Sodium nitroprusside in 2014: A clinical concepts review

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Abstract

Sodium nitroprusside has been used in clinical practice as an arterial and venous vasodilator for 40 years. This prodrug reacts with physiologic sulfhydryl groups to release nitric oxide, causing rapid vasodilation, and acutely lowering blood pressure. It is used clinically in cardiac surgery, hypertensive crises, heart failure, vascular surgery, pediatric surgery, and other acute hemodynamic applications. In some practices, newer agents have replaced nitroprusside, either because they are more effective or because they have a more favorable side-effect profile. However, valid and adequately-powered efficacy studies are sparse and do not identify a superior agent for all indications. The cyanide anion release concurrent with nitroprusside administration is associated with potential cyanide accumulation and severe toxicity. Agents to ameliorate the untoward effects of cyanide are limited by various problems in their practicality and effectiveness. A new orally bioavailable antidote is sodium sulfanegen, which shows promise in reversing this toxicity. The unique effectiveness of nitroprusside as a titratable agent capable of rapid blood pressure control will likely maintain its utilization in clinical practice for the foreseeable future. Additional research will refine and perhaps expand indications for nitroprusside, while parallel investigation continues to develop effective antidotes for cyanide poisoning.

Key words: Antihypertensives, cyanide, pharmacology, sodium nitroprusside, toxicity

Introduction and History

Sodium nitroprusside (SNP) is a well-known arterial and venous vasodilator used in clinical practice to lower blood pressure. Initially discovered in 1849 by Playfair, SNP’s first reported use in a patient was by Johnson in 1922. Its safety and efficacy in lowering blood pressure when given intravenously in severely hypertensive patients was established in 1955. After its successful use as an intraoperative antihypertensive in 1970, it quickly gained acceptance as a fast-acting agent useful to reduce intraoperative hypertension, induce hypotension to minimize surgical blood loss, and decrease afterload and improve cardiac output in heart failure. It has been used clinically in cardiac surgery, hypertensive crises, heart failure, vascular surgery, pediatric surgery, and other acute applications.

However, reports began to surface associating nitroprusside and cyanide toxicity, with the food and drug administration (FDA) issuing new labeling emphasizing this risk in 1991. In some practices newer agents including nitroglycerin, calcium channel blockers, β-blockers, and dopaminergic agonists, replaced SNP, either because they were recognized to be more arterial selective, or because of a more favorable side-effect profile. Despite the risks, nitroprusside has continued to be used in many of the above settings and others for its potent and fast-acting vasodilatory properties. In addition, the ongoing threat of cyanide as a chemical warfare agent in bioterrorism continues to fuel research to reverse or prevent cyanide poisoning, and thus by association retains an interest in nitroprusside.

The last prominent review of SNP was by Friederich and Butterworth in 1995. Since then, new research has deepened the understanding of its mechanism of action, refined its clinical application by comparing it to newer vasodilators, further elaborated its adverse effects and safety profile, and offered promise for reversing its significant potential toxicity.

Now 40 years since nitroprusside’s widespread adoption and almost 20 years since its last thorough review, we summarize...
the new salient developments for this agent. Our goal is to provide clinicians with a comprehensive, updated benefit-to-risk understanding of the current use of nitroprusside in clinical practice. In addition, we provide newer experimental data of an antidote for cyanide toxicity, which may lead to an expanded role of nitroprusside in the future.

Mechanism of Action and Hemodynamic Effects

Sodium nitroprusside is a water-soluble sodium salt comprised of Fe^{2+} complexed with nitric oxide (NO) and five cyanide anions [Figure 1]. In the body it functions as a prodrug, reacting with sulphydryl groups on erythrocytes, albumin, and other proteins to release NO. NO, or endothelium derived relaxing factor, stimulates guanyl cyclase to produce cyclic GMP, sequestering calcium and inhibiting cellular contraction. At the tissue level, these effects of NO result in reduced vascular tone in muscular conduit arteries. NO released from nitroprusside decreases cerebral vascular resistance, and in a canine study it has been shown to impair brain and myocardial tissue oxygenation due to increase in arterial-venous shunting. It decreases coronary flow reserve, which is the basis for the theory that nitroprusside can cause coronary steal syndrome, discussed further below.

The role of NO in the coagulation system and platelet function raised the concern that nitroprusside and other NO releasing drugs may affect coagulation, at least in theory. A few studies showed the ability of nitroprusside to inhibit platelet aggregation in vitro and in vivo. One study showed increased intraoperative blood loss in spinal surgery with nitroprusside compared with nicardipine, but the authors did not believe that this was necessarily due to any effect on platelets but rather might be explained by increased venous congestion. The clinical significance, if any, of nitroprusside administration on bleeding remains unproven.

Globally, the net hemodynamic effect of nitroprusside is to cause arterial and venous dilatation, reduce afterload, decrease ventricular filling pressures, lower the systemic blood pressure, and increase cardiac output, without significant lowering of the heart rate. These properties, together with nitroprusside’s rapid onset and ability to be titrated to a target blood pressure, make the agent highly effective in situations where rapid blood pressure lowering is indicated.

Clinical Use, Efficacy, and Comparative Advantages of Nitroprusside

Dosing and administration

Sodium nitroprusside is typically started as an intravenous infusion of 0.5 μg/kg/min and titrated to effect, with a maximum dose of 10 μg/kg/min (for short periods to establish blood pressure control). Limited data about pediatric dosing suggests that infusion rates should remain below 2 μg/kg/min, and reserve higher doses for short periods to establish urgent blood pressure control. SNP acts within minutes and is effective in clinical situations where urgent lowering of blood pressure is needed. However, this means that it requires vigilant monitoring to avoid the rapid onset of hypo-perfusion or potentially life-threatening hypotension. These properties have traditionally restricted its use to short duration therapy in the operating room, ICU, cardiac care unit, or other areas where continuous close monitoring by experienced professionals is possible.
Crossover study of 17 patients by Flaherty compared to nitroprusside in a randomized, open-label "gold standard" against which newer agents were studied and an increased heart rate, stroke volume, and cardiac pressure was increased. By comparison, patients treated with nitroprusside had significantly greater reductions in blood pressure than patients treated with nitroglycerin, while nitroprusside worsened these variables. The ideal intraoperative agent could be easily and rapidly titrated to effect with minimal swings in blood pressure or risk of hypotension.

Historically, nitroprusside has been a favored agent to control blood pressure intraoperatively, although it carries risk for hypotension in addition to toxicity. Once its efficacy during and after cardiac surgery was established, it became the “gold standard” against which newer agents were studied for efficacy and comparative advantages. Nitroglycerin was compared to nitroprusside in a randomized, open-label crossover study of 17 patients by Flaherty et al. While all patients responded to nitroprusside, a subset of patients achieved with nitroglycerin only 50% of the blood pressure reduction achieved with nitroprusside. The time to achieve blood pressure control was not reported. Pulmonary gas exchange parameters were improved during administration of nitroglycerin, while nitroprusside worsened these variables. No significant adverse effects were reported, but nitroprusside was noted to cause tachycardia in four patients.

The B-blockers esmolol and labetalol were compared with nitroprusside in postoperative cardiac surgical patients. Labetalol lowered blood pressure in magnitude similar to nitroprusside, but over a much slower timeframe and with a significantly different hemodynamic profile. Labetalol lowered the heart rate and cardiac index, while central venous pressure was increased. By comparison, patients treated with nitroprusside had significantly greater reductions in diastolic blood pressure (DBP) and mean arterial pressure, and an increased heart rate, stroke volume, and cardiac index. The authors speculated that the higher DBP and lower heart rate might improve coronary perfusion and reduce myocardial oxygen demand in patients treated with labetalol. No complications were noted in either group. Gray et al. compared esmolol with SNP in postcardiac surgical patients and observed similar results. SNP lowered DBP more than esmolol and caused an increase in heart rate. There was a nonsignificant trend of quicker blood pressure control with SNP over esmolol (21 ± 15 vs. 29 ± 14 min, respectively).

The calcium channel blockers nicardipine and clevidipine have been compared with nitroprusside. Nicardipine was compared with nitroprusside by Halpern et al. in cardiac and noncardiac surgical patients. Nicardipine controlled blood pressure more quickly and with less adverse effects, which included tachycardia and hypotension that resulted in discontinuation of the drug in 6 patients. None were discontinued from the nicardipine group. Both drugs exhibited similar effects on circulatory variables. Nitroprusside was shown by Aronson et al. to be inferior to clevidipine in controlling systolic blood pressure after cardiac surgery. They observed greater blood pressure variability and increased mortality with nitroprusside compared to clevidipine. An explanation for this may be because longstanding hypertensive patients with stiff ventricles are more susceptible to reductions in preload from nitroprusside, a direct arterial and venous vasodilator. On the other hand, clevidipine primarily dilates arterial smooth muscle, preserving preload.

Taken together, these studies do not identify a preferred agent in cardiac surgery. In one study, clevidipine appeared superior as a first line agent because it kept blood pressure within predefined ranges better than nitroprusside. However, mortality differences between clevidipine and nitroprusside were explained by sicker patients in nitroprusside patients. In other studies, nitroprusside controlled blood pressure more quickly and was often needed as a second line agent when other drugs failed. While nitroprusside may produce reflex tachycardia in some patients, there were no cases where this was directly attributed to cyanide toxicity.

Hypertensive crises
Hypertensive crises are elevations in systolic blood pressure ≥180 mmHg or DBP ≥110 mmHg and are divided into hypertensive urgencies or hypertensive emergencies, with the latter having clinical evidence of end organ damage. Blood pressure in hypertensive urgencies should be lowered over 24-48 h, while in hypertensive emergencies it should be lowered within minutes to hours. These events have many etiologies and present within a variety of clinical syndromes, and the choice of treatment depends on the target organ affected.
Despite a paucity of definitive comparative, prospective, randomized controlled trials, newer agents have replaced SNP in many of these contexts because of evidence of clinical equipoise, less stringent monitoring requirements, and more favorable side effect profiles. In an analysis of the Special Tertiary Admissions Test registry, investigators found that the most common parental agent given for hypertensive crises in an emergency room or Intensive Care Unit (ICU) setting was labetalol (48%), followed by nicardipine (15%), hydralazine (15%), and nitroprusside (13%). Treatment with nitroprusside and nitroglycerin were associated with a higher mortality, but this was of borderline significance and likely confounded by bias with regard to choice of agent.[38] One study by Immink et al. compared labetalol with nitroprusside in their effects on cerebral hemodynamics in the treatment of malignant hypertension. Nitroprusside preferentially lowered systemic vascular resistance more than cerebral vascular resistance, causing lower middle cerebral blood velocities, presumably by shunting of blood to the low resistance, dilated systemic vascular bed. Labetalol did not produce these effects.[39] Other small, prospective trials have compared nitroprusside to fenoldopam[40] and nicardipine[41,42] with results of similar efficacy and little observable differences in side effects. SNP continues to be used to lower blood pressure in acute aortic dissection and acute pulmonary edema, although the recommendation is to use it only when more preferred intravenous agents are unavailable.[37]

The vasodilatory properties of nitroprusside spurred interest in its use for hypertensive crises associated with cerebrovascular accidents, especially subarachnoid and intracerebral hemorrhage. Early animal studies concluded that nitroprusside could cause vasodilation, prevent vasospasm, and maintain cerebral blood flow immediately following subarachnoid hemorrhage.[43-45] One study showed reversal of cerebral vasospasm in humans after nitroprusside administration in three patients who suffered a subarachnoid hemorrhage.[46] Subsequent work conflicted with these results, however, and did not show any increase in cerebral blood flow.[47-49] The current American Heart Association guidelines recommend using nitroprusside, labetalol, or nicardipine to treat acute hypertension to a target of a systolic blood pressure below 180 mmHg in patients with intracerebral hemorrhage.[50] There is some evidence to support the use of nicardipine over nitroprusside in this setting, as it was associated with lower in-hospital mortality.[51]

Heart failure
Sodium nitroprusside was first studied as therapy for heart failure in the 1970’s. Since then many small studies have shown it to reduce afterload and improve left ventricular filling and cardiac output in acute decompensated heart failure, reviewed thoroughly by Opasich et al.[52] The 2010 Heart Failure Society of America comprehensive heart failure practice guidelines recommend nitroprusside among other vasodilators in the management of acute decompensated heart failure (Grade B recommendation).[53] Nitroprusside infusion should be monitored while its dosing titrated to appropriate clinical effect, observing for hypotension and signs of cyanide toxicity. These requirements have somewhat restricted its use, although at least one study found that with experienced providers, chronic heart failure patients who received low dose nitroprusside therapy showed reduced mortality and adverse outcomes were rare.[54] Another study showed that intermittent low dose nitroprusside infusion reduced mortality in patients with advanced heart failure awaiting transplantation.[55] It has been shown to benefit critically ill patients with left ventricular dysfunction and aortic stenosis as a bridge to valve replacement or oral vasodilator therapy.[56] Elkayam et al. provide an excellent review of the use of nitroprusside and vasodilator therapy in the management of acute decompensated heart failure.[57]

Aortic surgery
Cross-clamping of the aorta is commonly used to repair aortic aneurysms, coarctations, and traumatic injury, among other pathologies. This procedure can have dramatic effects on cardiovascular physiology and regional hemodynamics and oxygenation due to often severe hypertension proximal to the clamping and hypo-perfusion distally, presenting challenges for the anesthesiologist.[58] While outcomes after open and endovascular abdominal aorta surgery have improved dramatically,[59] the survival rate and complications associated with thoracic cross-clamping remain poor.[60] Few studies directly compare nitroprusside with other intravenous antihypertensives and their effects on surgical outcomes in aortic surgery. Early animal studies showed SNP to be associated with a poorer response of multiple variables in the setting of cross-clamping when compared to other antihypertensive agents or controls, including increased cerebral spinal fluid pressure,[61] lower spinal cord perfusion pressure, and increased neurologic injury[62-64] and mortality.[65] In one of the few head to head comparisons of nitroprusside and another antihypertensive agent, fenoldopam, during cross-clamping, no differences were found in intraoperative hemodynamic variables or renal indices. Patients treated with nitroprusside had a higher average heart rate precross clamp.[66] Another study showed decreased mixed venous oxygen saturation in patients controlled with nitroprusside versus amrinone during cross-clamping, but no difference in hemodynamic control.[67] In both studies, the complication rate was the same between nitroprusside and the alternative treatment. Further research
is necessary to elucidate a preferred agent in aortic surgery in adults.

Pediatric patients undergoing aortic surgery are particularly susceptible to changes in cerebral oxygenation induced by nitroprusside. One study showed decreased cerebral oxygenation after administration of nitroprusside in two children undergoing cross-clamping for coarctation repair. This decrease was over and above the decrease attributable directly to cross-clamping, as esmolol and ionotrope administration did not result in a similar decrease. Another study showed no differences in cerebral venous oxygenation when nitroprusside was compared with nitroglycerin or sevoflurane. Current practices are not well-described, but they favor control of perioperative hypertension in pediatric aortic surgery with esmolol and nitroprusside or nitroglycerin intravenously.

**Emerging applications**

Nitroprusside continues to be applied in new ways. In cardiology, the “no-reflow” phenomenon is defined as the lack of blood flow following an intervention to restore patency to coronary vessels. It is estimated to occur in 3.2-4.8% of all percutaneous coronary interventions, more after myocardial infarction, and adversely impacts outcomes. Vasodilation with nitroprusside has offered promise to both prevent and treat this potential complication. In a small, randomized, placebo-controlled trial, nitroprusside was recently shown to improve symptoms of schizophrenia after a single administration. The proposed mechanism for this effect is based on the derangements in cerebral NO regulation observed in schizophrenic patients and nitroprusside’s ability to increase NO production in the brain. This NO releasing property of nitroprusside has been shown to increase apoptosis in gastric cancer cells. Table 1 compares the pharmacological profile of SNP to other antihypertensives currently available for the acute control of perioperative hypertension.

**Metabolism, Safety, and Toxicity**

Nitroprusside reacts with oxyhemoglobin to form methemoglobin and release cyanide anions in vivo. These ions have multiple possible fates: 1. They may react again with methemoglobin to form cyanomethemoglobin and accumulate in erythrocytes. 2. They may be transported to the liver where they react with thiosulfate and cobalamin to form thiocyanate, which is excreted in the kidneys. 3. They may bind to tissue cytochrome oxidase, inhibiting oxidative phosphorylation.

It is this final pathway that produces “cyanide toxicity,” which has been well-documented in clinical cases and animal studies. Further research has attempted to characterize these toxic effects in specific tissues. Nitroprusside is toxic to cerebral endothelial cells, hepatocytes, and neural cell lines, generating reactive oxygen species and inducing apoptotic cell death. It is estimated that adults can detoxify 50 mg of nitroprusside (one vial of the traditional commercial formulation), but infusion rates higher than 2 μg/kg/min may lead to toxic cyanide accumulations.

Assessment of cyanide toxicity can be difficult if lab assays measure whole blood cyanide concentrations rather than serum cyanide concentrations, which are better correlated with cyanide toxicity. Elevated lactate concentrations are an excellent surrogate and serve as a marker of cyanide toxicity in patients; they can be used to support the diagnosis. Unfortunately, many of the clinical signs of cyanide toxicity, such as restlessness, agitation, and sinus tachycardia are difficult to evaluate intraoperatively and lead to a misdiagnosis.

Cheung et al. showed that the plasma free hemoglobin concentration correlated positively with time on cardiac
bypass and the cyanide anion concentration, suggesting that prolonged exposure to bypass increased a patient’s risk for cyanide toxicity because of increased erythrocyte shearing and intracellular cyanide release.\(^\text{[86]}\) Therefore, nitroprusside should be replaced in this setting with newer drugs.

In addition to cyanide toxicity, the concept of “coronary steal” associated with nitroprusside has long been reported. Mann et al. compared regional myocardial blood flow (RMBF) after administration of nitroprusside and nitroglycerin in normal patients and patients with coronary artery disease (CAD).\(^\text{[13]}\) They found some evidence of reduced RMBF in those patients receiving nitroprusside with well-developed collaterals compared to an increase in RMBF in similar patients treated with nitroglycerin. Left ventricular end diastolic pressure was not measured in either group, which may have influenced the myocardial blood flow. In addition, nitroprusside administration was noted to result in a lower average MAP than that achieved with nitroglycerin, further confounding the results because DBP provides the driving force for coronary perfusion pressure. It is postulated that these differences are due to nitroglycerin’s preferential effect on larger conductance vessels, while nitroprusside dilates smaller resistance vessels, creating a low pressure system distal to occluded vessels that diverts critical pressure-dependent flow from ischemic areas.\(^\text{[87]}\) The clinical significance of these observations is uncertain, and the true incidence of clinically significant coronary steal remains unknown. The more important clinical consideration in patients with CAD on a nitrovasodilator may be to prevent hypotension, which may be more easily achievable with alternative therapies.\(^\text{[135]}\)

The use of nitroprusside has been associated with increased intracranial pressure (ICP).\(^\text{[88,89]}\) The mechanism for this is due to increased cerebral blood flow and resultant increased blood volume in the setting of impaired autoregulation attributable to nitroprusside.\(^\text{[90]}\) Caution should be taken in patients with intracranial mass lesions, encephalopathy or other reasons for an elevated ICP.

**Antidotes: Mechanism and Clinical Application**

Knowledge of the metabolic pathways of nitroprusside and mechanism of cyanide toxicity has spurred the investigation of potential agents to reverse or prevent this. A review by Reade et al. of available evidence found both sodium thiosulfate and hydroxocobalamin equally effective in reversal of cyanide poisoning with no significant adverse effects to either.\(^\text{[91]}\) These medicines work by increasing the thiosulfate or hydroxocobalamin substrate normally present in serum to buffer against rising cyanide concentrations and minimize its reaction with mitochondrial cytochromes. The thiosulfate-associated antidotes depend on the enzyme rhodanese to catalyze the conversion of cyanide to the less toxic thiocyanate [Figure 2]. However, since this enzyme is predominantly localized to the liver and red blood cells, important tissues such as the brain and heart remain unprotected.\(^\text{[92]}\) Patients with conditions such as Leber’s hereditary optic neuropathy lack adequate rhodanase activity and are especially vulnerable to nitroprusside toxicity. Hydroxocobalamin-based therapies work by binding and trapping cyanide anions as cyanocobalamin which is excreted in urine, but clinical results have been mixed.\(^\text{[93]}\) Only the combination of sodium thiosulfate and sodium nitrite is currently approved by the FDA for treatment of cyanide poisoning. In addition, these treatments can be difficult or expensive to administer or have serious side effects.

Recently however, a new oral cyanide antidote, sulfanegen sodium, a prodrug of 3-mercaptopropionate, has been developed.\(^\text{[92]}\) It is readily formed from commercially available starting materials [Figure 4] and has additional advantages in that it is available orally and is effective when administered prophylactically up to 1 h before cyanide exposure. The sulfanegen sodium’s dimer dissociates nonenzymatically in physiologic conditions and pH of 7.4-3-mercaptopropionate, which through further metabolism ultimately captures and converts cyanide anions into SCN, excreted in the kidneys. The prodrug was shown in initial experiments to be effective in reversing sub lethal cyanide toxicity in murine and rabbit models.\(^\text{[92,94,95]}\)

Further experiments have characterized the effect of sulfanegen sodium in juvenile pigs.\(^\text{[96]}\) Lethal injections of SNP were administered, after which either sulfanegen sodium antidote or placebo was given. In the treatment groups, the antidote normalized blood lactate levels and hemodynamic variables, while pigs receiving placebo decompensated and succumbed [Table 2]. Additional research is underway to determine whether this drug may successfully reverse cyanide toxicity in humans.

**Summary**

Over 150 years since its discovery and 40 years since its widespread adoption into clinical practice, SNP
remains a frequently-used vasodilator in the management of acute and severe systemic hypertension and additional applications (such as treatment of cerebral vasospasm) still in development. Due to its ubiquitous availability and widespread use, clinicians must be cognizant about its high potency and potential toxicities, while using this drug, including cyanide toxicity, altered blood flow distribution to and within organs, increased pulmonary shunting, and excessive hypotension. Caution dictates heightened vigilance for worsening confusion, drug tachyphylaxis, and metabolic acidosis with a base deficit — all indicating possible cyanide toxicity. Future antidotes appear to hold promise and may be available for cyanide toxicity; there are no current data about their human efficacy or safety. Therefore, practitioners must balance these factors, while recognizing alternatives that are newer, possibly safer, but usually more expensive. Future prospective, randomized controlled trials that directly compare nitroprusside with other potent vasodilators should facilitate better treatment guidelines. In addition, further research is necessary to develop better ways to detect, prevent, and reverse cyanide toxicity.

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How to cite this article: Hottinger DG, Beebe DS, Kozhimannil T, Prielipp RC, Belani KG. Sodium nitroprusside in 2014: A clinical concepts review. J Anaesthesiol Clin Pharmacol 2014;30:462-71.

Source of Support: Work related to the new cyanide antidote was supported by Grant NIH NINDS/5U01NS058087. Conflict of Interest: None declared.