THE NORTHERN HOSPITAL

SODIUM NITROPRUSSIDE

Introduction

Sodium Nitroprusside (often abbreviated to **SNP**) is a potent, short-acting non-selective arteriolar and venous dilator, that is given by continuous IV infusion.

It is principally used for:

- Hypertensive crisis
- Acute heart failure (in selected cases)
- Controlled hypotensive anesthesia (in selected cases).

Its major immediate adverse reaction is precipitous falls in blood pressure, and so close invasive monitoring is required.

Its major adverse reactions with **prolonged** administration relate to the accumulation of toxic metabolites:

- Thiocyanate
- Cyanide.

The maximal duration of treatment therefore should not exceed **72 hours**, and **thiocyanate plasma concentrations** should be monitored.

It is very light sensitive and so must be protected from light.

History

Sodium nitroprusside was first used in human medicine in 1928.

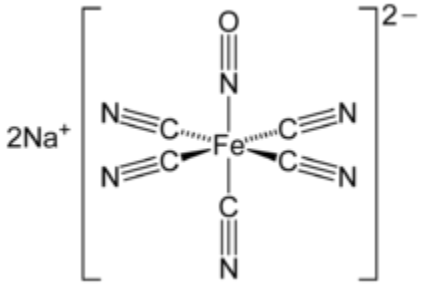
By 1955, data on its safety during short-term use in patients with severe hypertension had become available

Despite this, due to difficulties in its chemical preparation, it was not finally approved by the US FDA until 1974 for the treatment of severe hypertension

Chemistry

Sodium nitroprusside is an inorganic compound with the formula $Na_2[Fe(CN)_5NO]$

It is usually encountered as the dihydrate, $Na_2[Fe(CN)_5NO]\cdot 2H_2O$



Sodium nitroprusside dihydrate is a reddish - brown powder which is readily soluble in water.

Preparation

Sodium nitroprusside in aqueous solution is photosensitive and **must be protected from light.**

Vials: 50 mg vials (as powder for reconstitution)..

The freshly prepared solution has a **very faint brown tint.** If it is **highly coloured** it should be discarded.

Mechanism of Action

Action via NO generation:

Sodium nitroprusside + Hb → cyanmethaemoglobin + 4 CN^- + NO

It is the production of **NO** that is responsible for the vascular smooth muscle relaxation.

NO activates guanylate cyclase in vascular smooth muscle and increases intracellular production of cGMP.

cGMP activates protein kinase G which activates phosphatases which inactivate myosin light chains.

Myosin light chains are involved in muscle contraction.

The end result is vascular smooth muscle relaxation, which allow the blood vessels to dilate.

Blood pressure reduction:

The principal pharmacological action of sodium nitroprusside is relaxation of vascular smooth muscle and consequent **dilation** of **peripheral arteries and veins.**

Sodium nitroprusside is **more active on veins than on arteries**, but this selectivity is much less marked than that which is seen with nitroglycerin.

Reduction in myocardial work and oxygen demand:

Dilatation of the veins promotes peripheral pooling of blood and thereby decreases venous return to the heart, thereby reducing left ventricular end diastolic pressure and pulmonary capillary wedge pressure (preload).

Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure and mean arterial pressure (afterload).

Dilation of the coronary arteries also occurs.

Pharmacodynamics

Clinical effects include:

1. Fall in blood pressure:

    - The hypotensive effect of sodium nitroprusside is seen within 1 or 2 minutes after the start of an adequate infusion.

      Its effects dissipate almost as rapidly after an infusion is discontinued.

2. Mild tachycardia is common.

3. Renal:

    - In hypertensive patients, moderate doses induce renal vasodilatation roughly proportional to the general decrease in systemic blood pressure so there is no appreciable change in renal blood flow or glomerular filtration rate.

Other smooth muscle (e.g. uterus, GIT) is **not** affected.

Pharmacokinetics

Absorption:

- Sodium nitroprusside is given as a **continuous infusion.**

It should never be administered by direct injection.

Distribution:

- Infused sodium nitroprusside is rapidly distributed to a volume that is approximately equal to the extracellular space.

- It is cleared from this volume by an intra-erythrocytic reaction with haemoglobin and sodium nitroprusside's resulting circulatory half life is very short.

Metabolism and excretion:

The half-life of sodium nitroprusside is very short at less than 10 minutes.

Sodium nitroprusside combines with **haemoglobin** within the RBCs to produce:

- **Cyanmethaemoglobin**

And

- **Free cyanide ions**

The reaction can be represented as follows:

Sodium nitroprusside + Hb → cyanmethaemoglobin + 4 CN^- + NO

Cyanmethaemoglobin and cyanide are then enzymatically converted to **thiocyanate, via the liver enzyme rhodanese,** as follows:

CN^- + thiosulfate $\xrightarrow[\uparrow]{\text{Rhodanese}}$ thiocyanate and sulphite.

Thiocyanate, (**the major metabolite**) is then renally excreted and has a long half-life of 3 - 7 days in those with normal renal function.

Any cyanide not otherwise removed binds to cytochromes, preventing their action in oxidative metabolism and so causing toxicity.

Thiosulfate supplied only by normal physiological mechanisms can readily eliminate the cyanide produced by a sodium nitroprusside infusion up to a level of approximately:

- **2 microgram/kg/minute.**

  Cyanide ion begins to accumulate when this rate is exceeded.

The **thiocyanate** is removed almost exclusively by the kidneys, with a half life of up to 1 week in patients with normal renal function.

Toxic symptoms of thiocyanate begin to appear at plasma levels of **8 - 10 mcg/100mL**.

Indications

Indications for sodium nitroprusside include:

1. Urgent reduction of blood pressure in patients with hypertensive crises:

2. Producing controlled hypotension during anaesthesia in order to reduce bleeding in surgical procedures where surgeon and anaesthetist deem this to be appropriate.

3. Short-term therapy of some conditions of acute cardiac failure:

   To enhance cardiac output and lower myocardial oxygen requirements, primarily by reducing both preload and afterload.

Contra-indications/precautions

These include

1. Known hypersensitivity to sodium nitroprusside.

2. Hypotension

3. Uncorrected hypovolemia

4. Reduced peripheral vascular resistance:

   - Sodium nitroprusside should not be used in situations of **reduced peripheral vascular resistance**, such as high output cardiac failure or septic shock.

5. Renal impairment:

   - Delayed excretion of the **thiocyanate** metabolite which is toxic in **high concentrations.**

6. Hepatic impairment:

   - Caution should be observed in patients with severe liver impairment as the nitroprusside is largely metabolised by the **hepatic enzyme rhodanese** which is the enzyme responsible for the **conversion of cyanide ions to thiocyanate.**

Patients with liver disease are therefore more susceptible to toxic effects associated with accumulation of cyanide.

7. Drug interactions:

- **Sildenafil, tadalafil** or **vardenafil** should not be used concomitantly with sodium nitroprusside, because of the risk of **severe hypotension**.

- There should be caution with sodium nitroprusside use in combination with any agent capable of inducing hypotension, in particular antihypertensive medications, negative inotropes and inhaled volatile anaesthetic agents.

8. Nitroprusside ions react with a wide variety of inorganic and organic substances to form usually **highly coloured (blue, green or dark red) reaction products**.

   If this occurs, the infusion should be replaced.

9. Elderly:

- Use caution in the elderly, who may be more sensitive to the hypotension effects.

10. Anemia:

- Sodium nitroprusside should be used with caution in patients with significant anemia, as metabolism occurs predominantly within the RBCs.

Pregnancy

Sodium nitroprusside is classified as a category C drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Breast feeding:

Avoid, insufficient data.

Adverse Effects

These include:

1 Hypotension:

- Sodium nitroprusside can cause precipitous decreases in blood pressure and so close monitoring is essential.

2. Excessive accumulation of **cyanide** with prolonged use (> 72 hours) and/ or high dosing:

   - **This is a potentially lethal complication.**

     The risk is greater in those with impaired renal function

3. Excessive accumulation of thiocyanate with prolonged use (> 72 hours):

   - Thiocyanate is neurotoxic in excessive amounts.

     Thiocyanate levels can be measured.

4. Methemoglobinaemia:

   Nitroprusside metabolism can lead to methaemoglobin formation via two mechanisms:

   - Through **dissociation** of cyanmethaemoglobin formed in the original reaction of sodium nitroprusside with Hb

   - By direct oxidation of Hb by the released nitroso group.

   Relatively **large quantities** of sodium nitroprusside, however, are required to produce significant methaemoglobinaemia.

   Methaemoglobin levels can be measured by arterial blood gas co-oximetry.

5. Allergic reactions

6. Tachyphylaxis:

   - Tachyphylaxis to the hypotensive effects of sodium nitroprusside may occur with more prolonged use.

     The mechanism by which this happens is unknown.

7. Hypothyroidism:

   - Thiocyanate can inhibit both the uptake and binding of iodine by the thyroid.

     Caution should be exercised in using sodium nitroprusside in patients with hypothyroidism and severe renal dysfunction.

Thyroid hormone deficiency has been reported following prolonged infusions.

Dosing

Note that the administration of sodium nitroprusside is complex, and product information and local protocols should be consulted

Sodium nitroprusside can cause precipitous decreases in blood pressure and so close monitoring is essential.

Blood pressure should be closely monitored during administration and the dose titrated as necessary to avoid excessive hypotension.

Monitoring is best done by an **arterial line.**

The infusion solution is **light sensitive** and so both the infusion bag should be protected with **aluminum foil** (or other opaque material). It is not necessary to cover the infusion drip chamber or the tubing.

Sodium nitroprusside is given in **5 % dextrose only.**

One method is to add reconstituted solution to a 100 mL minibag of glucose 5%. This produces a solution of **500 microgram/mL**

The solution must be administered using an **infusion pump, microdrip regulator** or similar device.

Give: [1]

- Sodium nitroprusside **0.3 microgram/kg/minute** IV infusion,

  Increasing or decreasing by **0.3 microgram/kg/minute every 2 minutes**

  The usual *maintenance* dose in adults will be approximately:

  - **0.5 - 0.6 micrograms/kg/minute.** [2]

  The maximum dose is **10 micrograms/kg/minute**, (*though infusion at this maximum dose rate should never last more than 10 minutes*).

  Titrate to maintain the blood pressure in the target range.

  For an average 72 kilogram adult infusion doses range from 20 - 700 micrograms/minute.

Abrupt withdrawal of sodium nitroprusside may cause rebound hypertension; so it is best withdraw the infusion over at least 10 - 30 minutes to avoid rebound hypertension, where possible.

The usual duration of treatment should not exceed **72 hours** because of the accumulation of thiocyanate and the possibility of cyanide toxicity.

With more prolonged use, **thiocyanate concentrations should be monitored.**

References

1. eTG - March 2015.

2. Sodium nitroprusside in Australian Medicines Handbook Website, Accessed April 2015

3. Sodium nitroprusside in MIMs 1 August 2014

Dr J. Hayes
April 2015.