



Sodium Nitroprusside Toxicity in a Young Infant Following Cardiac Surgery

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Authors' contributions

This work was carried out in collaboration between all authors. Authors DS and MB wrote the first draft of the manuscript and managed the literature searches. Authors GBL, MAP and PS contributed to the correction of the draft. Author PB provided the case and supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Adverse effects associated with sodium nitroprusside (SNP) administration are rarely observed in children. Monitoring of metabolic changes appears to be the most sensitive and accurate indicator of early toxicity. We report a case of acute toxicity in a 3-month-old boy treated with high-dose SNP infusion for systemic hypertension after elective coarctectomy, who developed seizures and severe lactic acidosis. We suggest blood lactate levels and base excess levels should be carefully monitored during SNP treatment in children, in order to detect early signs of toxicity, particularly when using high infusion rates.

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1. INTRODUCTION

Sodium nitroprusside (SNP) is an NO-releasing vasodilator and is used in infants and children in the management of systemic hypertension and to reduce after-load following cardiac surgery [1,2]. However, when used in large doses, SNP and its metabolic products, cyanide (CN) and thiocyanate (SCN), may induce severe toxicity causing vomiting, bradycardia, hypotension, seizures, apnea, coma and death, associated with metabolic acidosis and increased lactate levels.

We report on an infant who suffered generalized seizures and severe metabolic acidosis during high-dose SNP therapy.

2. CASE REPORT

A 3-month-old boy, born at term with no congenital syndromes, developed severe systemic hypertension after a successful aortic coarctation repair. SNP infusion was started at $0.3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and progressively titrated up to $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to maintain a systolic blood pressure ≤ 110 mmHg. At 28 hours postoperatively the patient was transferred from the Cardiac Intensive Care Unit to our PICU in good conditions, with stable hemodynamics, arterial blood pressure 100/45 mmHg, pH=7.46, PaO₂ 110 mmHg, PaCO₂ 25 mmHg, BE=-5 mmol·l⁻¹ and lactate= 12 mmol·l⁻¹. Two hours later, due to his satisfactory clinical conditions and despite the high lactate levels, the patient was weaned off mechanical ventilation with normal chest and neurological examination. Markers of liver and renal function were within normal limits. About three hours later, despite a normal heart rate and a systolic blood pressure of 110 mmHg, systemic perfusion rapidly deteriorated, with mottling, prolonged capillary refill, obnubilation and onset of generalized seizures. Blood gas analysis revealed severe metabolic acidosis (pH=7.22, PaO₂ 72 mmHg, PaCO₂=25 mmHg, BE=-16 mmol·l⁻¹, lactate 18.7 mmol·l⁻¹). In the suspect of related toxicity, SNP infusion was discontinued, followed by a rapid clinical improvement. No other specific interventions were performed. A cardiac ultrasound evaluation was obtained urgently, showing normal heart function and a satisfactory aortic coarctation repair. At two and five hours

since SNP discontinuation, lactate levels decreased to 10.2 and 6 mmol·l⁻¹, respectively, returning within normal range by the seventh hour. The patient was discharged 12 days later in good clinical conditions, with normal systemic blood pressure and no pharmacological treatment.

3. DISCUSSION

This study emphasizes the risk of toxicity in patients treated with high-dose SNP infusion. Adverse effects associated with SNP administration are rarely observed in children. In four reported cases, one patient died, [3] three others had cardiovascular collapse and temporary blindness [4-6]. The onset of toxicity occurred from 80 minutes to 60 hours since initiation of SNP, maximum infusion rates ranged from 5 to $12 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and tachyphylaxis often heralded the onset of serious cyanide toxicity [3-6].

SNP toxicity occurs because CN hampers oxygen tissue release, causing cellular hypoxia and anaerobic metabolism [1,7]. Controversy exists about the SNP dose more likely to cause toxicity: $0.5\text{-}10.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ infusion rates and $0.5\text{-}5 \text{ mg}\cdot\text{kg}^{-1}$ total SNP doses have been reported as safe [1,8-10].

SNP toxicity relates more with infusion rate rather than with the total amount given. Amounts up to 1488 mg given continuously over a period of 12-314 hours did not cause toxicity, [1,7,9] whereas 400 mg given over 80 minutes were fatal [3]. SNP infusions above $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ can produce adverse metabolic and clinical effects [10]. Thus, maximum rate for long-term SNP infusion should be less than $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, possibly close to $4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, while maximum total SNP dose should not exceed $70 \text{ mg}\cdot\text{kg}^{-1}$ in periods shorter than 14 days. [9] Of notice Moffett and Price reported that even a dose of $1.8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ of SNP had a high sensitivity and specificity to predict elevated cyanide levels in a cohort of children who underwent cardio-thoracic surgery [11]. Patients undergoing cardiopulmonary bypass or hypothermia, treated with diuretics, malnourished, with hepatic or renal failure may be at greater risk owing to an impaired cyanide detoxification capability. Moreover infants may

have immature enzyme systems or lack of thiosulphate stores that may lead to toxicities [11]. Actually, coarctation repair in our patient, performed via lateral thoracotomy, was an off pump operation, i.e. neither cardiopulmonary bypass nor hypothermia were needed.

Diagnosis of SNP related toxicity relies on non-specific signs, such as nausea, vomiting, seizures, dyspnea or tachypnea, [12] often associated with metabolic acidosis, increased lactate or base deficit and altered mixed venous oxygen tension. Other specific investigations, namely red blood cell cyanide content, plasma cyanide and thiocyanate concentrations, usually are not readily available. Monitoring of metabolic changes (lactic acidosis, base deficits, increased mixed venous oxygen) appears to be the most sensitive and accurate indicators of early toxicity [2,11]. For decades SNP has been a popular drug for its rapid, powerful effect and the very short half-life. However, particularly when high doses are used, or hepatic and/or renal dysfunction are present, SNP may cause severe adverse events, due to accumulation of cyanide and its metabolites. In retrospect, the early onset of tachyphylaxis observed in our patient, which required an escalation of SNP doses, could have been interpreted as a risk factor for impending SNP-related toxicity, [5] suggesting either the use of alternative anti-hypertensive drugs for managing systemic blood pressure, or at least a combination with other agents, allowing decrease of the dose and/or duration of SNP treatment. Furthermore, sodium thiosulfate may have been added to the SNP infusion to prevent elevated cyanide concentrations and reduce the risk of poisoning.

On the other hand, severe clinical signs associated with SNP toxicity were not anticipated by relevant metabolic changes. In fact, despite some discrepancy between a normal pH and a mildly altered base excess (BE) value (7.46 and -5 mmol.l⁻¹, respectively) and a relatively high lactate (12 mmol.l⁻¹), metabolic acidosis and marked base deficit became apparent only after 30 hours of SNP infusion, possibly delaying the diagnosis. Nonetheless, the already high lactate level observed on admission, despite a normal pH value which was probably due to the compensatory decrease of CO₂, maybe should have prompted an earlier discontinuation of SNP therapy.

The phenomenon we observed in our patient, about the striking discrepancy between normal

blood pressure and normal heart rate vs prolonged capillary refill, mottling and altered mental status, remains to be further elucidated. A better scrutiny of initial lactate and base excess levels might have been decisive in early disclosing of metabolic derangements in our patient, prompting a modification of therapy.

Cyanide and thiocyanate levels were not included in our initial diagnostic work-up since not readily available. Unfortunately, serum samples were not preserved for further analysis of cyanide toxicity. Nonetheless, we believe the suspected diagnosis of SNP toxicity was reinforced by the rapid improvement observed once the SNP infusion was suspended, and by the fact no further treatment was required.

In theory, the occurrence of generalized seizures may have somehow contributed to the increase of lactate levels. In fact, early experiences in adults indicated a rise of lactate levels even after short "grand mal seizures", of 30 to 60 seconds' duration [13]. Then, although the seizure episode was very short in our case and did not require pharmacological treatment, we cannot exclude some additional effects on lactate accumulation.

Of note, the presented case was thoroughly discussed at subsequent multidisciplinary meetings and the practice of transferring infants with IV infusion of SNP was thereafter nearly discontinued in our centre. In fact, at present we are using SNP less frequently for severe systemic hypertension, preferring other drugs such as esmolol, which has a safer profile.

4. CONCLUSION

In conclusion, we report a case of acute toxicity in a young infant treated with SNP infusion for systemic hypertension after elective coarctectomy, who developed seizures and severe lactic acidosis. Clinical signs were not apparent until metabolic and lactic acidosis reached extreme values. In order to detect early signs of toxicity, we suggest blood lactate and base excess levels should be strictly monitored during SNP treatment in children, particularly when high infusion rates are required and when prompt measurement of blood cyanide concentration is not available.

CONSENT

The patient's parents have given their informed consent for the case report to be published.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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