Change in National Dosing Advice of Nitroprusside After Potentially Fatal Cyanide Intoxication

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Abstract

The aim of this brief communication is to provide a short overview of cyanide intoxication following infusion of sodium nitroprusside (SNP). SNP is a fast-acting antihypertensive drug frequently used in of hypertensive emergencies. Although SNP is widely known as a safe to use drug, it can cause a potentially lethal cyanide intoxication. The difficulty to diagnose cyanide intoxication and pharmacological principles will be discussed. Hereby, we like to regain attention for this severe complication. As a result of our experience, the Dutch national paediatric drug formulary has been updated with additional warnings and recommendations. Cyanide intoxication due to sodium nitroprusside is a severe and difficult to recognize complication with potentially lethal outcome. Clinicians prescribing sodium nitroprusside should always be aware of its toxic effects.

Keywords Nitroprusside · Toxicity · Acidosis · Critical care · Paediatrics · Drug safety

Abbreviations

ATP	Adenosine triphosphate
AVSD	Atrioventricular septal defect
CN	Cyanide molecules
CYANOHGB	Cyanomethemoglobin
METHGB	Methemoglobin
NO	Nitric oxide
OXYHGB	Oxyhemoglobin

PICU	Paediatric intensive care unit
SNP	Sodium nitroprusside

Introduction

Sodium nitroprusside (SNP) is a frequently used antihypertensive drug in intensive care settings after cardiac surgery. Due to its rapid vasodilatory effect, it can be used in case of hypertensive emergency. A known but only rarely reported side effect is cyanide intoxication. Generally, SNP is considered to be a safe drug to use; however, if unaware of its potential danger, it can be lethal [1–3]. In this brief communication, we would like to regain attention to the severe adverse effects of SNP and the difficulty to diagnose cyanide intoxication.

Clinical Experience

A 1-month-old girl was admitted to our paediatric intensive care unit (PICU) after uncomplicated surgical repair of atrioventricular septal defect (AVSD). Within hours after the procedure, the patient was clinically stable and was extubated. Immediately after extubation, she developed severe hypertension with arterial blood pressure levels rising above 140/90 mmHg (p95 for age = 102/69 mmHg). Sodium nitroprusside was started at a dose of 0.5 µg/kg/min and was stepwise increased up to 8 µg/kg/min because of insufficient decrease in blood pressure. An ACE

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inhibitor was added, aiming to obtain normal blood pressure. Effect on hypertension was still insufficient. Ten hours after the start of SNP, the patient developed tachycardia, tachypnea, dyspnea and abdominal distention and became agitated. Opiates and benzodiazepines had no effect on clinical presentation. Laboratory studies showed severe metabolic lactic acidosis. Due to the non-specific symptoms, several diagnostic tests were performed (laboratory studies, electrocardiogram, cardiac ultrasound, chest and abdominal X-rays), which did not explain symptoms. With no other explanation than possible cyanide intoxication, SNP was immediately discontinued despite persisting hypertension. The patient was re-intubated to minimize respiratory effort and start oxygen therapy to obtain optimal p_aO_2 levels for aerobic adenosine triphosphate (ATP) synthesis. Within 4 h after discontinuation of SNP, metabolic acidosis was completely resolved; blood pressure restored to normal; and her clinical symptoms disappeared. Further postoperative course was uneventful. An average SNP dose of 7.9 $\mu\text{g/kg/min}$ was given with a cumulative dose of 6.7 mg/kg (totally 20.0 mg) over a period of 14 h. Risk factors for developing cyanide toxicity, including kidney and liver failure and metabolic disorders, were excluded. Laboratory studies showed elevated thiocyanate level.

Pharmacological Principles

The molecular structure of sodium nitroprusside consists of sodium molecules and a ferric ion complex with nitric oxide (NO) and five cyanide molecules (CN). NO is the active substance causing the desired effect of lowering blood pressure, due to relaxation of smooth muscle cells in arterial and venous walls. For every NO molecule, five cyanide molecules are released as a coproduct during SNP metabolism, which can

cause the severe side effect of this drug. SNP and cyanide metabolism are illustrated in Fig. 1. Intravenously administered SNP reacts with oxyhemoglobin converting it into methemoglobin. As cyanide has strong affinity for iron molecules, one cyanide molecule binds methemoglobin converting it to cyanmethemoglobin. In this way, SNP may act as a (partial) buffer for released cyanide molecules. The remaining and potentially toxic molecules are mainly metabolized in the liver by rhodanase, which converts cyanide and thiosulfate to thiocyanate. The enzyme rhodanase is normally present in great excess in mitochondria. This makes thiosulfate stores the limiting factor in converting cyanide to the less toxic thiocyanate. Thiocyanate is a water-soluble molecule that is excreted in urine. If cyanide concentration exceeds the capacity of cyanide being converted into thiocyanate or buffered in cyanmethemoglobin, cyanide will bind to cytochrome c oxidase. Cytochrome c oxidase is located in the mitochondrial membrane and is the last enzyme in the respiratory electron transport chain, necessary to produce ATP. Cytochrome c oxidase contains a ferric ion to which cyanide molecules reversibly bind with high affinity. This way cyanide interferes with normal function of cytochrome c oxidase and blocks the aerobic pathway of producing ATP. Due to blocking this aerobic pathway, cells start utilizing anaerobic pathways generating large amounts of lactic acid. This results in severe acidosis and shortage of energy for organ function leading to cell damage and eventually death. Acidosis may however not be evident within the first hour after cyanide accumulates. Increasing dosage requirement of SNP to maintain blood pressure control may be the first manifestation of cyanide toxicity [4–6].

Fig. 1 Schematic overview of sodium nitroprusside metabolism. ATP, adenosine triphosphate; CN⁻, cyanide radical; CYANOHGB, cyanomethemoglobin; METHGB, methemoglobin; NO, nitric oxide radical; OXYHGB, oxyhemoglobin; SNP, sodium nitroprusside

Discussion

Limited literature is available on the use of sodium nitroprusside in the paediatric population. Only few trials are performed to investigate the efficacy and safety of SNP. In general, SNP is stated to be a safe antihypertensive drug [1–3]. However, this report shows that caution should be exercised.

Symptoms caused by cyanide intoxication are non-specific and include metabolic acidosis, headache, seizures, coma, delirium, weakness, dyspnea or tachypnea, vomiting, hypotension, tachycardia and even resulting in death. Typical cherry red skin and bitter almond odour are only found in few cases [7]. As most symptoms are aspecific and similar to common postoperative problems, the diagnosis can easily be overlooked, and therefore, prudence by the clinician is necessary.

Young patients are often unable to self-report on symptoms, such as discomfort, which can delay diagnosis. Routine laboratory tests may unexpectedly show severe lactic acidosis, which in itself can have many causes. In clinical practice, SNP toxicity often is not a very common explanation for a lactic acidosis and may therefore be easily overlooked. In severe cases, intervention is required quickly, which hampers usefulness of routine monitoring of cyanide levels because of the long turnaround time. Secondly, routine monitoring of cyanide levels is not recommended, as cyanide levels and symptoms often do not correlate [8–10]. A combination of these factors could lead to suboptimal treatment.

Because of reasons mentioned above, no golden standard for diagnosing cyanide poisoning is available, and diagnosis often is based on clinical symptoms resolving after discontinuation of SNP.

Risk factors for cyanide intoxication are described in literature: renal dysfunction (both cyanide and thiocyanate are excreted renally), hepatic dysfunction (liver is necessary for converting cyanide to thiocyanate) [2], prolonged infusion (> 24 h) and high dosage or infusion rate [4, 8]. Animal studies showed that the maximum amount of cyanide the body can buffer before creating an excess of cyanide is about 500 µg/kg. This amount is reached within an hour when the maximum recommended rate of 10 µg/kg/min is administered [11]. On the other hand, neonates who received doses of 6 µg/kg/min for periods over 48 h did not develop any signs of cyanide toxicity [3].

The national paediatric drug formulary was updated with an additional warning and recommendation [12]. This highlights the buffer capacity mentioned above and advises to discontinue SNP in case no decrease in blood pressure is reached within 10 min after reaching the maximum advised dosage. This illustrates the necessity to consider rare adverse effects of drugs in case of unexpected symptoms or signs and highlights the importance of reviewing and reporting severe adverse effects of drugs in order to decrease the risk in other patients.

Conclusion

Sodium nitroprusside is not as safe as stated, even in the absence of risk factors. Caution should be exercised by clinicians prescribing SNP, and SNP toxicity should be considered in case of unexplained lactic acidosis or absent clinical response shortly after reaching maximum advised dosage. National paediatric drug formulary was updated by adding a warning to discontinue SNP in case of absent clinical response on blood pressure shortly after reaching the maximum advised dosage was added.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from the patient's parents for publication of this report.

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