

Sodium nitroprusside-associated cyanide toxicity in adult patients – fact or fiction? A critical review of the evidence and clinical relevance

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Abstract: Since its US Food and Drug Administration (FDA) approval in 1974, sodium nitroprusside (SNP) has been fraught with controversy in regards to its safety. Over the years, a growing concern related to SNPs propensity to cause cyanide (CN) toxicity culminated into a series of case reports that led the FDA to develop a black-box warning with dose limitations of <2 µg/kg/min. These recommendations stemmed also from the reality of the difficulty of obtaining CN levels in a timely manner, as well as the presumed poor correlation of metabolic markers (lactate levels and pH) as it related to the severity of CN toxicity. All these issues have driven practitioners to the use of alternative agents. In this paper, we critically review the cases and the data that led to the development of these restrictive dosing recommendations and reveal several limitations of the data and assumptions that led to these recommendations. We conclude that SNP is still a reasonable agent to use in the management of patients with hypertension today and can safely be used beyond doses of 2 µg/kg/min. Furthermore, in lieu of CN levels, monitoring of lactic acid levels is also a reasonable measure to ensure safety.

Keywords: dose limits, monitoring, controversy, thiosulfate stores, cyanide levels

Introduction

Discovered in the late 1800s, but not incorporated into clinical practice until the 1950s, sodium nitroprusside (SNP) has been used in the management of hypertension in a myriad of medical conditions, as well as in the induction of hypotensive states for the reduction of intraoperative blood loss.^{1,2} Nonetheless, over the years, growing concerns over the risk of cyanide (CN) toxicity related to its use has led to various publications either pushing it to the end of the line or condemning its use.³⁻⁶ Is SNP a toxic drug that should be of only historical significance akin to chloramphenicol in the infectious disease realm? Or, like polymyxin, is there utility to this drug especially in our difficult to manage patients? There is no denying the fact that SNP carries with it a risk of causing CN toxicity. However, how significant is that risk and what are the risk factors? This review will hopefully unravel some of this information.

Generally accepted information regarding SNP Mechanism of action

SNP ($\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}] \cdot 2\text{H}_2\text{O}$) is comprised of a ferrous iron molecule complexed with 5 CN moieties and a nitrosyl group.² SNP interacts with oxyhemoglobin in the blood to produce methemoglobin while releasing CN and nitric oxide (NO).^{7,8} In contrast to nitroglycerin, which requires specific thiol-containing compounds to generate NO, SNP generates this product spontaneously.⁹ NO activates guanylate cyclase, which is located

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in the vascular smooth muscles, to produce cyclic guanosine monophosphate (cGMP). The increased intracellular concentrations of cGMP lead to inhibition of calcium entry into the cell, as well as an increased uptake of calcium by the smooth endoplasmic reticulum resulting in vasodilation.^{9,10}

Metabolism

Once SNP is broken down, the 5 molecules of CN that are generated have 2 generally accepted fates. CN can react with thiosulfate ions to produce thiocyanate, which is catalyzed by the mitochondrial enzyme rhodanase and subsequently renally eliminated.^{2,11–14} Rhodanase, also known as thiosulfate sulfurtransferase, is distributed widely throughout the body, with the highest concentrations located in the liver.¹⁵ The rate-limiting step for this reaction appears to be the availability of thiosulfate, which is generated endogenously from cysteine and methionine.^{1,15–17} Studies suggest that the body has a limited amount of thiosulfate and can detoxify a maximum of approximately 50 mg of SNP.^{16,18}

CN may also react with physiologically available methemoglobin to generate cyanomethemoglobin, which is in dynamic equilibrium with CN and nontoxic.^{7,8,19} CN accumulation is of concern as it halts aerobic metabolism by inhibiting the final step of oxidative phosphorylation. CN binds to ferric iron in cytochrome oxidase enzyme and renders it inactive. As a result, there is a shift in aerobic to anaerobic metabolism leading to cellular adenosine triphosphate depletion, reduction of pyruvate to lactate, and rapid accumulation of lactic acid.^{20–22} Although inhibition of mitochondrial oxidative phosphorylation is not the only consequence of CN accumulation, significant CN intoxication has been associated with the development of lactic acidosis both in animals and humans.^{20–24} Depending on the whole blood concentration of CN, clinically patients may present with mild symptoms such as tachycardia and flushing at 0.5–1 µg/mL (20–38 µmol/L), depressed levels of consciousness at 1–2.5 µg/mL (48–65 µmol/L), coma at 2.5–3 µg/mL (95–114 µmol/L), and death at levels >3 µg/mL (>114 µmol/L).²⁵

Evidence for CN toxicity associated with SNP

Tables 1 and 2 are a summary of all published cases that have been reported in the literature regarding either mortality or morbidity associated with CN toxicity related to SNP administration.^{26–45} Several things can be gleaned from these reports. Of the 4 cases related to intraoperative use, gross overdosing (>10 µg/kg/min) of SNP led to CN toxicity and death in 2 cases. In most of the other case reports, SNP was used for a prolonged period of time before CN toxicity

manifested. CN toxicity was typically presumed, for lack of measured CN levels, especially in the patients reported to have had morbidity related to CN. Finally, in the patients who died, other complications may have contributed to their demise as well. In addition to these reports, Patel et al⁴⁶ published a case series of 7 patients, out of a total of 292 patients undergoing coronary artery bypass graft (CABG) surgery, who developed CN toxicity related to SNP use for the management of postoperative hypertension. Of these, 3 patients died. Patients were administered SNP for 26–160 hours with doses ranging from 1.8–12 mg/kg body weight. All 7 patients had blood CN levels >500 µg/L, which was considered toxic by their laboratory (although this level is clinically associated with mild symptoms; see “Metabolism” section).²⁵ According to the authors, serum lactate, pH, and base excess did not correlate with elevated CN levels, although the timing of these measurements is not mentioned in the paper. Finally, Robin and McCauley⁴⁷ published a paper, which reviewed 52 cases that were reported to the FDA between 1974 and 1992, of which 29 died. Very few patients had CN levels measured, and from the paucity of data provided, it appears that many of these patients had complications, which could have significantly contributed to the morbidity and mortality. Nonetheless, the authors concluded that CN toxicity related to SNP is a frequent event, resulting in negative outcomes and thus routine use of SNP should be avoided. The authors also stated that lactic acidosis presented as a terminal event only and was not a useful marker for CN toxicity evaluation, although no supporting data were provided.

Based on the information presented thus far, SNP appears to be a vasodilator with a high potential for significant adverse events, primarily related to CN. But how unsafe is SNP, really? If this drug was truly toxic, it should have been withdrawn from the market years ago. How often is CN toxicity really a problem, and can this be avoided with prudent utilization and monitoring of the drug? We set to explore more about this complex drug and the challenges it is presumed to carry.

What we really know about SNP

There are several questions that have arisen over the years regarding the use of SNP. We feel that there is potential misinformation that has led clinicians to shy away from using this drug, which will be highlighted in the following sections.

What is the incidence of CN toxicity?

One of the common misgivings is that CN toxicity related to SNP is a very frequent phenomenon. Robin and McCauley's⁴⁷

Table I Mortality associated with SNP use

Cit	No. of patients	Age, y	Wt, kg	N ₂ O use	Dose	Duration	CN level	pH	Treatment	Comments
26	1	14	40	Y	120 µg/kg/min Total 400mg	80 min	0.5 mg/dL	6.92	Supportive	Used for controlled intraoperative hypotension. Patients developed tachyphylaxis. Postoperative complications
27	1	20	–	Y	750 mg (25 µg/kg/min if 100 kg)	5 h	–	6.8	Supportive	Used for controlled intraoperative hypotension. Patients developed tachyphylaxis. Arrested 20 min postoperative and died 32 h later. K ⁺ was 8.5 during arrest. Postoperative complications
28	1	40–50	–	Y	–	–	–	7.12	Supportive	Used for controlled intraoperative hypotension. Patients developed tachyphylaxis. Postoperative complications. Base excess = –22
29	1	43	–	N	2878 mg (0.5– 8 µg/kg/min)	14 d	–	–	Supportive	Hepatitis, ARF, HTN, encephalopathy, and obtunded on presentation. Cardiac arrest on day 12. Died day 47. Autopsy path suggestive of CN toxicity. Globus pallidus lesions
30	1	66	74	N	238 mg (max 2.3 µg/kg/min)	38 h	0.29 mg/dL	–	Supportive	ICH. ARF by day 3. Had some acidosis on admission. Base excess = –11
31	1	42	50	N	13.5 mg (max 3 µg/kg/min)	90 min	–	7.1	Supportive	Scleroderma, HTN emergency, ARF, and CHF. Developed profound hypotension unresponsive to intervention. Autopsy did not show obvious cause so assumed it was CN
32	1	78	75	N	1300 mg (max 4.4 µg/kg/min)	5 d	0.2 mg/dL	–	Na nitrite and thiosulfate	Aortic pseudoaneurysm. Patient developed tachyphylaxis. Death from CNS damage from trauma. Lactate increased from 2.4 to 4.3
33	1	1 day	4.4	N	Max 5 µg/kg/min	30 h	RBC CN 400 nmol/mL	7.19	Thiosulfate	HTN and tachyphylaxis. Gave SNP with thiosulfate for 3 days. CN level normal. Child died of other causes
34	1	59	–	N	2029 mg (max 8 µg/kg/min)	7 d	–	–	Supportive	Patient had CHF. No electrolyte or pH values were reported, but author stated they were “acceptable.” Patient had several days of confusion and agitation. SZ on day of death

Abbreviations: SNP, sodium nitroprusside; Cit, citation; Wt, weight; CN, cyanide; Y, yes; N, no; ARF, acute renal failure; HTN, hypertension; ICH, intracranial hemorrhage; CHF, congestive heart failure; CNS, central nervous system; RBC, red blood cell; SZ, seizure.

paper postulated >1% annual excess in mortality or 1,000 deaths related to CN toxicity alone. Sarvotham⁴⁸ also estimated about 1,000 deaths per year and 3,000 cases per year attributed to CN toxicity in patients undergoing CABG surgery. Estimates from Patel et al⁴⁶ suggest an incidence of 2.4% (7/292) for CN-related toxicity and a 1% mortality rate, which is significant considering the number of patients who undergo CABG surgeries annually in the United States. However, in a letter to the editor, McRae⁴⁹ reported only 1 incidence of metabolic acidosis related to SNP use and no deaths in over 1,000 patients that his center had treated. We conducted our own review of the published literature, searching

MEDLINE using the MeSH term “sodium nitroprusside” and limiting the search to “clinical trials, all.” The results were further reviewed by one of the authors (PA) and refined to ensure the citations met above criteria. These studies were then evaluated for reports of CN toxicity, lactic acidosis, and death from all causes. The final result included 50 trials that are summarized in Table 3.^{50–99} Approximately 4,100 patients were included in these trials of which 2,732 were exposed to SNP. Over 80% of the patients received SNP outside of the OR setting. CN toxicity or lactic acidosis was reported in 35 patients, and 16 patients died from any cause. This gives us an incidence of SNP-related adverse events of 1.87%

Table 2 Morbidity associated with SNP use

Cit	No. of patients	Age, y	Wt. kg	N ₂ O use	Dose	Duration	CN level	pH	Treatment	Comments
35	1	42		Y	250 mg	90 min	–	7.19	NaHCO ₃	Controlled intraoperative hypotension. Developed tachyphylaxis. Altered mental status postoperatively. Use in more than 600 patients. Rare occurrence
36	1	41	82	Y	15 µg/kg/min	75 min	–	7.35	Supportive	Controlled intraoperative hypotension. Patient developed tachyphylaxis
37	1	14	44	Y	10 µg/kg/min	300 min	–	7.34	Thiosulfate	Controlled intraoperative hypotension. Patient developed tachyphylaxis. Cardiac arrest for 45 min. Developed pulmonary edema with PaO ₂ of 44. Base excess –6
38	1	58	80	N	1,000 mg (max 3 µg/kg/min)	7 d	0.5 mg/mL	–	HD	CHF and aortic valve insufficiency. Patient developed tachyphylaxis
39	1	52	66	N	1093 mg (max 8 µg/kg/min)	34 h	–	7.08	NaHCO ₃	HTN and AMI. Smoker. Patient developed tachyphylaxis and lactic acidosis.
40	1	53		N	2.5 µg/kg/min	7 d	–	7.32	Dimethylaminophenol and thiosulfate	ICH from HTN. Base excess –7.4
41	1		70	N	215 mg (max 4.9 µg/kg/min)	33 h	–	–	Supportive	–
42	1	27	68	N	1,120 mg (max 12.5 µg/kg/min)	48 h	–	7.2	Supportive	Renal transplant patient with history of resistant HTN. Serum creatinine 1.6 µmol/L. Had gall bladder rupture. Base excess = –16. Cardiac arrest, no complications. No tachyphylaxis.
43	1	66		N	Max 5 µg/kg/min	29 d	–	–	Supportive	HTN, aneurysmal bleed. Patient developed tachyphylaxis in 48 h. No signs of metabolic derangements
44	1	66	21	N	490 mg (max 7 µg/kg/min)	28 h	–	7.21	NaHCO ₃	HTN emergency. ARF. Became agitated.
45	1	6		N	Max 5.5 µg/kg/min	22 d	–	–	Supportive	HTN. ARF with intermittent HD. No CN toxicity. Had elevated SCN levels that corrected with HD

Abbreviations: SNP, sodium nitroprusside; Cit, citation; Wt, weight; Y, yes; N, no; CN, cyanide; HD, hemodialysis; CHF, congestive heart failure; HTN, hypertension; ICH, intracranial hemorrhage; ARF, acute renal failure; SCN, thiocyanate.

(51/2,732) and a mortality rate of 0.6%. The 16 deaths come from 2 trials, where 11 patients died in the SNP group compared with 9 patients in the placebo group in the first study, and 5 patients died in the SNP group compared with 18 patients in the placebo group in the second study.^{77,78} Assuming that the 2 additional deaths in the first study (compared to the placebo group) were due to CN toxicity, the mortality rate is < 0.1% (2/2,732). Although this information is extracted from controlled trials and is thus a conservative estimate, it does suggest that prudent use of SNP is safe.

How much SNP can the human body handle?

Rhodanase, an enzyme which is found in the mitochondria, detoxifies CN by adding a sulfur atom to the CN molecule to form the much less toxic thiocyanate ion. Thiosulfate is a sulfur donor for rhodanase, which allows for the production of thiocyanate. It has been suggested that the human body possesses limited thiosulfate stores and, therefore, limited ability to detoxify CN.^{16,18} In a study by Ivankovich et al¹⁸ mean plasma thiosulfate concentrations in healthy individuals

Table 3 Review of adverse events related to SNP use in clinical trials

Study	Patient population	N	Treatment and control group regimens	Mean duration of study	Mean SNP dose	Outcomes		
						CN toxicity (#)	Deaths (#)	Lactic acidosis (#)
Intraoperative use of SNP								
Vesey, ⁵⁰ 1976	Orthopedic surgery	26	Prospective observational study in controlled intraoperative hypotension	NR (ranged from 90 to 168 min)	NR Total SNP dose (ranged from 4 to 95.4 mg) 0.5 mg/kg	7	0	0
Thompson, ⁵¹ 1978	Total hip arthroplasty	30	Prospective, randomized, controlled trial comparing effects of isoflurane (n = 10), SNP (n = 10) and placebo (n = 10) for controlled intraoperative hypotension on organ function and blood loss	NR (range 65–115 min)		0	0	0
Pasch, ⁵² 1983	Surgical patients	55	Prospective observational study in controlled intraoperative hypotension. Divided into 5 groups based on SNP dose and administration of thiosulfate	NR (range 103–152 min)	NR	8	0	0
Fahmy, ⁵³ 1985	Major orthopedic procedures	20	Prospective, randomized trial comparing SNP (n = 10) to SNP + trimethaphan (n = 10) for controlled intraoperative hypotension	SNP alone (258 min) SNP + trimethaphan (266 min)	SNP alone (5.82 µg/kg/min) SNP + trimethaphan (1.39 µg/kg/min)	4	0	0
Corr, ⁵⁴ 1986	CABG surgery on bypass	12	SNP (N = 6) or trimethaphan (N = 6) to maintain MAP 70–85 before and after bypass and ≤70 during bypass	63.5 min on bypass with SNP	25.4 mg over 63.5 min (400 µg/min)	0	0	0
Bernard, ⁵⁵ 1987	Total hip arthroplasty	16	Prospective, randomized trial comparing hemodynamic and metabolic effects isoflurane (n = 8) to SNP (n = 8) for controlled intraoperative hypotension	90 min	NR (range 1–6 µg/kg/min)	0	0	0
Cole, ⁵⁶ 1987	Major elective orthopedic procedures	30	Prospective, randomized trial comparing blood CN concentrations in patients who received TS with SNP (n = 15) and those who did not (n = 15) for controlled intraoperative hypotension	SNP alone = 98 min SNP + TS = 89 min	SNP alone = 0.36 mg/kg SNP + TS = 0.45 mg/kg	0	0	0
Simpson, ⁵⁷ 1987	Major middle ear surgery	30	Prospective, randomized, study comparing metoprolol 25, 50 mg and oxprenolol 20 mg for controlled intraoperative hypotension in addition to SNP and trimethaphan	NR	NR (range 0.25–1.75 µg/kg/min)	0	0	0

(Continued)

Table 3 (Continued)

Study	Patient population	N	Treatment and control group regimens	Mean duration of study	Mean SNP dose	Outcomes		
						CN toxicity (#)	Deaths (#)	Lactic acidosis (#)
van Wezel, ⁵⁸ 1987	CABG patients	20	Prospective, randomized trial comparing nifedipine (n = 9) to SNP (n = 11) effects on myocardial metabolism and coronary sinus blood flow	32 min	3.4 µg/kg/min	0	0	0
van Wezel, ⁵⁹ 1987	CABG patients	37	Placebo-controlled (n = 12) trial comparing effects of nifedipine (n = 12) vs SNP (n = 13) on myocardial metabolism and catecholamine balance	31 min	1.9 µg/kg/min	0	0	0
Porter, ⁶⁰ 1988	Spinal fusion	21	Prospective randomized study comparing nitroglycerin (n = 8), SNP + captopril (n = 6), and SNP (n = 8) for controlled intraoperative hypotension	SNP 194 min SNP + captopril 256 min	NR (max 2 µg/kg/min)	0	0	0
Hodsman, ⁶¹ 1989	CABG patients	41	Randomized, placebo controlled comparing 3 different doses of ketanserin. Patients also received closed-loop SNP	7.2 h in placebo group vs 2.1–3 h in ketanserin groups	0.57 mg/kg in placebo group vs 0.056–0.28 mg/kg in ketanserin groups	0	0	0
Geniton, ⁶² 1990	Undergoing elective carotid endarterectomy	19	Prospective, randomized trial comparing labetalol (n = 9) to SNP (n = 10) for controlled intraoperative HTN	12 h	1.2 µg/kg/min	0	0	1
Godet, ⁶³ 1990	CABG patients	20	Prospective, randomized study comparing isoflurane (n = 10) to SNP (n = 10)	26 min	7 µg/kg/min (total dose of 11 mg)	0	0	0
Ornstein, ⁶⁴ 1991	Deliberate hypotension (MAP 60–65) during intracranial AVM resection	29	Isoflurane (n = 9) SNP (n = 10), or esmolol (n = 10)	NR	2.3 ± 1.3 µg/kg/min	0	0	0
Owall and Sollevi, ⁶⁵ 1991	Abdominal aortic aneurysm	6	Prospective crossover study comparing myocardial effects of adenosine and SNP	20 min	0.7 µg/kg/min	0	0	0

Biau, ⁶⁶ 1992	Orthognathic surgery	30	Randomized study comparing esmolol (n = 15) to SNP (n = 15) for intraoperative blood loss (controlled intraoperative hypotension)	95 min	Median dose 1.75 µg/kg/min Total dose 10.5 mg	0	0	0
Chaudhri, ⁶⁷ 1992	Resection of intraocular melanoma	20	Patients randomized to receive closed-loop control or manual control of arterial pressure with a mixture of SNP and trimethaphan	204 min for closed loop and 158 min for manual	0.038 mg/kg in closed loop and 0.026 mg/kg in the manual	0	0	0
Bernard, ⁶⁸ 1993	Induced-hypotension in healthy patients undergoing spinal fusion for scoliosis	20	Diltiazem plus SNP (n = 10) or SNP (n = 10)	Diltiazem plus SNP (186 ± 17 min) SNP (214 ± 26 min)	Diltiazem plus SNP (0.24 ± 0.05 mg/kg) SNP (0.47 ± 0.07 mg/kg)	0	0	0
Dentz, ⁶⁹ 1995	Abdominal aortic aneurysms	20	Prospective randomized study comparing amrinone (n = 10) to SNP (n = 10) for hemodynamic control	NR	NR (range 1–8 µg/kg/min)	0	0	0
Newton, ⁷⁰ 1996	Induced-hypotension (MAP = 55) for middle ear surgery	30	Isoflurane (n = 9) SNP (n = 10), or trimethaphan (n = 9).	Isoflurane (105 ± 19 min) SNP (87 ± 6 min), or trimethaphan (85 ± 10 min)	0.18 ± 0.06 mg/min	0	0	0
van der Stroom, ⁷¹ 1996	CABG	60	Open-label, randomized study comparing effects urapidil (n = 31) and SNP (n = 29) on myocardial metabolism and hemodynamic state	59 min	1 µg/kg/min (range 0.1–2.6)	0	0	0
Tugrul, ⁷² 1997	Cardiac surgery	66	Prospective, randomized study comparing effects of isoflurane (n = NR) and SNP (n = NR) on rewarming after cardiopulmonary bypass	32.6 min	1.55 µg/kg/min	0	0	0
Deakin, ⁷³ 1998	CABG	120	Unknown study design. Comparing effects of SNP (n = 59) to placebo (n = 61) in rewarming after cardiopulmonary bypass	NR (max 490 min)	1.4 µg/kg/min	0	0	0
Suttner, ⁷⁴ 1999	Induced-hypotension in radical prostatectomy	30	SNP (n = 15) Control (n = 15)	97 ± 13 min	Total dose = 23.4 ± 7.8 min	0	0	0

(Continued)

Table 3 (Continued)

Study	Patient population	N	Treatment and control group regimens	Mean duration of study	Mean SNP dose	Outcomes		
						CN toxicity (#)	Deaths (#)	Lactic acidosis (#)
Postoperative/medical use of SNP								
Armstrong, ⁷⁵ 1975	Patients with MI and MAP \geq 105 and/or PCP $>$ 15	26	All (N = 26) received SNP gtt, 18 received NTG gtt	First 24 h post-MI	76 μ g/min	0	0	0
Kotter, ⁷⁶ 1977	Acute MI	29	SNP + phentolamine (n = ?) vs SNP + glyceril trinitrate (n = ?)	88 μ g/min (range 33–273 μ g/min)	NR	0	0	0
Cohn, ⁷⁷ 1982	Acute MI	812	Prospective, randomized double-blinded study comparing SNP (n = 407) to placebo (n = 405)	48 h	NR (range 72.8–94.4 μ g/min)	0	11 (9 in PC at 48 h)	0
Durrer, ⁷⁸ 1982	Acute MI	328	Prospective, randomized trial comparing effects of SNP (n = 163) to placebo (n = 165) on mortality	24 h	81.3 mg	0	5 (18 died in PC)	0
Schulz, ⁷⁹ 1982	Multiple indications	70	Prospective observation trial of SNP use for intraoperative hypotension in 51 patients and hypertensive crisis or aortic aneurysm (medical) in 19 patients	Intraoperative 80 min Medical – NR (up to 2 wk)	Intraoperative NR Medical – NR	9	0	0
Flaherty, ⁸⁰ 1983	Patients with MI	17	SNP and NTG in a randomized crossover protocol	At least 60 min	NR	0	0	0
Gray, ⁸¹ 1985	Post cardiac surgery	12	Crossover study comparing esmolol vs SNP	1.6 μ g/kg/min (range 0.5–2.75 μ g/kg/min)	NR	0	0	0
Vesey, ⁸² 1985	NR	30	Prospective, observation study of long term SNP infusion and CN levels	NR (range 12–314 h)	NR	5*	0	0
Gray, ⁸³ 1987	Postcardiac surgery	20	Prospective, randomized, open-label, crossover study comparing esmolol to SNP	NR	1.8 μ g/kg/min	0	0	0
Installe, ⁸⁴ 1987	Patients with NYHA class 3 or 4 HF	10	All patients received SNP, then dobutamine, then enoximone.	SNP titrated to goal then washout <8 h?	1.8 \pm 0.75 μ g/kg/min	0	0	0
Breisblatt, ⁸⁵ 1988	Unstable angina	40	(30–40 min washout after SNP)	SNP titrated to goal <8 h?	77 \pm 25 μ g/min	0	0	0
Mullen, ⁸⁶ 1988	CABG patients	62	NTG (N = 22) Prospective, randomized, study comparing diltiazem (n = 22), nifedipine (n = 20) and SNP (n = 20) for postoperative HTN	NR	NR	0	0	0
Underwood, ⁸⁷ 1989	CABG patients	20	Prospective, randomized, pilot dose finding study comparing isradipine (n = 10) to SNP (n = 10) for postoperative HTN	2 h	1.6 μ g/kg/min	0	0	0

David, ⁸⁸ 1991	CABG patients	74	Open-label, randomized trial comparing nicardipine (n = 38) to SNP (n = 36) for postoperative hypertension	1.43 µg/kg/min	NR (max range 18–24 h)	0	0	0
Underwood, ⁸⁹ 1991	CABG patients	20	Prospective randomized trial comparing isradipine (n = 10) to SNP (n = 10) for postoperative hypertension	1.6 µg/kg/min	2 h	0	0	0
Chitwood, ⁹⁰ 1992	Postcardiac surgery	1089	Prospective study of closed loop vs manual management of postoperative HTN with SNP	15 h in loop group vs 19 h in manual group	NR	0	0	0
Combes and Durand, ⁹¹ 1992	CABG patients	20	Prospective, randomized, open-label trial comparing nicardipine (n = 10) to SNP (n = 10) for postoperative HTN	Up to 24 h	4.5 µg/kg/min	0	0	0
Gretler, ⁹² 1992	Hypertensive emergencies	21	Prospective, randomized trial comparing ECG changes in patients treated with fenoldopam (n = 10) and SNP (n = 11)	NR	NR	0	0	0
Nathan, ⁹³ 1992	Post-CABG hypertension	60	SNP (n = 28) or nifedipine (n = 32)	2 h infusion, and 2 h follow-up monitoring	Not stated	0	0	0
Ruegg, ⁹⁴ 1992	CABG patients	198	Prospective, randomized trial comparing isradipine (n = 98) to SNP (n = 100) for postoperative HTN	6 h	0.45 mg/kg	0	0	1
Hill, ⁹⁵ 1993	CABG	20	Unknown study design	NR	1.36 µg/kg/min	0	0	0
Lestrade, ⁹⁶ 1993	CABG	27	Comparison of fenoldopam (n = 10) to SNP (n = 10) for postoperative hypertension	2 h	NR (max dose 8 µg/kg/min)	0	0	0
Pilmer, ⁹⁷ 1993	Hypertensive urgency	33	Open-label, randomized study comparing isradipine (n = 13) to SNP (n = 14) for postoperative hypertension	NR (range 6–24 h)	1.2 µg/kg/min	0	0	0
Panacek, ⁹⁸ 1995	Treatment of severe acute HTN (DBP ≥ 120 mm Hg)	183	Unknown study design	6–24 h	1.67 µg/kg/min	0	0	0
Hirschl, ⁹⁹ 1997	Treatment of hypertensive emergency	81	Comparison of fenoldopam (n = 15) to SNP (n = 18) for severe systemic HTN	5.5 h	0.5–3 µg/kg/min	0	0	0
			Fenoldopam (n = 90)					
			SNP (n = 93)					
			Urapidil (n = 46)					
			SNP (n = 35)					

Abbreviations: SNP, sodium nitroprusside; NR, not reported; CABG, coronary artery bypass graft; MAP, mean arterial pressure; TS, thiosulfate; HTN, hypertension; MI, myocardial infarction; PCP, pulmonary capillary pressure; NTG, nitroglycerin; CN, cyanide; HF, heart failure; ECG, electrocardiogram; DBP, diastolic blood pressure.

(24–45 years) were determined to be 1.13 ± 0.11 mg/dL (range 0.43 to 2.54 mg/dL), and healthy males produced 3 mg/d, regardless of dietary intake. Elevated thiosulfate concentrations were found in starving patients and children, possibly due to increased protein utilization.¹⁸ Based on these data, authors reported that adults should be able to detoxify 66 mg of SNP with endogenous thiosulfate stores; however, if thiosulfate concentrations need to be 3 times higher to act as a preferred substrate to rhodanase, this amount drops to <50 mg. With these considerations in mind, the authors recommended a maximum safe dose of 1–1.5 mg/kg of SNP based on clinical experience. A limitation of this data is that it was a short-term study and does not reflect the true amount of SNP that the body can handle as we will discuss in the “How was toxic CN level defined” section. They also recommended that sodium thiosulfate should be administered as a continuous infusion when SNP is administered over several hours. A 10:1 ratio of thiosulfate to nitroprusside as a mixed infusion provides enough sulfur to promote metabolism for excretion.¹¹

There are now data to suggest other enzymes also have the capability of metabolizing CN, and these include mercaptopyruvate sulfurtransferase and thiosulfate reductase in the mitochondria and cystathionine gamma lyase in the cytoplasm.¹⁰⁰ It appears now that mechanistically 2 enzyme systems, rhodanase and mercaptopyruvate sulfurtransferase, are key players in the detoxification of CN.^{101,102} Rhodanase is a nonspecific enzyme that can interact with many sulfur donors. Besides thiosulfates, other sulfane-sulfur (divalent sulfur bound to another sulfur ion) sources in the body include polythionates, thiosulfonates, persulfides, and elemental sulfur.¹⁰³ Thus, the “sulfane pool” is larger than initially proposed resulting in the body’s enhanced ability to detoxify CN. Mercaptopyruvate sulfurtransferase aids in the detoxification process by generating sulfane-sulfur from cysteine, hence adding to the sulfane pool.^{104,105} Patients who are receiving oral or enteral nutrition will have additional sources of cysteine, which may add to the sulfane pool, although there are no published data to support this hypothesis at this time. In addition, mercaptopyruvate sulfurtransferase plays a key role in incorporating exogenous thiosulfate into the sulfane pool, as thiosulfate by itself has poor intracellular penetration.¹⁰⁶

Although rhodanase is found in high concentrations in the liver, it is very scant in the brain.¹⁰⁷ The primary toxic effects of CN are elucidated in the brain as it has a high affinity for cytochrome a,a₃, the cytochrome oxidase found specifically in brain mitochondria.¹⁰⁸ Albumin also appears to play a role in CN detoxification as it has been reported to act as a

sulfur carrier, as well as it have the capacity to directly react with CN to form thiocyanate.^{109,110} This mechanism might be another way thiosulfate is able to relieve the toxic effects of CN particularly within the brain.

Besides enzymatic reactions, the body has other chemical pathways to inactivate/remove CN, and they include reactions with formic acid, 2-aminothiazoline-4 carboxylic acid, hydroxycobalamin, hemoglobin, exhalation of hydrogen cyanide (HCN), and incorporation into choline and methionine.^{25,111} In conclusion, the body possesses a much larger capacity for the detoxification of CN than once realized. Although there are a couple of primary pathways that account for the majority of the detoxification, it is unknown how the other systems interact *in vivo* (ie, in the presence of a large CN load can other systems upregulate to handle the burden). Nonetheless, the data suggest that larger doses of SNP may be used in patients, contrary to what has been proposed previously.^{11,16,18,50,112,113}

How was toxic level of CN defined?

CN has the potential to distribute into 3 general compartments – red blood cells (RBCs), plasma, and tissues.^{13,16,56} Most investigators believe that the conversion of SNP to CN takes place in extracellular space or plasma.^{8,13,16,52,114} CN becomes concentrated within erythrocytes; however, it is suggested that the plasma CN concentration remains in equilibrium with tissue and correlates to CN toxicity.^{16,25,52} The relationship between plasma and erythrocyte CN concentrations also is proportional; thus, a rise in erythrocytic CN correlates to a rise in plasma and tissue CN concentrations.²⁵ Because of ease of measurement, most investigators evaluate erythrocytic CN concentrations as opposed to plasma CN concentrations.²⁵ Most laboratories however, only report whole blood CN concentrations, which can take days to weeks to result and can be misinterpreted due to the significant distribution into erythrocytes.¹¹⁵ Whole blood CN levels may be elevated without manifestation of toxicity, or, in some case, may be falsely low due to a delay between sample collection and analysis.^{2,25,56} Therefore, most clinicians must rely on symptomatology rather than whole blood CN concentrations.

In 1976, Vesey and colleagues⁵⁰ studied the CN and thiocyanate concentrations following SNP infusion for controlled intraoperative hypotension in 26 patients undergoing major orthopedic surgery. The results indicated that for infusions lasting approximately 2 hours, plasma and erythrocyte CN concentrations were more closely related to the total dose of SNP than to the rate of infusion ($r = 0.924$, $P < 0.001$; $r = 0.849$, $P < 0.001$, respectively). Vesey and colleagues⁵⁰

found that 98.4% of blood CN was located in the red cells as previously described. Based on these results and previously published data, Vesey and colleagues⁵⁰ hypothesized that the lethal plasma CN concentration is between 10 and 20 $\mu\text{mol/L}$, and the lethal intravenous dose of SNP would be <250 mg. The authors recommended that the total dose of SNP be limited to 1.5 mg/kg for the duration of an average surgical operation lasting 1–3 hours.

Pasch and colleagues⁵² studied the CN concentrations in the blood following intraoperative SNP administration with and without thiosulfate. SNP was administered to produce controlled hypotension during surgery in 55 patients. Patients were divided into 5 groups. Groups 1 through 3 were retrospectively divided based on the rate of SNP infusion (<2 $\mu\text{g/kg/min}$, 2–4 $\mu\text{g/kg/min}$, and >4 $\mu\text{g/kg/min}$, respectively), group 4 received an intravenous bolus of sodium thiosulfate at set times in addition to SNP doses ≥ 2.4 $\mu\text{g/kg/min}$, and group 5 received SNP at doses ≥ 3.5 $\mu\text{g/kg/min}$ in addition to sodium thiosulfate continuous infusion. The authors determined that the mean values of erythrocyte CN concentrations increased with the quantity of SNP administered in groups 1 through 3. Most patients in group 1 had a CN level <10 $\mu\text{mol/L}$. In group 2, the mean CN concentration was 14.4 $\mu\text{mol/L}$, and in group 3, the mean CN concentration was 48.2 $\mu\text{mol/L}$. In patients not receiving thiosulfate, there was a clinically significant correlation between the SNP infusion rate and the maximum CN concentration ($r = 0.862$; $P < 0.01$). In groups 1 through 3, the concentration of CN increased with time, with the most notable increase in group 3, which received the greatest SNP infusion rate. Groups 4 and 5 had low CN concentrations due to the administration of thiosulfate.

According to previously published data and cases, Pasch and colleagues⁵² assumed that metabolic changes (increase in base deficit and a decrease in mixed venous oxygen saturation) were detectable at erythrocyte CN concentrations of 40 $\mu\text{mol/L}$; severe clinical symptoms occur at concentrations from 200–250 $\mu\text{mol/L}$ and upward, and concentrations from 400–500 $\mu\text{mol/L}$ are considered lethal. Based on the calculated CN detoxification rate of 0.1–0.2 mg/kg/h, the authors computed time to the development of significant CN levels for given SNP infusion rates (Table 4).

The authors concluded that infusion rates of up to 2 $\mu\text{g/kg/min}$ lead to a slight increase in red cell CN concentrations of <20 $\mu\text{mol/L}$ and presented no danger to the patient, whereas doses >2.5 $\mu\text{g/kg/min}$ led to significant elevations in CN levels in a matter of hours to minutes. Admittedly, the authors also noted considerable interindividual

Table 4 Time to projected cyanide concentrations based on SNP infusion rates

SNP infusion rate, $\mu\text{g/kg/min}$	Time needed to produce red cell cyanide concentrations, h	
	40 $\mu\text{mol/L}$	200 $\mu\text{mol/L}$
2.5	6.3	31.7
5	1	5
10	0.37	1.9

Notes: Adapted from Pasch et al.⁵²

Abbreviation: SNP, sodium nitroprusside.

fluctuation in the rate of SNP infusion and the red cell CN concentration.

In the 1970s, various authors published safe upper dosing limits for short SNP infusions during deliberate hypotension, but little was known about the toxicity of long-term SNP infusions.^{50,82,116} In 1985, Vesey and Cole⁸² studied plasma and red cell CN concentrations and thiocyanate concentrations in 30 patients receiving long-term therapy (12–314 hours) with SNP. Blood samples were obtained during and/or near the end of the SNP infusion. The authors found a significant correlation between plasma and red cell CN concentrations and the rate of SNP infusion but not to total dose ($r = 0.64$, $P < 0.001$; $r = 0.71$, $P < 0.001$). In addition, erythrocyte CN concentrations correlated closely with plasma CN concentrations ($r = 0.92$, $P < 0.001$). The authors showed that plasma CN concentrations may increase above normal values when SNP is infused at rates >1 $\mu\text{g/kg/min}$, but concerning CN levels did not occur until doses exceeded 4 $\mu\text{g/kg/min}$. They hypothesized that when SNP is infused at higher rates, HCN may be released faster than it can be detoxified by endogenous thiosulfate, which result in elevated CN concentrations. A limitation with this study is that there were only a handful number of levels measured at doses >4 $\mu\text{g/kg/min}$; therefore, it is not certain that there is a linear relationship with plasma CN levels at the higher doses. The study did demonstrate that there is a difference in toxicity when SNP is administered at lower doses over a longer period of time vs rapid boluses in the intraoperative setting and that there is safety with more chronic use. Admittedly, the authors did state that the safe CN level in long-term SNP infusions is unknown; however, they derived a lower and upper limit for SNP based on a couple of assumptions. There is data to suggest that in patients suffering from tropical ataxic neuropathies, which is believed to be due to CN, have a mean plasma CN concentration of 1.1 $\mu\text{mol/L}$.¹¹⁷ Vesey et al correlated this to a SNP dose of approximately 4 $\mu\text{g/kg/min}$, which the authors suggest as the upper limit of safety for SNP. The average smoker inhales 25 μg of HCN

a day, which is equivalent to about 1 µg/kg/min of SNP and they correlated this to the lower tolerable limit, as the average smoker has negligible CN level.

Although these assumptions provide us with useful guidance as to the safe administration of SNP, they cannot be taken at face value. The limitation with the above-mentioned studies is that estimations of toxicity were based on either RBC or plasma CN levels without correlations to clinical symptoms. The best data we have correlating levels to clinical symptoms is by Hall and Rumack,²⁵ which uses whole blood levels. Whole blood levels are generally what routine laboratories report. As such, it is difficult to suggest that the proposed dose limits by the previously mentioned studies are absolute. In routine clinical practice, as it relates to use in the postoperative or intensive care unit (ICU) setting, the proposed dose ranges are routinely exceeded without clinical symptomatology.

Are there limitations with CN level measurements?

It is important to note that all CN assays are not created equal. The most frequent procedure that had been used until at least the early 1980s is the colorimetric procedure, which in comparison to alternate methods like the potentiometric or spectrometry has the potential to introduce light to the biological assay. The significance of this lies in the fact that light converts SNP to aquapentacyanoferrate ion, which is still colorless, but readily decomposes to release CN.¹¹⁸ This is why SNP should be protected from light during administration. When CN levels were evaluated in a study by Bisset et al¹²⁰ using an ion-sensitive electrode, they were unable to measure CN in whole blood, plasma, and RBCs. Therefore, some of the data regarding CN levels pre-1980 may have been spuriously overestimated because of the assay technique. Also of note, sodium thiosulfate has the potential to interfere with several assays and cause falsely elevated CN levels.¹⁰⁴ Assays that require acidification as part of their process, or samples that are frozen and thawed, can have falsely elevated CN levels as well due to the artifactual generation of CN from thiocyanate.^{120,121} Finally, there are discrepancies in arterial vs venous samples.^{122,123} This calls into question the accuracy of estimations of CN levels from much of the data, making it difficult to correlate CN levels to outcomes.

Are there confounding factors associated with published data regarding CN toxicity?

Although there are several cases of CN-associated toxicity published in the literature, it is important to note that

CN levels were not drawn for all patients, so it is difficult to confirm the diagnosis of death related to CN toxicity (Tables 1 and 2). Moreover, many of the patients had multiple comorbidities that could have contributed to their demise. The data from the FDA are scant, which makes it difficult to make any true inferences about a causal relationship.⁴⁷ Furthermore, in several of the FDA reports, CN toxicity was assumed because there was no other explanation. Though rare, SNP has been reported to cause methemoglobinemia at high doses (>10 mg/kg).¹²⁴ Nitrous oxide, which was used in the OR frequently for the anesthesia, also has the potential to cause methemoglobinemia.¹²⁵ The combination of these agents could, theoretically, increase the risk of a patient developing methemoglobinemia. This highlights the concern that there are potentially other causes for negative outcomes, especially in the intraoperative setting. Nonetheless, we do want to emphasize the obvious: although there are confounders related to the data, indiscriminate use of SNP does cause CN toxicity, as evident from several of the cases.

Safe use of SNP today – clinical monitoring and prophylaxis

Even with the limitations of the current data, one is still left with the question: how do I safely use this drug? We believe this drug still has great utility and can be monitored for safety without the use of CN levels, which are impractical today. The utilization of lactate levels does provide clinical utility. As reviewed previously, CN accumulation results in halting of aerobic metabolism by inhibiting the final step of oxidative phosphorylation, leading to the generation of lactic acid. Although inhibition of mitochondrial oxidative phosphorylation is not the only consequence of CN accumulation, significant CN intoxication has been associated with a various degree of lactic acidosis both in animals and humans.^{20–24} Baud et al²³ conducted a prospective study of 39 smoke-inhalation victims without severe burns and found a serum lactate level of >10 mmol/L (>90 mg/dL) to significantly correlate ($r = 0.47$, $P < 0.001$) with toxic CN levels of >40 µmol/L or >1.0 mg/L (whole blood CN concentrations <40 µmol/L were defined as nontoxic, >40–100 µmol/L as potentially toxic, and >100 µmol/L as potentially lethal). Furthermore, based on their results, the authors reported that the sensitivity of plasma lactate concentration >10 mmol/L for CN poisoning (blood level >40 µmol/L) was 87%, with 94% specificity and the positive predictive value of 95%. Baud and colleagues,²³ therefore, concluded that high plasma lactate concentrations were largely indicative of CN intoxication in smoke-inhalation victims with no or minor burns (<15% of

body surface area). Although this information was useful for patients involved in fires, little was known about the correlation between acute pure CN poisoning and plasma lactate concentration. Baud et al²³ hypothesized that serial plasma lactate concentrations could be used as a marker for the evolution of CN toxicity and have confirmatory and therapeutic value. To test their hypothesis, Baud et al²² conducted a retrospective study of 11 patients in the toxicologic ICU, who had confirmed exposure to CN. Victims of smoke inhalation were excluded from the study. The median age was 38 years and the majority of patients ingested potassium cyanide (7/11). At baseline, there was a significant correlation ($r = 0.74$, $P = 0.017$) between the median blood CN concentration of 4.2 mg/L ($n = 10$, 0.34–6.9 mg/L) and median plasma lactate concentration of 168 mg/dL ($n = 10$, 43–477 mg/dL). It was determined that plasma lactate concentration of 72 mg/dL (8 mmol/L) had the best sensitivity and specificity (94% and 70%, respectively) in predicting CN toxicity (blood CN concentration of >1.0 mg/L) with positive and negative predictive values of 64% and 98%, respectively. In patients who did not receive catecholamine infusion, the specificity and the positive predictive values increased to 85% and 86%, respectively. Although limited by a small sample size, the authors concluded that immediate and serial measurement of plasma lactate concentrations would be useful in assessing severity of CN poisoning, especially in a situation where immediate laboratory confirmation of CN intoxication is not possible.²² Finally, Fahmy⁵³ demonstrated a correlation between base excess and whole blood CN levels in patients who received SNP for controlled intraoperative hypotension. The available literature supports positive correlation between plasma lactate and CN concentrations, although most of the data are in acute CN poisonings. Although it is not certain that plasma lactate level is a sensitive or a diagnostic marker in cases of gradual CN accumulation (ie, administration of SNP) due to lack of randomized controlled trials, the current data suggest that it is a reasonable monitoring tool.

For the skeptic, who is still concerned about the risk of CN toxicity associated with SNP, there are data to support its coadministration with sodium thiosulfate as a prophylactic agent. Several investigators have reported that coadministration of SNP and thiosulfate significantly diminished CN accumulation regardless of SNP infusion rate and duration of infusion.^{13,18,52,56,79} One of the very first human studies by Schulz and colleagues⁷⁹ presented results on 19 patients receiving mixed infusion of thiosulfate and SNP for hypertensive emergency in whom no toxicologically relevant levels were reached even at high doses for up to

2 weeks (highest CN level around 20 $\mu\text{mol/mL}$ with infusion rates >10 $\mu\text{g/kg/min}$). Furthermore, thiosulfate did not affect the efficacy of SNP when admixed together as long as the mixture was protected from direct sunlight. The authors also reported that although monosolution (SNP alone) was more stable, the mixed solution could, however, be used for up to 8 days without any significant loss of effectiveness.⁷⁹ Other studies reported on thiosulfate effectiveness as intermittent bolus injections.^{52,56} Cole and Vesey⁵⁶ measured CN and thiocyanate concentrations in 30 patients undergoing intraoperative SNP-induced hypotension with half of the patients receiving a bolus of thiosulfate (10.6–38.5 mg/kg) immediately after discontinuation of SNP infusion. The average infusion rate and duration of SNP in the control and intervention group were 3.89 $\mu\text{g/kg/min}$ for 98.7 minutes and 5.43 $\mu\text{g/kg/min}$ for 88.9 minutes, respectively. The authors demonstrated that CN levels were significantly lower in the intervention group at 10, 30, and 60 minutes postinfusion ($P < 0.05$) and that thiosulfate significantly shortened the time to 50% decrease in CN levels ($P < 0.001$). Another study by Pasch et al⁵² investigated protective effects of thiosulfate as either intermittent bolus injections ($n = 8$) or when co-infused with SNP ($n = 8$) during controlled intraoperative hypotension. Thiosulfate boluses were administered 55 minutes post-SNP initiation and then at intervals of 60 minutes. In the bolus group, the maximal erythrocyte CN concentration was 13.0 ± 5.0 nmol/mL at a mean infusion rate of 4.79 ± 1.10 $\mu\text{g/kg/min}$. With simultaneous infusion of SNP and thiosulfate, no CN levels exceeded 10 nmol/mL, despite higher mean infusion rate of 5.56 ± 0.77 $\mu\text{g/kg/min}$. The authors concluded that the safest method of administering SNP is to infuse it in combination with thiosulfate as long as light protection can be reliably ensured.

Co-infusion of SNP with thiosulfate may result in higher levels of thiocyanate, which is approximately 100 times less toxic than CN. Thiocyanate is excreted by the kidneys with elimination half-life of 2.7 days in patients with normal renal function, which is increased, to up to 9 days in patients with renal dysfunction. Prolonged exposure to thiocyanate may result in its toxicity after approximately 9 days in patients with normal renal function and after approximately 3 days in those with renal failure. The clinical symptoms of serious thiocyanate toxicity are nonspecific and primarily neurologic including confusion, hallucinations, convulsions, and coma. Since thiocyanate competes with iodine for thyroidal uptake, antithyroidal effects should be considered when patients receive prolonged infusions of SNP. In addition, unlike CN, thiocyanate toxicity is not associated with metabolic acidosis

and decreased oxygen consumption. Although thiocyanate serum concentrations are not useful in detecting CN poisoning, they could be of value in diagnosing thiocyanate toxicity. Serious thiocyanate toxicity has been reported with serum concentrations exceeding 100 mg/L (normal concentration in nonsmokers is <4 mg/L and in smokers is <8 mg/L). In case of thiocyanate toxicity, hemodialysis effectively removes this compound leading to rapid improvement in central nervous system function.^{11,13,16}

Conclusion

In conclusion, SNP is a potent vasodilator with excellent blood pressure-lowering effects; however, health care providers must be aware of its limitations. With close monitoring of arterial blood pressure, serum lactate levels, and clinical symptoms of CN toxicity, SNP can be a safe first-line agent in hypertensive emergencies or as an adjunct in difficult to control patients.

Disclosure

The authors report no conflicts of interest in this work.

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