THE TOXICITY OF SODIUM NITROPRUSSIDE

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SODIUM NITROPRUSSIDE ($\text{Na}_2\text{Fe}(\text{CN})_5\text{NO}$) has been used for the treatment of hypertensive crises¹ to provide controlled hypotension during anaesthesia² to improve left ventricular function,³ and to treat ergotamine-induced peripheral ischaemia.⁴

The action of sodium nitroprusside is one of direct dilatation of the vasculature. Sodium nitroprusside acts predominately on the tonic smooth muscle of the blood vessels. The nitroso group ($-\text{NO}$) interferes with excitation-contraction coupling by inhibiting both the influx of and the intracellular activation of calcium ion.⁵

Intravenous infusion of sodium nitroprusside produces an immediate and profound response which is evanescent, necessitating the continuous infusion of a weak solution (0.01 per cent sodium nitroprusside) at a rate gradually increased to provide the hypotensive response required. Constant vigilance to the dose response characteristics of the patient and continuous direct intra-arterial pressure monitoring are mandatory.

Adverse Reactions to Sodium Nitroprusside

A review of the reported experience of the use of sodium nitroprusside is instructive and permits a safe and more rational use of a potentially lethal drug.

With disciplined use sodium nitroprusside has proved to be a valuable pharmacological agent. However, in the past two years, three deaths⁶⁻⁸ and one case of severe acidosis⁹ associated with the use of sodium nitroprusside have been reported. Each of these incidents has been associated with an abnormal response to sodium nitroprusside. McDowall, *et al.*¹⁰ in England have reported on the toxicity of sodium nitroprusside in baboons. Davies, *et al.*¹¹ have reported on the metabolic changes observed during abnormal responses to this drug in children and adolescents.

The patient of Jack⁶ was a previously healthy middle-aged man undergoing stapedectomy. This patient exhibited early resistance to the hypotensive effects of sodium nitroprusside. The average rate of infusion is calculated to have been approximately $370 \mu\text{g}/\text{kg}/\text{min}$ to a total of 750 mg. No acid-base evaluations of the patient were made until the heart arrested during the early post-operative period. At that time the patient exhibited a severe metabolic acidosis.

The patient of Merrifield, *et al.*⁷ was a 20-year-old previously healthy male undergoing mandibular osteotomies. This patient exhibited tachyphylaxis to sodium nitroprusside within the first hour of its infusion. Sodium nitroprusside was infused

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at an average rate calculated to have been $33 \mu\text{g/kg/min}$ to a total of 750 mg in five hours. The first acid-base evaluation of the patient was made at the time of his cardiac arrest in the early post-operative recovery period. A severe metabolic acidosis was apparent.

The fatal case of Davies, *et al.*⁸ was a previously healthy 14-year-old male undergoing mandibular osteotomies. This patient showed almost immediate resistance to the hypotensive effects of sodium nitroprusside. He received 400 mg in 80 minutes at an average rate of $120 \mu\text{g/kg/min}$. The patient's heart arrested within thirty minutes of discontinuing the sodium nitroprusside infusion and at that time had a severe metabolic acidosis.

The case of severe metabolic acidosis associated with the use of sodium nitroprusside reported by McCrae, *et al.*⁹ was a 42-year-old previously healthy female undergoing stapedectomy. This patient exhibited resistance to the hypotensive action of sodium nitroprusside. The sodium nitroprusside was infused at an average rate calculated to have been approximately $43 \mu\text{g/kg/min}$ to a total of 250 mg in 90 minutes. The acid-base status in this patient was first measured about one hour post-operatively because of tachypnoea and an incomplete and bizarre neurological recovery from anaesthesia. She was found to have a severe metabolic acidosis.

McDowall¹⁰ has shown that four of eight baboons were resistant to the hypotensive action of sodium nitroprusside. These animals which received high doses of sodium nitroprusside, calculated to be in excess of $80 \mu\text{g/kg/min}$, incurred a severe metabolic acidosis and a marked decrease in cerebral oxygen uptake. These baboons did not survive.

Abnormal responses to sodium nitroprusside in children and adolescents have been reported in some detail by Davies, *et al.*¹¹ and the experience of these workers can be summarized as follows.

Four distinct responses to the infusion of sodium nitroprusside were recognized:

1. A constant response to low doses of sodium nitroprusside ($<10 \mu\text{g/kg/min}$) which is the usual clinical experience.
2. A constant response to high doses of sodium nitroprusside ($>10 \mu\text{g/kg/min}$).
3. A tachyphylaxis to sodium nitroprusside apparent in 30 to 60 minutes of starting the infusion.
4. A definite resistance to the action of sodium nitroprusside which becomes apparent within 5 to 10 minutes of starting the infusion. Resistance is defined¹¹ as an inability to attain or maintain safe minimal levels of systolic blood pressure even with increasing doses of sodium nitroprusside.

These latter three abnormal responses may occur in either sex and are potentially lethal. Tachyphylaxis or the need for a constant high dose of sodium nitroprusside appears to occur in about 30 per cent of the paediatric population. Each of these abnormal responses was associated with (a) an increasing metabolic acidosis, which can be severe, (b) an increasing mixed venous oxygen tension and (c) a decreasing arterial-mixed venous oxygen content difference. These metabolic

changes are thought to be due to cyanide (an intermediate metabolite of nitroprusside metabolism) intoxication and cellular hypoxia. One lethal case⁸ associated with the use of sodium nitroprusside revealed lethal levels of cyanide in the blood (0.5 mg/100 ml) and no measurable levels of thiocyanate (the relatively innocuous end metabolite of nitroprusside metabolism) in blood or urine.

The Toxicity of Sodium Nitroprusside

The toxicity of nitroprusside appears to be related to the rate of infusion rather than the total amount given. Amounts in excess of 2.7 gm have been given continuously over a five-day period¹² without mishap whereas 400 mg given over 80 minutes has been fatal.⁸

The fastest safe rate of infusion for sodium nitroprusside is not known because the dynamics of its metabolism are not yet determined. Taylor, *et al.*¹³ have infused sodium nitroprusside at rates calculated to be as high as 40 $\mu\text{g/kg/min}$ with no reported ill effects; however, no clinical or metabolic parameters were recorded other than blood pressure and pulse responses before, during and after the infusion of sodium nitroprusside.

The maximal rate of 1.6 mg/kg/hr (26.6 $\mu\text{g/kg/min}$) suggested by McDowall¹⁰ is far too high. Any rate of infusion of sodium nitroprusside above 10 $\mu\text{g/kg/min}$ usually has been associated with at least adverse metabolic disturbances, or more often, disaster.

Possible Mechanisms of Abnormal Responses to Sodium Nitroprusside

Sodium nitroprusside reduces systemic and pulmonary arterial and venous pressures by direct vasodilation. Hypotension produced in this manner can activate renin-angiotensin release. Angiotensin causes vasoconstriction and increases cardiac rate and contractility. These responses will tend to antagonise the hypotensive action of sodium nitroprusside. Possibly these sequences of physiological responses to sodium nitroprusside may be responsible for the need for high doses ($> 10\mu\text{g/kg/min}$) of sodium nitroprusside to produce the hypotensive effect required. The judicious use of propranolol will block all the compensatory physiological responses including renin release.

There is some evidence to suggest that tachyphylaxis to sodium nitroprusside is related to abnormalities of thiosulphate metabolism or depletion of endogenous thiosulphate supplies.^{6,8}

If endogenous thiosulphate is present in reduced amounts, then the conversion of the intermediate metabolite (cyanide ion) to the end metabolite (thiocyanate ion) is reduced. The availability of thiosulphate is the rate-limiting factor in the conversion of cyanide to thiocyanate by tissue rhodanese. Consequently cyanide ion will accumulate with the continued infusion of sodium nitroprusside if there is insufficient thiosulphate.

The hypothesis that resistance to the hypotensive effect of sodium nitroprusside represents antagonism of the vasodilator action of this drug by increasing amounts of cyanide is presently being tested.¹⁴

Further studies in this area are needed before one can reasonably rely on thiosulphate replacement as a safe and rational concomitant therapy when using

sodium nitroprusside. Even if thiosulphate depletion is confirmed it may well prove less than satisfactory therapy as cyanide-thiocyanate metabolism is an intracellular enzymatic process and only very small fractions of exogenous thiosulphate will penetrate cell membranes.

The Rational and Safe Use of Sodium Nitroprusside

The following are suggested as mandatory disciplines to adhere to when using the drug.

1. Absolute contraindications to its use exist in patients who have (1) Resistance to sodium nitroprusside, (2) Leber's hereditary optic atrophy, (3) tobacco amblyopia, (4) severe liver disease, (5) severe renal disease, (6) malnutrition, (7) vitamin B12 deficiency, (8) hypothyroidism.
2. The use of solutions of not more than 0.02 per cent sodium nitroprusside suitably protected from light and heat.
3. The administration of infusions of sodium nitroprusside by a separate intravenous infusion by a microdrip or infusion pump.
4. Direct and continuous intra-arterial pressure monitoring.
5. Frequent (half-hourly) arterial acid-base determinations.
6. Constant attention to the patient's dose-response characteristics, particularly in the first thirty minutes.
7. If infusion rates are in excess of $10 \mu\text{g/kg/min}$ determine the nature of the response: constant, tachyphylactic or resistant?
8. If constant or tachyphylactic temporarily discontinue the sodium nitroprusside, administer another hypotensive agent e.g. pentolinium 0.1–0.2 mg/kg. After five minutes re-start the infusion of nitroprusside if further hypotension is required. The new infusion rate is usually 10–20 per cent of the original requirements of nitroprusside.¹⁵
Alternately, one can use propranolol. If the infusion of sodium nitroprusside evokes a tachycardia, administer propranolol intravenously by increments, until the apex rate is reduced to pre-tachycardia levels. The total amount of propranolol required is usually less than 0.5 mg (0.007 mg/kg). This also reduces the dose of sodium nitroprusside to 10–20 per cent of the previous requirements.¹⁶
9. Resistance to sodium nitroprusside is an absolute indication to abandon the use of the drug and to use a different drug altogether.
10. Maintain normothermia throughout.⁸
11. Prolonged infusions of sodium nitroprusside even at low dosage should be monitored by daily thiocyanate measurements of the patient's blood. If levels above 10 mg of thiocyanate per 100 ml patient blood are recorded, then the sodium nitroprusside should be discontinued.¹⁷
12. Whenever using sodium nitroprusside one must have available cyanide antidote therapy.⁶ This includes (1) inhalations of amyl nitrite every two minutes, (2) intravenous infusion of sodium nitrite 5 mg/kg in 20 ml H₂O given over 3 to 4 minutes, (3) intravenous infusion of sodium thiosulphate 150 mg/kg in 50 ml water over 15 minutes. The nitrites will produce methaemoglobin which has a

much higher affinity for cyanide than cytochrome oxidases. Thiosulphate is given to supply necessary substrate to convert cyanide to thiocyanate. Hydroxocobalamin, if available, can be given 0.1 mg/kg which will combine with cyanide and render it inactive.

RÉSUMÉ

Le nitroprussiate de soude est utilisé comme vasodilatateur puissant chez l'homme depuis 1929. A partir de communications à propos de trois décès reliés au NPS on retient: l'acidose grave et le taux de dosage élevé de nitroprussiate de soude. Ces derniers effets peuvent se rencontrer chez des cas de réponses anormales, non-mortelles au nitroprussiate de soude.

La réponse à l'action du nitroprussiate de soude est l'une des suivantes:

- Normale 1. vasodilatation à bas taux de dosage ($<10 \mu\text{g/kg/min}$)
- Anormale 2. vasodilatation à haut taux de dosage ($>10 \mu\text{g/kg/min}$)
- 3. tachyphylaxie
- 4. résistance

La manifestation anormale de l'action du nitroprussiate de soude est une des suivantes:

- réaction physiologique excessive (rénine-angiotensine-aldostérone), traité par blocage beta ou ganglioplégie;
- acidose et accumulation de cyanure de la biotransformation du NPS, traité comme une intoxication au cyanure.

On donne la conduite à suivre pour l'utilisation sûre de nitroprussiate de soude les contre-indications, l'administration du nitroprussiate de soude, la surveillance requise, la conduite à tenir face aux réactions anormales.

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