide toxicity to be present
- thiocyanate levels reflect the cyanide burden
- nitroprusside degrades rapidly to cyanide in vitro while protected from light

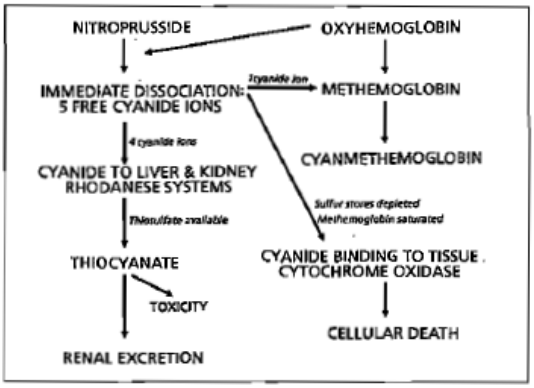
In April 1990 the FDA published a comprehensive review that emphasized the biochemistry of nitroprusside metabolism and the risk of cyanide poisoning.[3] An understanding of the information summarized in that review is important for safe administration of nitroprusside and prevention of significant iatrogenic morbidity and mortality.

This article summarizes information pertaining to metabolism of nitroprusside and the toxicities that may result from its infusion. The simultaneous infusion of thiosulfate to prevent cyanide toxicity is also described.

Normal methemoglobin content in the blood is only 0.5%, however, corresponding to a binding capacity of 18 mg of nitroprusside.[3,4,10,19,21] The four remaining free cyanide ions undergo a detoxification process called transulfuration, in which a sulfhydryl group is donated primarily by endogenous thiosulfate.[3,4] A healthy adult in steady state has adequate sulfur stores to detoxify 50 mg of nitroprusside (one vial).[10,20] Available thiosulfate combines with cyanide and is converted irreversibly to thiocyanate in the liver via the action of rhodanese, a sulfur transferase enzyme present in abundance within the mitochondria of the liver and kidneys (Figure 3). Thiocyanate is then excreted by the kidneys, with an elimination half-life of 2.7 days in the patient with normal renal function. The elimination time is increased in those individuals with renal insufficiency, which can predispose them to thiocyanate toxicity, discussed later.[10,12,21-22]

Once the stores of thiosulfate are depleted and available methemoglobin is saturated, cyanide levels in both the blood and tissues rise. The free cyanide binds and inactivates the ferric containing enzyme cytochrome oxidase, which is found in the mitochondria of the cell and is essential for cellular respiration. Cytochrome oxidase is the final step in the electron transport chain and results in the formation of adenosine triphosphate (ATP) and water.[24] The inactivation of cytochrome oxidase results in tissue anoxia and anaerobic metabolism resulting in lactic acid formation. Oxidative phosphorylation is a major buffer of hydrogen ions and when inactivated, results in metabolic acidosis.[10,19,22]

Figure 3 Metabolism of nitroprusside. Generation of cyanide takes three primary pathways: (1) binding with available methemoglobin to form cyanmethemoglobin, (2) converting to thiocyanate in the presence of thiosulfate for renal excretion, (3) binding with tissue cytochrome oxidase with resultant cyanide accumulation and tissue asphyxiation.[3,4,10,13,19]



Risk Factors for Nitroprusside-Induced Cyanide Toxicity

Current labeling lists acceptable dosage range from 0.5 to 10 μg/kg per minute for parenteral nitroprusside. The manufacturer does emphasize that infusion at maximum dose rate should not exceed 10 minutes,[13] but even the range is thought to be excessive by researchers who acknowledge that metabolism of nitroprusside is species-dependent.[4,25] The spontaneous detoxification rate in humans is approximately 2 μg/kg per minute, slower than data obtained from animal studies.[4,6,12,25] The patient is at risk for cyanide accumulation if more than 1.5 mg/kg is given over a 3- to 4-hour period, and life-threatening intoxication can ensue with 5 to 10 μg/kg per minute given over a 5- to 10-hour period.[3,10,26] However, elevated cyanide levels, metabolic acidosis and marked clinical deterioration have been reported in patients who received nitroprusside infusion at recommended rates for only a few hours and in one case, after only 35 minutes.[13]

As previously stated, the rate-limiting factor in cyanide metabolism is available sulfur stores. Factors such as malnutrition, surgery, and diuretic administration can lower the body's stores of thiosulfate,[10,24] predisposing to cyanide poisoning. Neonates and newborns may also have inadequate stores of this sulfur donor.[8,21,27,28] It must be recognized that any patient receiving nitroprusside is at risk for developing cyanide poisoning and should be continually assessed for impending toxicity.

Clinical Manifestations of Cyanide Toxicity

The existing Spontaneous Reporting System Database of the Food and Drug Administration (FDA) reveals 142 case reports involving nitroprusside, including 25 fatalities.[3] The infrequency of these reports may be partially attributable to the vagueness of clinical manifestations in cyanide poisoning (Table 1). The etiology of symptoms may be ascribed to a multiplicity of problems a critically ill adult could experience, or may simply be attributed to too much nitroprusside. Those unaware of the cyanide risk will treat the symptoms as they arise without treating the cause.

Primary symptoms can be clustered into a diagnostic triad of central nervous system (CNS) dysfunction, cardiovascular instability, and changes in oxygenation/pH. The presence of these physiologic clues should be considered indicative of cyanide poisoning until proven otherwise.[10]

Although the first clinical indicators of cyanide toxicity may be behavioral, too often these changes are

CNS dysfunction
- Headache
- Anxiety
- Disorientation
- Lethargy
- Seizures
- Coma
- Cerebral death

Cardiovascular instability
- Hypertension (tachyphylaxis) ——> hypotension
- ECG changes
  - Tachycardia—> bradycardia
  - ST-T wave changes
  - Dysrhythmias
  - AV block
  - Cardiovascular collapse

Changes in oxygenation/pH
- Tachypnea—> apnea
- Venous hyperoxemia
  - Red venous blood
  - Increased mixed venous O_2 content (SvO_2)
  - Decreased O_2 consumed (VO_2)
  - Narrow arteriovenous oxygen difference (AvO_2diff)
  - Brick-red skin (occasional cyanosis)
- Metabolic acidosis
  - Elevated blood lactate and/or
  - Elevated lactate:pyruvate ratio

Other
- Nausea, vomiting, abdominal pain
- Increased salivation

Table 1 Symptoms of cyanide poisoning

Level	Symptomatology
< 0.05 µg/mL	Normal
> 0.15 µg/mL	Headache, palpitations, tachypnea
> 0.25 µg/mL	Seizures, acidosis, coma
> 0.3 µg/mL	Death
Cost	
Routine	$37.80
Stat	$46.80
Time Required	
Routine	24-48 hours
Stat	3-6 hours
Blood Collection	
7 mL in two purple-top tubes	

* Cyanide levels differ based on (1) specimen source (red blood cells, whole blood, plasma), (2) unit of measurement (Système International vs traditional units), and (3) interlaboratory variation.

† Symptoms of cyanide poisoning vary based on individual differences and comorbidity factors.

Cost, time and collection based on Denver Department of Veterans Affairs Medical Center criteria.

Table 2 Measurement of whole blood cyanide * †

attributed to "ICU psychosis" in the critically ill. Therefore, the first red flag of impending toxicity may be the presence of tachyphylaxis, necessitating increasingly higher doses of nitroprusside to control the rising blood pressure. Increasing the rate of infusion only compounds the primary problem of cyanide accumulation and resultant life-threatening complications.

Lactic acidosis develops as ATP production falls and anaerobic metabolism ensues. Because metabolic acidosis occurs late in the course of cyanide toxicity, it is not a sensitive diagnostic marker. In fact, the presence of acidosis may indicate that cyanide levels are already critical.[4,10] In acidosis induced by toxins, clinical indicators of poor tissue perfusion or oxygenation (eg, hypotension, cyanosis, cool and clammy extremities) may be absent.[10,22] Venous blood may approximate arterial blood in color because of decreased tissue consumption of oxygen and increased venous oxygen content.

Cyanide levels can be measured (Table 2), but in a critical situation, therapeutic intervention cannot wait for laboratory results, which may take hours. Furthermore, blood levels cannot reflect the dynamic process unique to the person's threshold for toxicity. For example, a patient may be able to tolerate a slight reduction in oxidative phosphorylation without significant decompensation, due to adequate energy reserves. However, the more compromised the patient, the more likely even small reductions in ATP production may result in irreversible ischemic injuries or death.[10,27]

Thiocyanate levels are of no value in determining the presence of cyanide toxicity. Historically, thiocyanate levels were thought to represent cyanide levels due to a conversion from a hypothetical enzyme, thiocyanate oxidase.[27] It is now recognized that cyanide metabolism to thiocyanate is an irreversible process, and that thiocyanate and cyanide levels represent two distinct toxicologic syndromes. One cannot be evaluated in terms of the other.

Treatment of Cyanide Toxicity

Cyanide poisoning is a life-threatening emergency. Foremost, the infusion of nitroprusside must immediately be discontinued. The patient should be placed on 100% oxygen, even in the presence of a normal partial oxygen pressure (Po_2), because of inadequate oxygen utilization by the cells. Intubation

with assisted ventilation and treatment of a pH of less than 7.16 with sodium bicarbonate may be required if the patient is not responsive to antidote therapy as outlined below. Normal saline will provide volume support to maintain blood pressure, although pressor support such as dopamine hydrochloride also may be necessary.[10,27]

Treatment is aimed at protecting the body against cellular anoxia while inactivating and removing the cyanide. The priorities are airway management with supportive care and administration of the Lilly Cyanide Antidote Kit (Eli Lilly, Indianapolis, Ind). The kit is designed for all types of cyanide poisoning such as industrial accidents and ingestions; therefore, not all items will be used for nitroprusside-induced cyanide exposure (Table 3).

The antidote kit contains three drugs: amyl nitrite, sodium nitrite and thiosulfate. Amyl nitrite and sodium nitrite displace the cyanide from cytochrome oxidase, and thiosulfate facilitates excretion. The pearls of amyl nitrite are a temporizing measure, necessary only if intravenous access is unavailable. In the event of nitroprusside-induced cyanide poisoning where intravenous access is available, the first drug administered should be sodium nitrite. One 10-mL vial of 3% sodium nitrite given intravenously over 2 to 4 minutes is normal dosing for an adult to induce the desirable 27% methemoglobinemia. Because special dosing is necessary for children and patients with significant anemia, a guide for correct calculation is included in the package insert. The purpose of both these drugs is to induce methemoglobinemia, delaying the toxin's entrance into the tissues by providing another source of Fe^{3+} to which the cyanide can attach. Methemoglobin frees cyanide from the cytochrome oxidase because of higher affinity for cyanide.[13,26]

Table 3 Contents of cyanide antidote kit

Induce methemoglobin production
• Pearls of amyl nitrite (12)
• Sodium nitrite 300 mg vial (2)
10-mL syringe with 22-gauge needle
Provide sulfur donor
• Sodium thiosulfate 12.5 g vial (2)
60-mL syringe
20-gauge needle
Other
• Tourniquet
• 16F nasogastric tube
• 60-mL Toomey syringe

Sodium thiosulfate, given as a sulfur donor, enhances rhodanese activity and accelerates the conversion of cyanide to thiocyanate for renal excretion. A 12.5-g vial is given intravenously over 2 to 4 minutes. If, after 2 hours, the symptoms persist or reappear, half the original drug dose may be readministered.[13,27]

Alternative Treatments for Cyanide Poisoning

Some investigators have identified hydroxocobalamin (vitamin B_{12}) as a therapy for cyanide poisoning.[28-30] However, its use has been found to be impractical in the clinical setting because of the large dosing volume required and the prohibitive cost of the drug.[10]

The German *Rote Liste* lists a "new, rapid-acting antidote" for cyanide poisoning, called 4-dimethylaminophenol hydrochloride (4 DMAP, Kohler-Chemie).[3] This drug functions in the same way as sodium nitrite, by inducing the formation of methemoglobin. The manufacturer recommends that 4 DMAP be followed by 10 g thiosulfate.

Prevention of Nitroprusside-Induced Cyanide Intoxication

Cyanide poisoning with nitroprusside is entirely preventable. Investigators have demonstrated that providing the sulfur donor thiosulfate as a mixed infusion with nitroprusside accelerates the detoxification of cyanide, making toxicity virtually impossible.[3,4,9,10,21-23]

A 10:1 ratio of thiosulfate to nitroprusside (ie, 500 mg thiosulfate to 50 mg nitroprusside) as a mixed infusion provides enough sulfur to promote metabolism for excretion.[10,22,23] Nitroprusside is diluted in the usual fashion with 5% dextrose solution prior to admixture, and is stable for at least 7 days (although adherence to individual hospital policy is recommended) if protected from bright sunlight.[3] The half-life of thiosulfate is 20 minutes,[3] dismissing intermittent dosing as a viable option. The cost of a 1-g vial needed for a 100-mg nitroprusside mixture ranges in price at institutions surveyed from $0.74 to $7.00. Thiosulfate does not affect the pharmacologic benefits of nitroprusside[3,4,10] and is without any significant toxicities of its own.[3,4,23] Each gram of thiosulfate contains 290 mg sodium.[3]

Nitroprusside and Thiocyanate Toxicity

One of the earliest treatment modalities used for arterial hypertension was potassium thiocyanate. However, its margin of safety was low and use

markedly decreased after 1945.[4] The hypotensive effects are minimal in comparison with nitroprusside.

Thiocyanate toxicity is a separate clinical syndrome from cyanide poisoning with regard to symptoms, risk factors and treatment. Again, thiocyanate results from the conversion of cyanide by the mitochondrial enzyme rhodanese in the presence of a sulfur donor. Thiocyanate is approximately 100 times less toxic than cyanide.[10,22] It is excreted by the kidneys at a relatively slow rate, because nearly 90% of that filtered by the glomeruli is reabsorbed. The elimination half-life of thiocyanate is 2.7 days in a patient with normal renal function.[4] Those with renal dysfunction excrete this metabolite much more slowly, taking as long as 9 days.[12,23]

Thiocyanate toxicity occurs only after approximately 9 days in those with normal renal function and after approximately 3 days in those with renal failure. The clinical symptoms are primarily neurologic[10] but may also include other vague symptomatology (Table 4). Prolonged exposure to thiocyanate can result in reversible hypothyroidism due to thiocyanate's competition with iodine for thyroidal uptake.[3,10,24,28]

Patients receiving infusions of nitroprusside mixed with thiosulfate may have higher levels of thiocyanate than those who do not. This is a reflection of the cyanide metabolism and in principle should not be a concern,[10] unless the values or symptoms (Table 5) demonstrate toxicity.

Treatment of Thiocyanate Toxicity

Both peritoneal dialysis and hemodialysis have been used effectively in clearing thiocyanate, although this treatment is rarely indicated.

Table 4 Measurement of sodium thiocyanate

Level	
• Nonsmoker	< 4 mg/L
• Smoker	< 8 mg/L
• Toxicity	> 100 mg/L
Cost	
• Routine	$37.80
• Stat	$46.80
Time required	
• Routine	24 hours
• Stat	1-2 hours
Blood collection	
• 5-mL red-top tube	

Cost, time, and collection based on the Denver Department of Veterans Affairs Medical Center criteria.

Neurogenic	Other
• Confusion	• Muscle fatigue
• Miosis	• Hyperreflexia
• Hallucinations	• Nausea and vomiting
• Toxic psychosis	• Tinnitus
• Convulsions	• Decreased T_4
• Coma	
• Death	

Table 5 Symptoms of sodium thiocyanate poisoning

Thiocyanate toxicity may occur with or without cyanide poisoning.

Nursing Implications

Any patient receiving nitroprusside without simultaneous infusion of thiosulfate is at risk for developing cyanide toxicity. The signs and symptoms may be vague, but the triad of CNS dysfunction, cardiac instability (particularly tachyphylaxis), and oxygenation/pH changes should alert the nurse to the possibility of cyanide poisoning. Treatment should begin without delay if there is a reasonable suspicion of cyanide toxicity.

The nurse can promote the use of thiosulfate with all nitroprusside infusions to increase the drug's margin of safety. This intervention will prevent cyanide accumulation and its complications in all patients receiving the drug, regardless of the dose or duration of infusion. Incorporating a mixed-infusion protocol into hospital policy will require a proactive multidisciplinary approach involving nursing, medicine, surgery, anesthesia and pharmacy.

Also, the nurse may advocate and assist in development and implementation of a research study within the institution. The study would compare measurable endpoints in patients receiving nitroprusside alone with those receiving a mixed infusion of nitroprusside/thiosulfate. Prospective randomized clinical trials in this area are lacking in the United States, and the FDA cannot make further recommendations without them.

Summary

Nitroprusside remains an invaluable adjunct in a variety of clinical settings. However, education is needed at the clinical level to prevent further nitroprusside-related morbidity and mortality. Although the approved infusion rates far exceed the spontaneous detoxification rate in humans, reported cases of nitroprusside-induced cyanide poisoning remain infrequent in the critical care setting. Clearly, the clinician must be able to recognize cyanide poisoning and

differentiate the symptoms from other disorders before it can be diagnosed or reported. An understanding of cyanogenesis and transulfuration validates the role of thiosulfate as an admixture with all nitroprusside infusions. Thiocyanate toxicity is a separate clinical entity from cyanide toxicity. Thiocyanate is less toxic and rarely a problem, but it is effectively cleared with dialysis when necessary.

As we strive to provide the best, most cost-effective care available to critically ill patients, it is incongruent to ignore a life-threatening complication that is effectively and easily prevented.

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