

# PRODUCT MONOGRAPH

<sup>Pr</sup> **Nipride®**  
**(Sodium Nitroprusside for Injection, USP)**

**(50 mg/vial)**

**THERAPEUTIC CLASSIFICATION**  
**Antihypertensive Agent**

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### THERAPEUTIC CLASSIFICATION

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### ACTIONS AND CLINICAL PHARMACOLOGY

Nipride® (sodium nitroprusside) is a potent, rapid-acting, intravenous antihypertensive agent. The antihypertensive action of Nipride® is probably due to the nitroso (NO) group. Its effect is almost immediate and usually ends when the IV infusion is stopped. The brief duration of the drug's action is due to its rapid biotransformation. The hypotensive effect is augmented by ganglionic blocking agents. The hypotensive effects of Nipride® are caused by peripheral vasodilation as a result of a direct action on the blood vessels, independent of autonomic innervation. No relaxation is seen in the smooth muscle of the uterus or duodenum *in situ* in animals.

Sodium nitroprusside administered intravenously to hypertensive and normotensive patients produced a marked lowering of the arterial blood pressure, a slight increase in heart rate, a mild decrease in cardiac output and a moderate diminution in calculated total peripheral vascular resistance.

The decrease in calculated total peripheral vascular resistance suggests arteriolar vasodilation. The decreases in cardiac and stroke index noted may be due to the peripheral vascular pooling of blood.

## INDICATIONS AND CLINICAL USES

Nipride® (sodium nitroprusside) is indicated for the treatment of acute hypertension, refractory to standard therapeutic measures.

Nipride® is also indicated for producing controlled hypotension during anesthesia in order to reduce bleeding in surgical procedures, where surgeon and anesthesiologist deem it appropriate. In each case, the benefit-risk ratio should be carefully considered on an individual basis.

## CONTRAINDICATIONS

Nipride® (sodium nitroprusside) should not be used in the treatment of compensatory hypertension (e.g., arteriovenous shunt or coarctation of the aorta). It is also contraindicated in physically poor-risk patients (A.S.A. Risk 5), in patients with uncorrected anemia or hypovolemia, or in those with known inadequate cerebral circulation.

Controlled hypotension during anaesthesia induced by sodium nitroprusside is contraindicated in patients with liver disease, severe renal disease, Leber's optic atrophy, tobacco amblyopia and disease states associated with vitamin B<sub>12</sub> deficiency.

## WARNINGS

**NIPRIDE® (SODIUM NITROPRUSSIDE) IS ONLY TO BE USED AS AN INFUSION WITH STERILE 5% DEXTROSE IN WATER. NOT FOR DIRECT INJECTION.**

**NIPRIDE® CAN CAUSE PRECIPITOUS DECREASES IN BLOOD PRESSURE. IN PATIENTS NOT PROPERLY MONITORED, THESE DECREASES CAN LEAD TO IRREVERSIBLE ISCHEMIC INJURIES OR DEATH. NIPRIDE® SHOULD BE USED ONLY WHEN AVAILABLE EQUIPMENT AND PERSONNEL ALLOW BLOOD**

**PRESSURE TO BE CONTINUOUSLY MONITORED.**

**EXCEPT WHEN USED BRIEFLY OR AT LOW (< 2 µg/kg/min) INFUSION RATES, SODIUM NITROPRUSSIDE FOR INJECTION GIVES RISE TO IMPORTANT QUANTITIES OF CYANIDE ION, WHICH CAN REACH TOXIC, POTENTIALLY LETHAL LEVELS. THE USUAL DOSE RATE IS 0.5 TO 8 µg/kg/min, BUT INFUSION AT THE UPPER DOSE RATE SHOULD NEVER LAST MORE THAN 10 MINUTES. IF BLOOD PRESSURE HAS NOT BEEN ADEQUATELY CONTROLLED AFTER 10 MINUTES OF INFUSION AT 8 µg/kg/min, ADMINISTRATION OF NIPRIDE® SHOULD BE TERMINATED IMMEDIATELY. INFUSION RATES GREATER THAN 8 µg/kg/min ARE VIRTUALLY NEVER REQUIRED.**

**ALTHOUGH ACID-BASE BALANCE AND VENOUS OXYGEN CONCENTRATION SHOULD BE MONITORED AND MAY INDICATE CYANIDE TOXICITY, THESE LABORATORY TESTS PROVIDE IMPERFECT GUIDANCE.**

**FATALITIES DUE TO CYANIDE POISONING HAVE OCCURRED FOLLOWING SODIUM NITROPRUSSIDE ADMINISTRATION. ONE FACTOR IS COMMON TO ALL KNOWN CASES, NAMELY THAT LARGE AMOUNTS OF NITROPRUSSIDE WERE INFUSED AT HIGH RATES. SINCE DETOXIFICATION RELIES UPON ENZYMATIC ACTION, THE RARE POSSIBILITY OF DEFICIENT OR ATYPICAL ENZYMES OCCURRING IN HUMANS SHOULD ALWAYS BE CONSIDERED. PATIENTS MOST APT TO RUN INTO DIFFICULTY ARE THOSE WHO ARE RESISTANT TO THE HYPOTENSIVE EFFECT OR THOSE IN WHOM MAINTENANCE AT THE SELECTED BLOOD PRESSURE LEVEL IS DIFFICULT OR IMPOSSIBLE.**

**CONSTANT ATTENTION TO THE PATIENT'S DOSE-RESPONSE CHARACTERISTICS IS MANDATORY. IF INFUSION RATES ARE IN EXCESS OF 8 µg/kg/min DETERMINE THE NATURE OF THE RESPONSE (EFFECTIVE CONSTANT RESPONSE AT HIGHER DOSE; TACHYPHYLACTIC; RESISTANT - NONE OR LESS THAN THE EXPECTED).**

**AS SOON AS EITHER TACHYPHYLAXIS OR RESISTANCE IS DETERMINED, THE INFUSION OF NIPRIDE® SHOULD BE DISCONTINUED IMMEDIATELY. IN ABNORMAL RESPONDERS, ACID-BASE BALANCE SHOULD BE MONITORED SINCE METABOLIC ACIDOSIS IS EVIDENCE OF CYANIDE TOXICITY.**

Sodium nitroprusside infusions at rates above 2 µg/kg/min generate cyanide ion (CN<sup>-</sup>) faster than the body can normally dispose of it. When sodium thiosulfate is given, the body's capacity for CN<sup>-</sup> elimination is greatly increased. Methemoglobin, normally present in the body, can buffer a certain amount of CN<sup>-</sup> but the capacity of this system is exhausted by the CN<sup>-</sup> produced from about 500 µg/kg of sodium nitroprusside (see **PHARMACOLOGY**). This amount of sodium nitroprusside is administered in approximately one hour when the drug is administered at 8 µg/kg/min.

Nipride® is metabolized to cyanide and then to thiocyanate which in turn is excreted by the kidney (see **PHARMACOLOGY**). If excessive amounts of Nipride® are used, thiocyanate toxicity (e.g., tinnitus, blurred vision (miosis), delirium hyperreflexia) may occur. Estimating the thiocyanate blood levels, will help to determine thiocyanate toxicity but may not reflect cyanide toxicity. Thiocyanate is mildly neurotoxic at serum levels of 60 mg/L (1 mmol/L). Thiocyanate toxicity is life-threatening when levels are three or four times higher (200 mg/L).

Since thiocyanate inhibits both the uptake and binding of iodine, caution should be exercised in using Nipride® in patients with hypothyroidism and patients with severe renal impairment.

Blood levels of thiocyanate should be determined if treatment is to be extended. This monitoring is critical in patients with severe renal dysfunction. Although intravenous infusions of Nipride® are not intended for long-term use, as long as blood thiocyanate levels are measured daily and do not exceed 10 mg percent (100 mg/L), it is probably safe to continue with the infusion until the patient can be safely treated with oral antihypertensive medications. Peritoneal dialysis can be helpful if too high levels of thiocyanate are found.

Hypertensive patients are more sensitive to the intravenous effect of sodium nitroprusside than are normotensive subjects. Patients who are also receiving concomitant antihypertensive medications (specifically, hydralazine or hexamethonium) are more sensitive to the hypotensive effect of sodium nitroprusside, and the dosage of Nipride® should be adjusted downward accordingly.

Signs of cerebral underperfusion, such as confusion and somnolence, may occur if blood pressure is reduced too rapidly, especially in hypertensive patients with encephalopathy.

There is marked variation in individual sensitivity to the antihypertensive action of sodium nitroprusside.

The following warnings apply to the use of Nipride® for controlled hypotension during anaesthesia:

1. Extreme caution should be exercised in patients who are especially poor surgical risks (A.S.A class 4 and 4E).
2. Tolerance to blood loss, anemia and hypovolemia may be diminished. If possible, pre-existing anemia and hypovolemia should be corrected prior to employing controlled hypotension.
3. Hypotensive anaesthetic techniques may alter pulmonary ventilation perfusion ratio. Patients intolerant of additional dead air space at ordinary oxygen partial pressure may benefit from higher oxygen partial pressure.
4. Resistance and tachyphylaxis occur more frequently in normotensive patients infused with sodium nitroprusside. Induction of deliberate hypotension in healthy young individuals may prove to be more difficult than in other segments of the population.
5. Upon discontinuation of the sodium nitroprusside infusion, for the purpose of controlled hypotension during anaesthesia, a rebound hypertension has been observed on rare occasions.

### Use in Pregnancy:

The safety of Nipride® in women who are or who may become pregnant has not been established. Hence, it should be given only when the potential benefits have been weighed against possible hazard to the mother and child.

## **PRECAUTIONS**

Adequate facilities, equipment and trained personnel should be available for frequent and vigilant monitoring of blood pressure. The hypotensive effects of Nipride® (sodium nitroprusside) occurs rapidly and blood pressure usually begins to rise immediately and returns to pre-treatment levels within one to ten minutes when the infusion is slowed or stopped. It should be used with caution and initially in low doses in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

Because of the rapid onset of action and potency of Nipride®, it should be administered with the use of an infusion pump, micro-drip regulator or any similar device that would allow precise measurement of the flow rate.

If in the clinical situation, stress, induced by pain or manipulation, is reduced or eliminated during Nipride® infusion, the patient could experience a greater than expected reduction in blood pressure unless the rate of infusion is adjusted downward as required.

Several authors have reported tachyphylaxis in young male patients during hypotensive anaesthesia. However, tachyphylaxis has not been reported to date with sodium nitroprusside in the treatment of hypertensive emergencies.

Once dissolved in solution, Nipride® tends to deteriorate in the presence of light. Therefore, it should be protected from light by wrapping the container of the prepared solution with aluminum foil or other opaque materials. Storage period of solutions of Nipride® from the time of

reconstitution to the completion of IV administration should not exceed 24 hours. Nipride® in aqueous solution yields the nitroprusside ion, which reacts with even minute quantities of a wide variety of inorganic and organic substances to form usually highly coloured reaction products (blue, green or dark red). If this occurs, the infusion should be replaced as quickly as possible.

### ADVERSE REACTIONS

Fatalities due to cyanide poisoning have occurred following sodium nitroprusside administration (see **WARNINGS**).

Nausea, retching, emesis, diaphoresis, apprehension, headache, restlessness, agitation, muscle twitching, retrosternal discomfort and chest pain, palpitations, dizziness, faintness, weakness, rash, abdominal pain, confusion and somnolence have been noted with too rapid reduction in blood pressure. However, these symptoms rapidly disappeared with slowing of the rate of the infusion or temporary discontinuation of infusion, and did not reappear with continued slower rate of administration.

Irritation of the injection site may occur.

One case of hypothyroidism following prolonged therapy with intravenous sodium nitroprusside has been reported. Thiocyanate blood levels were 9.5 mg/100 mL after 21 days of administration of sodium nitroprusside to a patient with severe hypertension and renal disease.

Methemoglobinemia has been reported in the literature. Sodium nitroprusside infusions can cause sequestration of hemoglobin as methemoglobin (see **PHARMACOLOGY**). Clinically significant methemoglobinemia (> 10%) is seen only rarely in patients receiving Nipride®. Methemoglobinemia should be suspected in patients who have received > 10 mg/kg of sodium nitroprusside and who exhibit signs of impaired oxygen delivery.



## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of nitroprusside can be manifested as excessive hypotension or cyanide toxicity or as thiocyanate toxicity. In moderate cases, the signs are dyspnea, headache, vomiting, dizziness, ataxia and loss of consciousness. Massive overdosage produces coma with imperceptible pulse, absent reflexes, widely dilated pupils, pink colour, distant heart sounds, hypotension and very shallow breathing. Relief with oxygen only is not seen. Death may result. High overdosage also results in the occurrence of hyperkalemia and metabolic acidosis which will require appropriate measures for correction.

Treatment of cyanide toxicity: Cyanide levels can be measured by many laboratories, and blood-gas studies that can detect venous hyperoxemia or acidosis are widely available. Acidosis may not appear until more than an hour after the appearance of dangerous cyanide levels, and laboratory tests should not be awaited. Reasonable suspicion of cyanide toxicity is adequate grounds for initiation of treatment.

The treatment of cyanide toxicity consists of: discontinuing the administration of Nipride®; providing a buffer for cyanide by using sodium nitrite to convert as much hemoglobin into methemoglobin as the patient can safely tolerate; and then infusing sodium thiosulfate in sufficient quantity to convert the cyanide into thiocyanate.

### Treatment:

- \*a. Immediate discontinuation of Nipride® infusion or any other medication.
  
- \*b. Should the patient be conscious, amyl nitrite ampoules should be administered by inhalation immediately, one for 30 seconds every two minutes, unless pressure is below 80 mm Hg. If there is a delay in obtaining 3% sodium nitrite solution, amyl nitrite may be repeated as indicated.

- \*c. Follow as soon as possible (but not together with amyl nitrite) by intravenous injection of 10 mL of 3% sodium nitrite over a three-minute period (IV infusion of noradrenaline may be necessary to maintain blood pressure during this injection).
- \*d. 50 mL of 25% sodium thiosulfate should be administered intravenously over a ten-minute period following the administration of sodium nitrite.
- \*e. Supportive measures should be instituted as soon as possible (e.g. artificial respiration with 100% oxygen).
- \*f. Administration of sodium nitrite and sodium thiosulfate may have to be repeated if symptoms re-appear, but doses should be reduced by 50%.
- \*g. The institution of peritoneal dialysis may be helpful in the reduction of thiocyanate levels.
- \*h. Constant monitoring for cyanide and thiocyanate blood levels should be undertaken.
- \*i. If a severe and prolonged hypoxemia results due to excessive methemoglobinemia, inhalation of pure oxygen or a blood transfusion may be required.
- \*j. Further treatment should be symptomatic.

\*F.H. Lovejoy, C.H. Linden, "Acute Poison and Drug Overdosage" in Harrison's Principles of Internal Medicine, ed by Wilson, Braunwald, Isselbacher, Petersdorf, Martin, Fauci and Root, 12th ed., McGraw-Hill, 1991:2172, also, J.G. Gerber and A.S. Nies in Goodman and Gilman's, The Pharmacological Basis of Therapeutics. 8th ed., Pergamon Press, (New York), 1991:803-4.

A cyanide antidote kit is available from Eli Lilly Canada Inc., Scarborough, Ontario.

## DOSAGE AND ADMINISTRATION

USE OF NIPRIDE® (SODIUM NITROPRUSSIDE) IN ANAESTHETIZED NORMOTENSIVE PATIENTS UNDERGOING DELIBERATE HYPOTENSIVE SURGERY MUST BE RESTRICTED TO CAREFULLY SELECTED CASES. THERE IS A POSSIBILITY OF AN ABNORMAL RESPONSE OCCURRING IN NORMOTENSIVE PATIENTS. IN THE EVENT OF AN ABNORMAL RESPONSE, THE INFUSION OF NIPRIDE® SHOULD BE DISCONTINUED IMMEDIATELY (See **WARNINGS**).

The contents of a 50 mg Nipride® container should be dissolved in 3 mL of 5% Dextrose Injection (D5W) without preservatives. **No other diluents should be used.** Depending on the desired concentration, all of the prepared stock solution should be diluted in 500 to 1,000 mL of 5% Dextrose Injection and promptly wrapped in aluminum foil or other opaque materials to protect from light. Both the stock solution and the infusion solution should be freshly prepared and any unused portion discarded. The freshly prepared solution for infusion has a very faint brownish tint. If it is highly coloured, it should be discarded (see **PRECAUTIONS**).

**Storage period from the time of reconstitution to the completion of IV administration should not exceed 24 hours. The infusion fluid used for administration of Nipride® should not be employed as a vehicle for simultaneous administration of any other drug.**

The intravenous infusion of Nipride® should be administered by an infusion pump, micro-drip regulator or any similar device that will allow precise measurement of the flow rate. Care should be taken to avoid extravasation.

### 50 mg Nipride® in 1,000 mL D5W (50 µg/mL)

<u>Dose/kg</u>	<u>µg/kg/min</u>	<u>mL/kg/min</u>
Average	3.0	0.06
Range	0.5 to 8.0	0.01 to 0.16

### 50 mg Nipride® in 500 mL D5W (100 µg/mL)

<u>Dose/kg</u>	<u>µg/kg/min</u>	<u>mL/kg/min</u>
Average	3.0	0.03
Range	0.5 to 8.0	0.005 to 0.08

In patients who are not receiving antihypertensive drugs, the average dose of Nipride® for both adults and children is 3 µg/kg/minute (range of 0.5 to 8 µg/kg/minute). Usually, at 3 µg/kg/minute, blood pressure can be lowered by about 30 to 40% below the pre-treatment diastolic levels and maintained.

In hypertensive patients receiving concomitant antihypertensive medications, smaller doses are required.

In order to avoid excessive levels of thiocyanate and to lessen the possibility of a precipitous drop in blood pressure, infusion rates greater than 8 µg/kg/minute should rarely be used. If an adequate reduction of blood pressure is not obtained within ten minutes at this rate, administration of Nipride® should be stopped.

Nipride® dosage varies considerably from patient to patient, hence the need for individual titration. The infusion should be started at the lower dosage range (0.5 µg/kg/minute) and adjusted in a stepwise fashion (e.g. increments of 0.2 µg/kg/minute usually every five minutes) until the desired reduction in blood pressure is obtained. Continuous careful monitoring of the blood pressure on a minute to minute basis is necessary. Adjustments in the rate of infusion may be required to keep the blood pressure smoothly controlled and prevent extremes of hypotension and hypertension.

The blood pressure usually starts to drop immediately or at least within a few minutes. It is recommended that the blood pressure should not be allowed to drop at a too rapid rate and that the systolic pressure not be lowered below 60 mm Hg. Too rapid a reduction in blood pressure may result in retching or vomiting, muscular twitching, diaphoresis and agitation. These symptoms subside promptly when the rate of infusion is slowed or temporarily stopped.

In hypertensive emergencies, Nipride® infusion may be continued until the patient can safely be treated with oral antihypertensive medications alone.

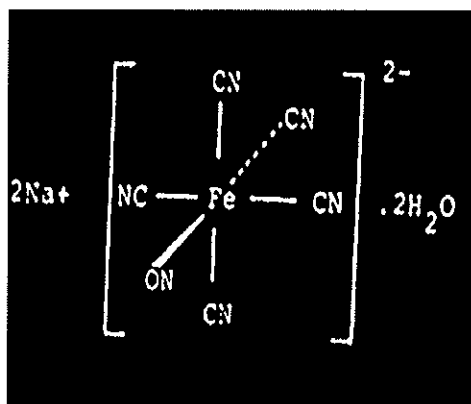
## PHARMACEUTICAL INFORMATION

### Drug Substance

**Proper Name:** Sodium nitroprusside

**Chemical Name:** Pentakis (cyano-C) nitrosylferrate(2-) disodium

**Chemical Structure:**



**Molecular Formula:**  $\text{Na}_2\text{Fe}(\text{CN})_5\text{NO}\cdot 2\text{H}_2\text{O}$

**Molecular Weight:** 297.95

**Description:** Reddish-brown, almost odourless crystals or powder.

**Solubility:** Freely soluble in water and slightly soluble in alcohol.

**pH:** 3.5-6.0 (reconstituted with 3 mL of 5% Dextrose Injection).

**Composition:** Each vial of Nipride® (Sodium Nitroprusside for Injection, USP) contains the equivalent of 50 mg Sodium Nitroprusside. There are no non-medicinal ingredients.

**Stability and Storage Recommendations:**

Store the powder at 15-30°C. Protect the reconstituted powder and intravenous infusion fluid from light. Single use vials. Discard unused portion.

**Preparation for Use and Reconstitution:**

Reconstitute with 3 mL of 5% Dextrose Injection only and dilute with 500-1,000 mL of 5% Dextrose Injection only.

Storage period from the time of reconstitution to the completion of IV administration should not exceed 24 hours.

**As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.**

**AVAILABILITY OF DOSAGE FORM**

Nipride® is available as 50 mg/vial single use vials. Packs of 5.

## PHARMACOLOGY

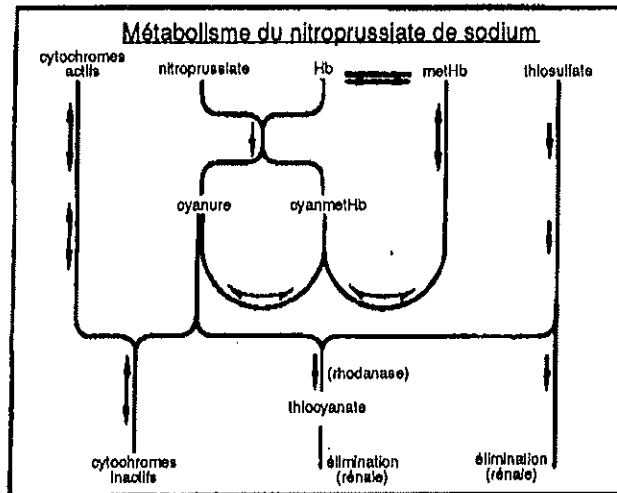
### Human Pharmacology

The hypotensive effects of intravenously administered sodium nitroprusside are due to peripheral vasodilatation and reduction in peripheral resistance as a result of a direct action on the blood vessel walls, independent of autonomic innervation. The active component in sodium nitroprusside is the free nitroprusside radical. The evanescent nature of the drug's hypotensive effect is due to the destruction of the active radical. Infused sodium nitroprusside is rapidly distributed to a volume that is approximately coextensive with the extracellular space. The drug is cleared from this volume by intraerythrocytic reaction with hemoglobin (Hgb), and sodium nitroprusside's resulting circulatory half-life is about two minutes.

The products of the nitroprusside/hemoglobin reaction are cyanmethemoglobin (cyanmetHgb) and cyanide ion ( $\text{CN}^-$ ). Safe use of sodium nitroprusside injection must be guided by knowledge of the further metabolism of these products.

As shown in the diagram below, the essential features of nitroprusside metabolism are:

- One molecule of sodium nitroprusside is metabolized by combination with hemoglobin to produce one molecule of cyanmethemoglobin and four  $\text{CN}^-$  ions;
- Methemoglobin, obtained from hemoglobin, can sequester cyanide as cyanmethemoglobin;
- Thiosulfate reacts with cyanide to produce thiocyanate;
- Thiocyanate is eliminated in the urine.
- Cyanide not otherwise removed binds to cytochromes; and
- Cyanide is much more toxic than methemoglobin or thiocyanate.



Cyanide ion is normally found in serum; it is derived from dietary substrates and from tobacco smoke.

Cyanide binds avidly (but reversibly) to ferric ion ( $\text{Fe}^{+++}$ ), most body stores of which are found in erythrocyte methemoglobin (metHgb) and in mitochondrial cytochromes. When  $\text{CN}^-$  is infused or generated within the bloodstream, essentially all of it is bound to methemoglobin until intraerythrocytic methemoglobin has been saturated.

When the  $\text{Fe}^{+++}$  of cytochromes is bound to cyanide, the cytochromes are unable to participate in oxidative metabolism. In this situation, cells may be able to provide for their energy needs by utilizing anaerobic pathways, but they thereby generate an increasing body burden of lactic acid. Other cells may be unable to utilize these alternate pathways, and they may die hypoxic deaths.  $\text{CN}^-$  levels in packed erythrocytes are typically less than 1 mmol/L (less than 25  $\mu\text{g/L}$ ); levels are roughly doubled in heavy smokers.

At healthy steady-state, most people have less than 1% of their hemoglobin in the form of methemoglobin. Nitroprusside metabolism can lead to methemoglobin formation (a) through dissociation of cyanmethemoglobin formed in the original reaction of sodium nitroprusside with Hgb and (b) by direct oxidation of Hgb by the released nitroso group. Relatively large quantities of sodium nitroprusside, however, are required to produce significant methemoglobinemia.

At physiologic methemoglobin levels, the  $\text{CN}^-$  binding capacity of packed red cells is a little less



than 200  $\mu\text{mol/L}$  (5 mg/L). Cytochrome toxicity is seen at levels only slightly higher, and death has been reported at levels from 300 to 3,000  $\mu\text{mol/L}$  (8 to 80 mg/L). Put another way, a patient with a normal red-cell mass (35 mL/kg) and normal methemoglobin levels can buffer about 175  $\mu\text{g/kg}$  of  $\text{CN}^-$ , corresponding to little less than 500  $\mu\text{g/kg}$  of infused sodium nitroprusside.

Some cyanide is eliminated from the body as expired hydrogen cyanide, but most is enzymatically converted to thiocyanate ( $\text{SCN}^-$ ) by thiosulfate-cyanide sulfur transferase (rhodanase, EC 2.8.1.1), a mitochondrial enzyme. The enzyme is normally present in great excess, so the reaction is rate-limited by the availability of sulfur donors, especially thiosulphate, cystine and cysteine.

Thiosulfate is a normal constituent of serum, produced from cysteine by way of  $\beta$ -mercaptopyruvate. Physiological levels of thiosulfate are typically about 0.1 mmol/L (11 mg/L), but they are approximately twice this level in children and in adults who are not eating. Infused thiosulfate is cleared from the body (primarily by the kidneys) with a  $t_{1/2}$  of about 20 minutes.

When thiosulphate is being supplied only by normal physiologic mechanisms, conversion of  $\text{CN}^-$  to  $\text{SCN}^-$  generally proceeds at about 1  $\mu\text{g/kg/min}$ . The rate of  $\text{CN}^-$  clearance corresponds to steady-state processing of a sodium nitroprusside infusion of slightly more than 2  $\mu\text{g/kg/min}$ .  $\text{CN}^-$  begins to accumulate when sodium nitroprusside infusions exceed this rate.

Thiocyanate ( $\text{SCN}^-$ ) is also a normal physiological constituent of serum, with normal levels typically in the range of 50 to 250  $\mu\text{mol/L}$  (3 to 15 mg/L). Clearance of  $\text{SCN}^-$  is primarily renal, with a  $t_{1/2}$  of about three days. In renal failure, the  $t_{1/2}$  can be doubled or tripled.

Oral administration of sodium nitroprusside does not produce the dramatic decrease in blood pressure seen with intravenous administration. The effects of chronic oral administration are similar to those obtained with oral potassium thiocyanate.

In hypertensive patients, moderate depressor doses of sodium nitroprusside induce renal vasodilation roughly equivalent to the decrease in pressure, without an appreciable increase in renal blood flow or a decrease in glomerular filtration.

In normotensive subjects, acute reduction of mean arterial pressure to 60-75 mm Hg by infusion of sodium nitroprusside caused significant increase in renin activity of renal venous plasma in correlation with a degree of reduction in pressure. Renal response to reduction in pressure was more striking in renovascular-hypertensive patients, with significant increase in renin release occurring from the involved kidney at mean arterial pressures ranging from 90-137 mm Hg. Furthermore, the magnitude of renin release from the involved kidney was significantly greater when compared to that in normotensive subjects; while in the contralateral, uninvolved kidney, no significant release of renin was detected during the reduction of pressure.

### Animal Pharmacology

Intravenous administration of Nipride® in doses of 0.125, 0.5 and 2.0 mg/kg/day (as 1 mL injections given in a two-minute period) was tolerated in dogs for a two-week period. The results noted were consistent with the transient vasodilation and lowering of blood pressure known to occur with intravenous sodium nitroprusside.

In dogs, the myocardial contractile force measured by a strain gauge arch showed no definite change with the administration of smaller doses of sodium nitroprusside (1 to 4 µg/kg), while with high doses (8 to 16 µg/kg) there was a decrease in the contractile force in about 60 to 90 seconds. The decrease was preceded by a fall in blood pressure occurring about 15 seconds post-infusion, suggesting that decrease in myocardial contractile force is not a primary effect of sodium nitroprusside but perhaps is due to the decrease in cardiac filling from relative peripheral pooling of blood. Adrenergic blocking agents failed to abolish its action, and autonomic ganglionic blocking agents markedly augmented the hypotensive response.

In dogs, intravenous infusion of sodium nitroprusside caused a slight increase in renal blood flow and decrease in vascular resistance, with no effect on the maximal tubular excretory capacity for PAH or the maximal tubular capacity for reabsorption of glucose.

## TOXICOLOGY

The LD<sub>50</sub>'s of intravenously administered Nipride® determined according to the method of Miller and Tainter (Proc Soc Exp Biol Med, 1944;57:261) in four different species of animals are as follows: mice, 8.4 ± 0.3 mg/kg; rats, 11.2 ± 1.1 mg/kg; rabbits, 2.8 ± 1.1 mg/kg; and dogs, 5 mg/kg (approximate).

Sodium nitroprusside was injected intravenously to 12 beagle dogs of both sexes over a period of two minutes, at doses of 0.125, 0.5 and 2.0 mg/kg/day for two weeks. All dogs survived the two weeks. After each injection, the dogs demonstrated signs consistent with the transient vasodilatation and lowering of blood pressure known to occur with sodium nitroprusside administered intravenously. Blood glucose was elevated temporarily after injections at the high and mid doses. Slight increases in the relative weights of the liver and adrenals at the high dose may have been related to vasodilation. Microscopic examination of the tissues showed congestion (vascular dilatation) of the liver, kidney and spleen at the high- and mid-doses, and of the liver at the low dose. There were no adverse cellular changes related to the vasodilation caused by sodium nitroprusside. No other changes were noted.

McDowall and co-workers (1974) have studied induced hypotension by intravenous infusion of sodium nitroprusside in baboons and reported that in four of eight animals receiving doses considered to be four to six times higher than "normal" in this species there was failure to recover normal arterial pressure after discontinuation of the infusion. These animals were in a state of metabolic acidosis and exhibited a markedly depressed cerebral oxygen uptake. In the four animals receiving doses considered "normal" for this species it was found that arterial pressure recovered rapidly. The early appearance of metabolic acidosis appeared to be coincident in animals resistant to nitroprusside induced hypotension.

Another study conducted in dogs (Stoyka and Schultz, 1975), reported that physiologic cerebral oxygenation was maintained at low perfusion pressures achieved with sodium nitroprusside infusion.

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