

Review Article

Sodium Nitroprusside:

Pharmacology, Toxicology and Therapeutics

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THE ABILITY of sodium nitroprusside to lower blood pressure is reported to have been known to Claude Bernard.²⁴ The potential therapeutic merit of nitroprusside in the treatment of hypertension, particularly in crisis, was suggested first by Johnson in 1928⁴¹ and 1929.⁴² However, it was not until 1951-1955 that this potential was clinically realized, when Page^{64,65} described its extensive use in hypertensive emergencies, including encephalopathy. By 1959, nitroprusside was recognized as an effective, if last resort, drug for use in the management of malignant hypertension.²⁷ Remarkably, it was not until 1974 that an approved sterile preparation of this inexpensive chemical was made available commercially in the United States.

The potential toxicity of nitroprusside has been long suspected. Indeed, its chemical structure (fig. 1) should cause any informed observer to speculate that mammalian organisms ought to be capable of breaking this molecule apart, releasing cyanide. Speculation that CN⁻ is released *in vivo* dates to the observation in 1886 by Hermann²⁷ that "bitter almond," the characteristic odor of cyanide poisoning, could be detected in livers of animals after oral administration of nitroprusside.

Nitroprusside has recently come into widespread usage, not only for the treatment of severe hypertension,^{2,6,16,27,29,36,37} but for intraoperative induction of arterial hypotension

during surgery,^{20,19,74,77,81,83,86,91,94} for reduction of afterload by peripheral vasodilation after myocardial infarction, and during severe congestive failure.^{8,10,13,25,36,68} This increasing interest, coupled with developing knowledge of the toxicity of the drug, occasions the present review.

Hemodynamic Effects

Davidsohn,¹⁷ in 1887, reported that parenteral administration of nitroprusside produced a profound decrease in blood pressure in a cat. Charles Johnson first tried the drug in man in 1929, after an extensive series of animal experiments convinced him that the hypotensive effect could be achieved with doses lower than those that would liberate cyanide, and, further, that the efficacy of the drug was due to the nitroso (NO) group, not to a cyanide effect.^{41,42} Johnson believed nitroprusside had a "typical nitrite action," though 50 to 1,000 times more potent.⁴² He used the drug in three patients who had blood pressures (whether systolic, diastolic, or mean is not specified) of 144, 106, and 240 mm Hg, giving total doses "hypodermically" of 0.015, 0.02, and 0.05 mg, respectively. This resulted in 8, 10, and 136 mm Hg decreases in blood pressure, lasting 20, 6, and more than 120 minutes.⁴¹ He found no side effect, and suggested use of the drug for alleviation of severe hypertension.

Nitroprusside has been administered orally to man in the treatment of hypertension, with results indistinguishable from those of orally administered thiocyanate^{64,65,75} (to which some of the released cyanide is converted—see toxicology). Dogs with neurologic or renal hypertension did not respond to oral administration of the drug.²³

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That intravenous administration of nitroprusside causes immediate decreases in arterial pressure and total peripheral resistance is undisputed.^{10,20,21,26,42,43,58,65,73,75,82,93} Because there are no data at present to indicate any consistent effect of the drug on the autonomic or central nervous system, on uterine or duodenal smooth muscle, or on cardiac muscle, it is commonly stated that nitroprusside is a "direct" vasodilator.

In early studies by Schlant *et al.*⁷⁵ and in many subsequent studies^{10,20,21,26,42,58,73,75,82,93} of cardiovascular effects, nitroprusside given intravenously markedly lowered systemic arterial pressure and moderately lowered peripheral vascular resistance. Schlant *et al.*⁷⁵ administered the drug to 13 normotensive and 17 hypertensive patients. Cardiac index decreased in nine of the normotensive and 11 of the hypertensive patients. In the other ten patients, cardiac index increased. The average change for the entire group of 30 patients was a decrease of 10 per cent. This overall average decrease in cardiac index was thought due to arteriolar and venular dilation with subsequent peripheral pooling, rather than to a specific myocardial depressant effect.⁷⁵ Heart rate increased in most, but not all, patients, averaging 17 per cent; the change observed was considered secondary to the expected reflex response of heart rate to acutely lowered arterial pressure.⁷⁵ Similar findings (little or no change in cardiac index, decreased filling pressure, decreased peripheral resistance) have subsequently been reported by other investigators.^{1,6,8,10,20,29,31,36,43,58,68,71,73,75,82,93,92} There is agreement that dilation of peripheral resistance vessels plus dilation of peripheral capacitance vessels with pooling of blood and afterload reduction are together responsible for the decreased ventricular filling pressures and generally improved cardiac function observed in patients treated with nitroprusside after infarction^{10,25} and in patients with myocardial failure.³⁶

Rowe and Henderson⁷³ studied the systemic and coronary hemodynamic effects of nitroprusside in dogs. A dose of the drug that decreased mean arterial pressure only 8 per cent produced a 53 per cent increase in coronary blood flow and a 30 per cent in-

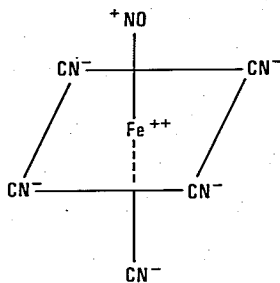


FIG. 1. Schematic of nitroprusside molecule.

crease in coronary sinus oxygen content. Cardiac output increased 30 per cent (17 per cent increase in heart rate and 8 per cent increase in stroke volume), indicating to the authors the occurrence of expected reflex compensation for the 26 per cent decrease in peripheral resistance observed. The increases in coronary blood flow and coronary sinus oxygen content were interpreted as evidence of improved myocardial perfusion and oxygenation.⁷³ Lactate, cyanide, and thiocyanate levels were not reported. An alternative or additional explanation for the increased coronary sinus oxygen content might be that it was secondary to a decrease in aerobic myocardial tissue respiration due to cyanide toxicity (see Toxicology).

The effects of nitroprusside on the lesser circulation in man are not so extensively documented. Chatterjee *et al.*,¹⁰ in a study of patients treated after myocardial infarction found significant reductions in mean pulmonary arterial pressures in all patient groups with an average decrease of 33 per cent in the group that had the greatest prior elevation of left ventricular filling pressure. Nitroprusside administered to nine patients by Pamley *et al.*⁶⁸ resulted in a significant reduction in mean right atrial pressure, which did not decrease further with external counterpulsation. Other studies also report that nitroprusside reduces pulmonary arterial pressure and right atrial pressure.^{36,68,91} The reduction in right atrial pressure is considered secondary to dilation of peripheral

capacitance vessels, whereas reduction of pulmonary arterial pressure is due to a direct dilation of pulmonary vasculature.^{36,68,91}

The renal effects of nitroprusside have been carefully examined. Page *et al.*⁶⁵ demonstrated a slight increase in para-aminohippurate (PAH) clearance (to 119 per cent of control) in normal dogs, a decrease to 95 per cent of control in hypertensive dogs, and variable effects on PAH and creatinine clearance in seven patients. Bastron and Kaloyanides⁵ reported that nitroprusside caused a marked increase in renal blood flow and natriuresis in the isolated perfused kidney, but in the intact animal a reduction in arterial pressure from 134 to 69 mm Hg resulted in expected pressure-related decreases in renal function, as measured by inulin and PAH clearances, and by sodium excretion. Kaneko *et al.*⁴⁴ demonstrated release of renin in response to nitroprusside-induced decreases in arterial pressure in normotensive and hypertensive patients, indicating decreased renal perfusion due to a decrease in perfusion pressure despite a presumed renal vasodilating effect.

The effects of clinical doses of nitroprusside on brain, liver, and other organs have not been examined thoroughly. As is emphasized below, increased cerebral venous P_{O_2} and increased brain lactate observed during and after nitroprusside-induced hypotension (using large doses), significantly in excess of those values obtained with other methods of inducing the same degree of hypotension, have been interpreted as evidence for cyanide toxicity.⁵⁴

Mechanism of Action

The mechanism of action of such a potent and effective peripheral vasodilator would be expected to have been the subject of considerable investigation. Johnson (1929)⁴² concluded that the nitroprusside molecule itself, not its metabolites, was responsible for the dilating effect of the drug, a conclusion in agreement with more recent evidence.^{65,67,68} As might also be expected, activation of adenylcyclase⁶⁴ and inhibition of phosphodiesterase⁵⁰ have been investigated as possible mechanisms. Rat aortic strips,

relaxed by isoproterenol, do show increased cyclic 3',5'-adenosine monophosphate (cAMP) levels,^{84,85} yet epinephrine, which contracts aortic strips, also increases cAMP levels.⁸⁴ However, even with large doses of nitroprusside, Triner *et al.*^{84,85} were able to demonstrate only slight increases in cAMP.

Needleman *et al.*⁶⁰ have recently shown that prior incubation of aortic strips with ethacrynic acid (known to alkylate sulfhydryl groups) abolishes the vascular relaxation produced by many "direct" vasodilators, including isoproterenol, papaverine, various nitrites and nitroprusside. They postulated that the receptor(s) involved with the vasodilating effect of these agents might act through a common intermediate vasodilator site, which somehow involves sulfhydryl (SH) groups bound in the vascular smooth muscle membrane. The common intermediary is not adenyl cyclase.⁶⁰ Nitroprusside is so effective an oxidizer of SH groups as to have been used as a laboratory reagent in the determination of glutathione.³⁵ Another effective SH oxidizer is cystamine, which is also a pronounced vasodilator.⁸⁸ The hypothesis, developed by Needleman *et al.*,⁶⁰ that the cellular mechanisms of action of such diverse vasodilators as nitroprusside, papaverine, theophylline, isoproterenol, acetaldehyde, and diamide involve different receptors at the outer membrane, but a common intermediate vasodilator site at which SH groups are functionally important, is shown diagrammatically in figure 2.

Metabolism and Toxicology

The nitroprusside molecule contains five cyanide groups (fig. 1). That cyanide (CN^-) is somehow released from the molecule and transformed at least in part into relatively nontoxic thiocyanate (SCN^-) is accepted. The transformation of cyanide into thiocyanate is mediated by a hepatic and renal enzyme system, rhodanase (often spelled rhodanese) a sulfuryl transferase capable of detoxifying cyanide into thiocyanate.^{46,57,76,78,89} The rhodanase enzyme system is apparently a mitochondrial enzyme system, thus located in close proximity to cytochrome oxidase.⁷⁶ The conversion of CN^- to thiocyanate proceeded

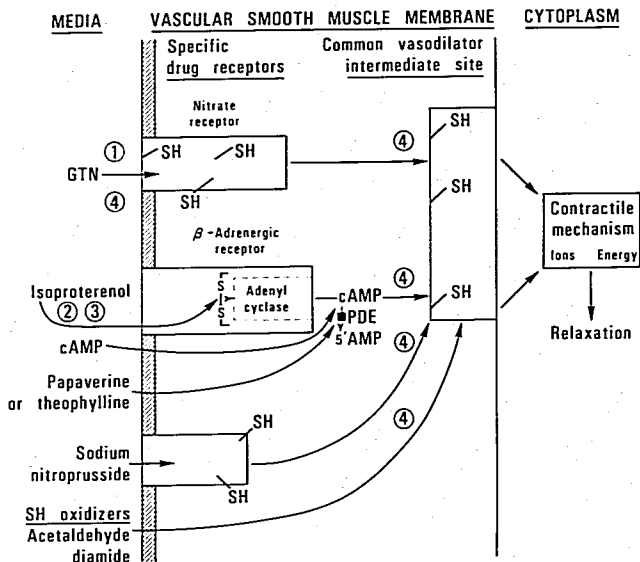


FIG. 2. Possible intracellular mechanisms of action for a wide variety of vasodilator compounds. Different receptors exist at the outer surface of the cell membrane, but all appear to act via a common intermediate vasodilator site, which involves sulfhydryl (-SH) groups. The numbers indicate the following: 1) the nitrite receptor, can be blocked by development of tolerance to glyceryltrinitrate (GTN); 2) blocked during isoproterenol tachyphylaxis; 3) blocked by propranolol; 4) blocked by ethacrynic acid. PDE = phosphodiesterase. Reproduced from Needleman *et al.*⁶⁸ with permission of the author and publisher.

relatively slowly unless exogenous sulfur is supplied, usually as thiosulfate.⁷⁶ Vitamin B₁₂ (cyanocobalamin) is reported to decrease as plasma cyanide concentration increases,⁸³ indicating that B₁₂ may be a rhodanase system cofactor. Endogenous thiosulfate is normally obtained from the amino acid cysteine by way of β -mercaptopyruvate⁸⁹ as an intermediary. Another enzyme, β -mercaptopyruvate sulfur transferase, has also been reported to be capable of converting cyanide to thiocyanate.²³ This enzyme occurs in erythrocytes, but activity in human erythrocytes is quite low, and it is doubtful that this pathway is of more than theoretical interest.⁸⁹

Although Johnson (1929)¹² was convinced that therapeutically effective doses of nitro-

prusside would not liberate cyanide, earlier workers had already suspected that CN⁻ could be released,^{4,15,17,24} based on detection of the odor of bitter almond and the development of signs in animals similar to those of poisoning with sodium or potassium cyanide. *In vitro*, cyanide liberation from nitroprusside has been shown when incubated with liver,²⁸ blood,⁷⁹ washed erythrocytes,^{79,80} plasma,[†] plasma-free hemoglobin solutions,⁷⁹ and urine.^{65,†} There are three recorded suicides with the drug,^{38,48} and in each case free cyanide was found in stomach contents. Mahaffey (1942)¹² found that guinea-

† Vesey CJ, Wilson J: In preparation (cit. Vesey *et al.*⁶⁵).

pigs succumbed to an average dose of 7.5 mg nitroprusside, whereas only 1.9 mg sodium cyanide proved fatal. Signs and symptoms of cyanide poisoning were delayed for 45-60 minutes after nitroprusside administration but only 5 minutes when sodium cyanide was given, but were otherwise quite similar.⁵²

Three deaths associated with the use of nitroprusside for induction of hypotension during surgery have been reported.^{18,40,53} Cyanide levels in blood and urine were high in the one patient tested, and inability to detoxify cyanide was thought to be causal.¹⁸ A companion paper reports two additional patients who, as was the case with the patient who died, required larger than usual doses of nitroprusside to maintain desired hypotension for surgery.¹⁹ Both patients developed pronounced base deficits, indicative of increased anaerobic metabolism, and elevations of mixed venous blood P_{O_2} 's. This was accompanied in one patient by measurable free blood CN^- levels.¹⁹

Thus, it is known that CN^- can be released from nitroprusside, that some patients require larger than usual doses of the drug, and that these patients are at greatest risk of cyanide toxicity, even if the drug is administered for only short periods. Why such "resistance" is sometimes encountered remains unknown.

The mechanism whereby CN^- is liberated from nitroprusside has been explored. Early evidence indicated that nitroprusside reacted non-enzymatically with various free sulfhydryl groups.^{65,67} The most likely source of these in blood should be glutathione,⁷⁹ yet a dose of methyl-iodide that decreased hepatic and blood glutathione levels by 40 per cent had no effect on rat mortality after nitroprusside,⁷⁹ indicating that cyanide liberation *in vivo* is not dependent upon this mechanism.⁷⁹ Extensive kinetic studies also indicate that the reaction of nitroprusside with SH groups is too slow to account for the breakdown of the drug *in vivo*. The metabolism of nitroprusside by the hepatic microsomal mixed-function oxidase system is apparently insignificant, because animal mortality after nitroprusside is unaltered by either

enzyme induction produced with phenobarbital pretreatment or enzyme inhibition produced with SKF 525A pretreatment.⁷⁹

More recent evidence indicates^{79,80} that nitroprusside can be rapidly broken down by free and intracellular hemoglobin by a non-enzymatic reaction that proceeds more rapidly than the reaction between nitroprusside and sulfhydryl groups. These data suggest the following sequence: first an electron is transferred without enzyme catalysis from hemoglobin iron (Fe^{++} to Fe^{+++}) to nitroprusside, yielding methemoglobin and an unstable nitroprusside radical. The latter quickly breaks down, releasing all five cyanide ions, one of which reacts with the methemoglobin to form cyanmethemoglobin.⁷⁹ This leaves four free cyanide ions, some of which are converted to thiocyanate in the liver and kidneys by rhodanase. Largely ignored in many studies concerned with nitroprusside is the likelihood that the liberated cyanide that is not rapidly detoxified in liver or kidney will cause biochemical abnormalities (*i.e.*, inactivation of cytochrome oxidase), which in sufficient degree will be manifested as cyanide poisoning. Figure 3 is a schematic summary of the present concepts of the metabolic fate of nitroprusside, including the likelihood of tissue toxicity of some of the released cyanide.

The cyanide eventually converted to thiocyanate is still not completely detoxified. Thiocyanate has been used as an antihypertensive drug^{82,83} but abandoned due to side effects such as miosis, toxic psychosis, hyperreflexia, and convulsions. The half-life of thiocyanate is relatively long (about a week), and it is excreted largely unchanged,⁷⁸ although some of the CN^- seems to be utilized from the single-carbon pool for protein synthesis.⁷⁹ Oxyhemoglobin can slowly oxidize thiocyanate back to sulfate and CN^- , with hemoglobin converting to methemoglobin and then to cyanmethemoglobin.^{12,20} That methemoglobin does not protect against thiocyanate toxicity⁷⁸ indicates that thiocyanate toxicity, a neurotoxic syndrome, is not due to the conversion of thiocyanate back to cyanide.

Davies *et al.*,¹⁸ in 1975, reported a case in which nitroprusside was used to induce hypo-

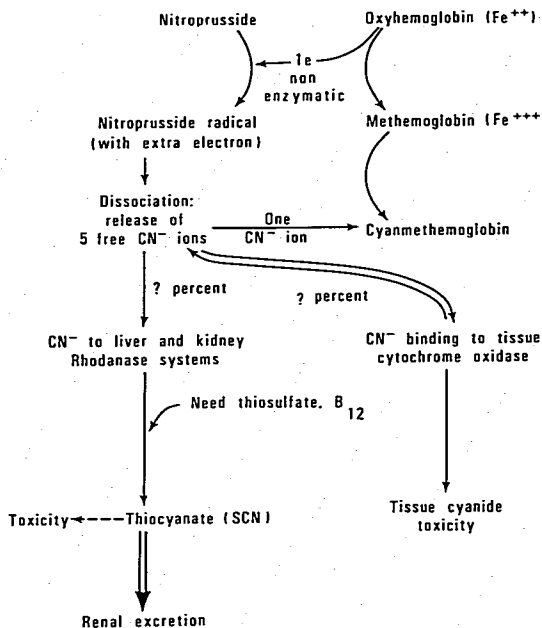


FIG. 3. Schematic representation of the current concept of nitroprusside breakdown releasing cyanide, with cyanide taking three paths: 1) reacting with methemoglobin; 2) reacting with tissue cytochrome oxidase (cyanide toxicity); 3) converted by rhodanase into thiocyanate for excretion. Adapted in part from Smith and Kruszyna⁷⁹ and Vesey *et al.*⁸⁰

tension in a 14-year-old boy who underwent bilateral mandibular osteotomies under halothane-nitrous oxide anesthesia. The patient received approximately 400 mg (10 mg/kg) nitroprusside to maintain hypotension at a level of 70 mm Hg for approximately 80 minutes. The patient required this large dose from the beginning; tachyphylaxis was not involved. Upon discontinuation of nitroprusside, arterial blood pressure rose to 75 mm Hg (mean), but then fell slowly over 30 minutes to 50 mm Hg, followed by bradycardia, severe acidosis, and death. Blood cyanide content at autopsy was 0.5 mg/100 ml, which is within the known toxic range. No thiocyanate could be detected in blood or urine. The authors concluded that this death was due to cyanide poisoning. They urged that the administration of nitroprusside be

predicated not on requirements to maintain some desired blood pressure, but on the total dosage projected to be needed based upon the earliest possible assessment of patient requirement and surgical time.^{18,19} In animals, Smith and Kruszyna⁷⁹ showed that nitrite and thiosulfate, the usual treatment for cyanide poisoning, produced significant protection against otherwise lethal doses of nitroprusside. They tested various tissues (including liver and kidney), but found blood to be by far the most active in breakdown of nitroprusside.⁷⁹ They produced methemoglobin *in vitro* with potassium ferricyanide, added sodium cyanide, and compared the absorption spectrum (cyanmethemoglobin) thus produced with that of a mixture *in vitro* of oxyhemoglobin and nitroprusside after incubation. The latter reaction

required considerably longer (approximately 30 minutes), but the final spectrum was indistinguishable from the cyanmethemoglobin produced in the usual fashion.⁷⁹ Thus, it appears that nitroprusside releases free cyanide into blood following reaction with hemoglobin, and that the oft-stated breakdown of the drug by blood glutathione or tissue sulfhydryl groups is so much slower as to be of unlikely significance *in vivo* (see fig. 3).

Recent physiologic studies have attempted to quantitate cyanide effects related to nitroprusside administration. McDowall *et al.*,⁵⁴ in 1974, studied eight baboons given whatever dose of nitroprusside was necessary to lower arterial pressure to 40 mm Hg for two hours. Half the baboons died, and this group had required four to six times more nitroprusside to achieve the same arterial pressure than the animals that recovered. The circulatory collapse that occurred in the high-dose group was related to severe systemic metabolic acidosis, indicative of decreased oxygen utilization and resulting anaerobic metabolism. Decreased cerebral oxygen utilization was reflected by increased cerebral venous oxygen content in the large-dose group.

Recent canine studies by Michenfelder (in preparation) were carried out for one hour at pressures of 40 mm Hg, using whatever nitroprusside dose each animal required to maintain that pressure, and comparing the effects of nitroprusside-induced hypotension with those of equal hypotension induced with halothane, hypovolemia, or trimethaphan. Again, two distinct groups with respect to nitroprusside emerged: a normally responsive group, and a resistant group requiring much more drug. In the high-dose (resistant) group, elevated cerebral venous oxygen content, severe metabolic acidosis, elevated brain lactate levels, elevated lactate/pyruvate ratios, and reduced brain energy stores were observed, indicating severe interference with oxygen utilization and secondary anaerobic metabolism. Although 3–3.5 mg/kg was reported by Davies *et al.*^{18,19} to be a dose of nitroprusside that should not be exceeded during intraoperative induced hypotension in man, the changes in dogs observed by Michen-

felder occurred with doses exceeding 1 mg/kg. More direct evidence that cyanide toxicity is responsible for the above-described toxicity emerged from this study. When hemoglobin withdrawn previously from each animal was converted *in vitro* to methemoglobin by sodium nitrite and then reinfused, the animals were protected when similar high doses of nitroprusside were then given. Further, in these protected animals, blood cyanide measurements (captured as cyanmethemoglobin) revealed concentrations equivalent to 35–60 per cent of the total cyanide administered as nitroprusside (Michenfelder, in preparation).

Analysis for blood cyanide is possible^{3,7,83} but frequently not available. Vesey *et al.* studied plasma cyanide levels associated with nitroprusside administration during surgery and found elevations to as much as four times control values. Thiocyanate levels remained unchanged, as would be expected after administration of nitroprusside for only short periods. Chronic administration of the drug, on the other hand, has resulted in early elevation of plasma cyanide with later increases in thiocyanate level measured in two cases.⁸⁹ Measurement of blood cyanide levels alone might not be expected to detect evidence of significant cyanide toxicity (in the absence of significant methemoglobinemia), since much of the freed cyanide would be expected to bind quickly to tissue cytochrome oxidase.

The cobalamin group of compounds has also been suggested as an effective means of detoxifying cyanide. Hydroxocobalamin has been evaluated in animals^{26,32,69} and in man and considered to be an effective cyanide antidote, apparently via conversion to cyanocobalamin. Large doses of hydroxocobalamin (no specific amount stated) prior to and during infusion of nitroprusside have been recommended by Vesey *et al.*⁸⁹

The phenomenon of resistance to nitroprusside, defined by Davies *et al.*^{18,19} as a requirement for more than a total acetate administered dose of 3–3.5 mg/kg, is poorly understood. It may be related to an abnormality in the cyanide–thiocyanate pathway.¹⁹ For example, patients who have Leber

optic atrophy or tobacco amblyopia are known to have high cyanide and low thiocyanate blood levels,³² indicating that this pathway is capable of disturbance in man. These diseases may be contraindications to nitroprusside.^{19,67}

Considerable importance has been attached to the measurement of thiocyanate blood levels during therapy with nitroprusside as an indication of developing toxicity.^{28,63,67} The more recent evidence cited above, however, indicates that early detection of increased anaerobic metabolism (base deficit, elevated blood lactate, and elevated lactate/pyruvate ratios) or elevation of mixed venous blood oxygen content would more accurately reflect the onset and severity of cyanide toxicity. Measurement of blood cyanide levels may be of limited value because cyanide released may rapidly bind to tissue cytochrome oxidase in the absence of significant methemoglobinemia.

It should be re-emphasized that nitroprusside should not be administered on the basis of blood pressure levels alone, but rather on the basis of total dose. The maximal dose of 3–3.5 mg/kg recommended by Davies *et al.*^{18,19} may prove too high, but at present it is the only recommendation for man that has been published. No investigator has yet recommended a maximum total dose per 24-hour period for patients receiving long-term therapy with nitroprusside. Shubert and Brill⁷⁶ measured percentage inhibition of hepatic cytochrome oxidase by potassium cyanide administered intraperitoneally in mice and rats. Their data indicate that times to full recovery of function of cytochrome oxidase after binding by cyanide range from half an hour in the mouse to an hour in the rat. This suggests that, at least in these laboratory animals, normal cytochrome oxidase activity is restored in a relatively short period, presumably by the nearby intramitochondrial rhodanase system.⁷⁶ However, the fact that the times to recovery varied by 100 per cent in the two animal species studied indicates the existence of considerable species variation. There are no data concerning the kinetics of binding of cyanide to human cytochrome oxidase *in vivo*.

Further, there are no meaningful data concerning the cumulative effects of nitroprusside when given over a period of several days.

Therapeutic Indications

HYPERTENSION

By 1961, nitroprusside was listed among other standard remedies for hypertensive emergencies.^{27,28} The drug is generally reserved for use when other less potentially dangerous antihypertensive drugs have failed.^{2,6,16,27,28,33,46,47} Studies of combinations of nitroprusside with hydralazine,⁶⁵ ganglionic blockers such as tetraethylammonium chloride (TEAC),⁶⁵ and trimethaphan⁶ reveal additive effects only. The ability of nitroprusside to lower blood pressure rapidly in patients who have hypertension has been employed in studies of such patients' abilities to liberate renin,⁴⁴ making nitroprusside potentially useful as a diagnostic tool in "essential" hypertension.

USE OF NITROPRUSSIDE DURING ANESTHESIA

Although nitroprusside has not been officially approved in the United States for uses other than management of hypertension, it has been used for induction of hypotension during anesthesia since 1966.⁷⁴ There is general agreement that nitroprusside provides two distinct advantages over other methods of inducing hypotension for surgery: a very rapid return to control values following discontinuation, and little tachyphylaxis.^{8,21,23,33,38,74,77,82,91,94} The indications for and the physiology of deliberate intraoperative hypotension are beyond the scope of this review; however, nitroprusside is now considered by many to be the agent of first choice in this usage.

The observation that nitroprusside is altogether devoid of tachyphylaxis has, however, recently been modified by the demonstration that some patients^{18,19,21} and animals⁵⁴ are "resistant" to the drug, requiring much larger than usual doses initially, with continually increasing needs to maintain a given arterial pressure. The "sensitive" patients (the large

majority) can sometimes be shown to require slightly more drug per minute as time passes, but there is no evidence that tachyphylaxis with nitroprusside occurs to the extent seen with trimethaphan.⁴⁸⁻⁵¹ Patients who are hypovolemic and/or dehydrated are often quite sensitive to the agent, and judicious infusion of Ringer's lactate solution may be necessary to smooth the "peaks and valleys" of blood pressure during nitroprusside administration. §

Upon discontinuation of nitroprusside, blood pressure usually rises within several minutes to control levels.^{1, 74, 91} The administration of pressors should seldom, if ever, be necessary to increase arterial pressure after nitroprusside. Delay in return of pressure to preinfusion levels may reflect cyanide toxicity^{18, 19} or relative hypovolemia. § Theoretically, an alpha-adrenergic-stimulating agent (e.g., phenylephrine, methoxamine, metaraminol) would best counter the known resistance-vessel effects of nitroprusside, although the vasoconstrictive effect of dopamine might also be desirable. In general, however, the need for therapeutic reversal of nitroprusside-induced hypotension has not been a clinical problem except where toxicity has occurred.^{18, 19}

Other than the remote possibility of allergy, there is no known specific contraindication to the use of nitroprusside in patients for whom controlled hypotension is considered indicated. Should the initial dosage requirement be such that the total dose is likely to exceed 3-3.5 mg/kg, Davies *et al.*^{18, 19} recommend cessation of nitroprusside and use of alternative methods of inducing hypotension. The dangers of intraoperative nitroprusside use include all those of induced hypotension itself, in addition to the possibility of cyanide poisoning when large doses are given. There is one case report⁶¹ of hypothyroidism following prolonged use of the drug.

Griffiths *et al.*²³ reported no significant decrease in cerebral blood flow, or change in jugular venous blood oxygen tension, in 20 patients during cerebral-aneurysm surgery,

at a time when arterial pressure had been reduced an average 42 per cent by nitroprusside. Ivankovich *et al.*²⁹ have recently demonstrated that nitroprusside is a direct cerebral vasodilator in the goat. Siegel *et al.*⁷⁷ considered the agent safe and effective during operations on patients with intracranial aneurysms, on the basis that there was no increase in morbidity or mortality compared with results obtained when other methods of inducing hypotension for this type of surgery were employed.

Other intraoperative uses of nitroprusside are relatively anecdotal. During surgery for coarctation of the aorta and abdominal aortic aneurysm, arterial hypertension may be severe proximal to the clamp when the aorta is occluded. We have found nitroprusside to be useful in reducing this hypertension. Hypertension during cardiopulmonary bypass can also be controlled with nitroprusside; increased acidosis has not been reported. Nitroprusside has been used during resection of a "phentolamine-resistant" pheochromocytoma²² (in the usual case, specific alpha blockade would seem more logical).

There is a clinical impression that the dosage requirement for nitroprusside is altered inversely by the concentration of volatile anesthetic administered. § No studies to document this have been reported. There is no known specific interaction between nitroprusside and any anesthetic agent, although the peripheral arteriolar and venous dilation caused by nitroprusside would be expected to combine additively with the myocardial depression and peripheral vasodilation observed with many of the volatile anesthetics. It is generally agreed that nitroprusside does not cause myocardial depression *per se* (see Hemodynamic Effects).

At present, anti-cyanide measures are not routine during nitroprusside administration in most institutions. Davies *et al.*^{18, 19} suggest that gradually appearing tachyphylaxis in a previously sensitive patient be treated in the operating room with sodium thiosulfate, 150 mg/kg, infused over 15 minutes. If cyanide toxicity is suspected because of persistent hypotension after cessation of the drug, and/or development of metabolic acidosis, sodium nitrite, 5 mg/kg, in a 20 ml

§ Messick JM, Gronert GA (Department of Anesthesiology, Mayo Clinic): Personal communication.

volume over 3-4 minutes, or amyl nitrite inhaled for 30 seconds, followed by the above-mentioned dose of thiosulfate, is the recommended treatment.^{18,19} Hydroxocobalamin is under investigation as a possible cyanide antidote. Success in reversal of cyanide poisoning with this compound has been achieved in the guinea pig.⁶⁹ Human toxicology and pharmacology of this promising antidote are largely unexplored at present; however, the drug appears to react with cyanide to produce cyanocobalamin (vitamin B₁₂). Vesey *et al.*⁸⁰ suggest that either hydroxocobalamin or chlorocobalamin be given concurrently during administration of nitroprusside. Dosage is not known, but would be expected to correlate with possible maximum cyanide released from the projected dose of nitroprusside. We are not aware of any human trial of this treatment.

Monitoring of patients given nitroprusside for deliberate hypotension should include frequent arterial blood-gas and acid-base determinations. The development of significant metabolic acidosis, especially in conjunction with increasing drug requirements, should signal the need for cessation of the drug and administration of thiosulfate alone or, in severe cases, in combination with sodium nitrite.

USE OF NITROPRUSSIDE IN HEART DISEASE

Franciosa *et al.*²⁵ reported in 1972 the use of nitroprusside to reduce left ventricular filling pressure and decrease afterload in acute myocardial infarction. In the 15 patients, hemodynamic changes after nitroprusside were characterized by decreases of previously elevated left ventricular filling pressures by an average of 50 per cent, with only a 15 per cent average reduction in arterial pressures. Doses given to some patients could be titrated to a point at which arterial pressure remained unaffected while left ventricular filling pressure fell significantly. Cardiac output increased in all but three patients, a finding interpreted by the authors as evidence of improved cardiac function secondary to reduction in afterload.²⁵ Grossman *et al.*³¹ recently reported similar improvement in a patient who had severe mitral regurgitation.

Chatterjee *et al.*¹⁰ studied vasodilator therapy with nitroprusside in 38 patients who had acute myocardial infarction. Their report confirms the above-described beneficial hemodynamic effects, as do several other recent reports.^{8,26,28,68} The study by Chatterjee *et al.*¹⁰ included coronary sinus catheterization before and shortly after starting the nitroprusside. During the short period (exact length not reported) of administration of the drug before sampling, myocardial oxygen consumption tended to decrease, achieving statistical significance in the patients who had had the most severe myocardial dysfunction.¹⁰ Decreased myocardial oxygen consumption observed within a short period after infusion of nitroprusside is reasonable evidence of a beneficial effect due to decreased afterload and filling pressure, as interpreted by the authors.¹⁰ However, after several days of nitroprusside administration one must consider the possibility of a trade-off between reduction in ventricular filling pressure and afterload (and therefore myocardial oxygen requirements) and the possibility of interference with myocardial oxygen utilization by cyanide toxicity. Increased coronary sinus oxygen content would be expected with either or both of these effects, and evidence of increasing myocardial anaerobic metabolism would be needed to separate toxic from therapeutic effects.

The only evidence to date that such a trade-off may be clinically important is found in two anecdotal reports. One indicated that an "angina-like" syndrome was produced in a child during treatment with an unspecified amount of nitroprusside.⁶⁷ The other described a 48-year-old man who had had no prior evidence of cardiac difficulty in whom severe anginal pain became a problem during treatment of a hypertensive crisis with nitroprusside.²⁴

Because the question of cardiac cyanide toxicity has not been answered, we temper our enthusiasm for nitroprusside therapy in the treatment of myocardial failure and ischemia, especially if treatment must last several days. The widespread acceptance of use of the agent in this manner, before adequate documentation of animal or human myocardial toxicology has been obtained,

seems premature. The acidotic, obtunded, gravely ill patient treated for several days with nitroprusside for cardiogenic shock following myocardial infarction, for example, may be dying of cardiogenic shock, but the contribution of cyanide poisoning to that shock is a sobering possibility.

OTHER USES

Dissecting aortic aneurysms are theoretically amenable to vasodilator therapy because depression of the initial ventricular impulse results in reduction of forces impinging on the aortic wall.⁶⁶ Six cases in which treatment with reserpine and trimethaphan without surgery was successful were reported in 1965 by Palmer *et al.*,⁶⁶ and a more recent series in which nitroprusside was used has been reported by Wheat and Palmer.⁹⁰

One case of severe peripheral ischemia of all four extremities due to an overdose of ergotamine tartrate is reported to have been quickly resolved by nitroprusside infusion after failure of standard supportive therapy.⁹ Because of little agreement on the method for treating this condition, this recent report is encouraging.

We are unaware of any report of treatment of any other peripheral vascular ischemic disease with nitroprusside. Perhaps direct vasodilation with nitroprusside would be useful in management of diabetic peripheral small-vessel ischemic problems, or in peripheral arterial embolization followed by vasospasm. Similarly, a trial of nitroprusside during the 24–48-hour period following peripheral vascular operations such as femoral–popliteal bypass grafting might prove beneficial.

Cerebral vasospasm refractory to all present treatment following operations for cerebral aneurysm is a perplexing and disastrous complication. There is no report at present on the use of nitroprusside in this desperate situation, but when spasm proves refractory, a trial might be warranted. Ivankovich *et al.*²⁹ report that nitroprusside infused into the cerebral arterial circulation in goats in amounts too small to lower arterial pressure resulted in 31 per cent

sustained increases in cerebral blood flow, supporting such a trial in human cerebral vasospasm.

Dosage and Administration

Nitroprusside is commercially available,[†] and should be used quickly after dilution as recommended by the manufacturer. The infusion container and all tubing must be kept from light, as breakdown of nitroprusside in light is rapid. The nitroprusside ion reacts with minute quantities of many organic and inorganic substances, forming products that are often highly colored (blue, green or dark red). Breakdown of the drug to cyanide with light in the infusion apparatus is not a problem.

Palmer and Lassiter⁶⁷ recommend that the initial infusion for intraoperative use be started at 0.5–1.5 $\mu\text{g}/\text{kg}/\text{min}$. Davies *et al.*,^{18,19} urge that this initial flow rate be quickly titrated to achieve desired arterial pressure, and then the total dose projected by using the surgeon's estimated time for requiring the hypotension and the initial dose rate. A projected requirement of more than a total dose of 3–3.5 mg/kg is considered by these authors to be an indication for immediate cessation of nitroprusside and production of the desired controlled hypotension by other means. Recent studies in dogs by Michenfelder (in preparation) indicate that the maximum safe dose per four-hour period may be as little as 1 mg/kg.

Because little is known about tissue accumulation of cyanide during nitroprusside administration in man, it is not possible to estimate a maximum safe dose that could be repeated every 24 hours in a patient receiving prolonged infusion of the drug. Blood thiocyanate and cyanide levels are probably not very useful indications of the development of toxicity. It is recommended instead, that biochemical evidence of progressive anaerobic metabolism, namely, base deficit, elevated lactate level, elevated lactate/pyruvate ratio, and elevated mixed venous blood oxygen content, be relied upon as evidence of developing toxicity during chronic infusions of nitroprusside.

† Nipride, Roche.

Summary

Sodium nitroprusside is a potent, effective, and readily reversible direct vasodilating agent. It is broken down by hemoglobin into cyanide, which is in part detoxified by liver and kidney to thiocyanate. Some cyanide, especially in nitroprusside-"resistant" individuals who need large amounts of the drug, appears to remain free to cause cyanide poisoning. Patients requiring inordinate amounts probably should not continue to receive the drug, although maximum dosage limits for long-term therapy are not established. Blood thiocyanate levels do not indicate the extent to which free cyanide is limiting oxygen utilization in essential tissue, nor do blood cyanide levels. Metabolic acidosis, elevated lactate levels, elevated lactate/pyruvate ratios, and elevated mixed venous blood oxygen content are at present the best indications of the presence of cyanide poisoning during nitroprusside administration.

Nitroprusside appears useful for induction of hypotension during surgery, and for treatment of hypertensive emergencies from all causes, although continuance for more than a few days is probably unwise. The reductions of cardiac afterload and ventricular filling pressure by nitroprusside appear useful in treatment of severe myocardial failure or infarction, but studies of myocardial cyanide toxicity are needed before complete acceptance of this therapy is warranted. Initial dose rates between 0.5 and 1.5 $\mu\text{g}/\text{kg}/\text{min}$ are recommended only as starting points for very careful titration. Total projected intraoperative dosage should be calculated as quickly as possible and should not exceed 3-3.5 mg/kg. It is hoped that future studies will reveal the maximum dose of nitroprusside that can safely be metabolized in a 24-hour period, and may indicate that cofactors of rhodanase such as thiosulfate, or cobalamins such as hydroxocobalamin, can be administered with nitroprusside to prevent cyanide poisoning.

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Research

EVALUATION OF RESEARCH SUPPORT

Recent governmental policy has strongly supported so-called "targeted" research. An example of the background for such policy is a recent Department of Defense report (Project Hindsight), which concluded that "the contributions of university research were minimal. Scientists contributed most effectively when their effort was mission-oriented." The authors question whether "objective, scientific techniques . . . can be used to design and justify a national biomedical research policy." Because they had expertise in the area of cardiovascular and pulmonary disease, and because these diseases are responsible for more than 50 per cent of annual deaths in the United States, they selected this field for detailed examination. Forty physicians were asked to suggest advances made since the 1940's which they considered to be most important for their patients. The authors then identified essential basic knowledge that had to be attained before such clinical advances could

be accomplished. The literature was reviewed extensively in order to determine whether significant research was basic or not. More than 4,000 scientific articles were screened, 2,500 selected for further evaluation, and 525 finally judged essential. Of the latter articles, 62 per cent described basic research, while 41 per cent were "not clinically oriented." An example of such investigation (prior to the 1940's) is the fact that Roentgen was studying "a basic problem in the physics of rays emitted from a Crookes' tube" when he discovered x-irradiation. It is concluded that a scientific rather than anecdotal approach indicates "basic research . . . pay-off in terms of key discoveries almost twice as handsomely as other types of research and development combined." It is therefore necessary that generous support be granted for basic research done for the sake of knowledge rather than for any obvious immediate goals. (Comroe JH, Dripps RD: *Scientific basis for the support of biomedical science. Science* 192: 105-111, 1976.)