Sitaxentan is highly metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 to weakly active metabolites. About 50 to 60% of a dose is excreted in the urine with the remainder appearing in the faeces; less than 1% is excreted unchanged. Sitaxentan has a terminal elimination half-life of 10 hours and steady state is achieved within about 6 days.

Uses and Administration

Sitaxentan is an endothelin receptor antagonist (p.1155) with similar actions to bosentan (p.1235), although it has a higher selectivity for the endothelin ET_A-receptor. It is used in the management of pulmonary hypertension functional class III (p.1179). It is also being investigated in the management of heart failure.

In the treatment of pulmonary hypertension sitaxentan sodium is given orally in a dose of 100 mg once daily. Alternate therapy should be considered if there is no response after 12 weeks but a further 12 weeks of treatment may be tried.

◊ Reviews.

1. Wittbrodt ET, Abubakar A. Sitaxsentan for treatment of pulmonary hypertension. *Ann Pharmacother* 2007; **41:** 100–105.
2. Benedict NJ. Sitaxsentan in the management of pulmonary arterial hypertension. *Am J Health-Syst Pharm* 2007; **64:** 363–8.
3. Scott LJ. Sitaxentan: in pulmonary arterial hypertension. *Drugs* 2007; **67:** 761–70.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Thelin; ***Cz.:*** Thelin; ***Fr.:*** Thelin; ***Port.:*** Thelin; ***UK:*** Thelin.

Sodium Apolate *(BAN, rINN)*

Apolate de Sodium; Apolato de sodio; Lyapolate Sodium *(USAN)*; Natrii Apolas; Natriumapolaatti; Natriumapolat; Sodium Lyapolate. Poly(sodium ethylenesulphonate).

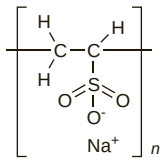
Натрия Аполат

$(C_2H_3NaO_3S)_n$.

CAS — 25053-27-4.

ATC — C05BA02.

ATC Vet — QC05BA02.



Profile

Sodium apolate is a synthetic heparinoid anticoagulant. It has been used in the topical treatment of haematomas and superficial thromboses and for the relief of sprains and contusions.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Pergalen.

Sodium Nitroprusside

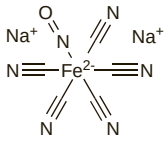
Disodium (*OC*-6-22)-Pentakis(cyano-*C*)nitrosylferrate Dihydrate; Natrii nitroprussias; Natrii Nitroprussias Dihydricus; Natrii Nitroprussicum; Natrio nitroprusidas; Natriumnitroprussid; Natriumnitroprussidi; Nitroprusiato sódico; Nitroprussid sodný dihydrát; Nitroprusszid-nátrium; Sodium Nitroferricyanide Dihydrate; Sodium Nitroprussiate; Sodium, nitroprussiate de; Sodu nitroprusydek; Sodyum Nitroprusid. Sodium nitrosylpentacyanoferrate(III) dihydrate.

$Na_2Fe(CN)_5NO,2H_2O$ = 297.9.

CAS — 14402-89-2 (anhydrous sodium nitroprusside); 13755-38-9 (sodium nitroprusside dihydrate).

ATC — C02DD01.

ATC Vet — QC02DD01.



(anhydrous sodium nitroprusside)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Sodium Nitroprusside). Reddish-brown crystals or powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Sodium Nitroprusside). Reddish-brown, practically odourless crystals or powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; insoluble in benzene. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Sodium nitroprusside has been reported to be visually incompatible with cisatracurium besilate[1] and with levofloxacin[2] during simulated Y-site administration.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54:** 1735–41.
2. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability in solution. Solutions of sodium nitroprusside decompose when exposed to light and must be protected during infusion by wrapping the container with aluminium foil or some other light-proof material. Nitroprusside will react with minute quantities of organic and inorganic substances forming highly coloured products. If this occurs the solution should be discarded. Solutions should not be used more than 24 hours after preparation.

The instability of sodium nitroprusside solutions has been the subject of considerable investigation. Although stated to be more stable in acid than in alkaline solution,[1] a later study[2] found that whereas the initial light-induced darkening of a 1% solution was independent of pH, further degradation leading to the development of a blue precipitate required an acid pH. If protected from light by wrapping in aluminium foil, sodium nitroprusside 50 or 100 micrograms/mL was found to be stable in 5% glucose, lactated Ringer's, and normal saline solutions for 48 hours.[3] In clinical practice the infusion container should be opaque or protected with foil, but an amber giving set may be used, to allow visual monitoring.[4,5]

Various substances have been reported to increase the stability of nitroprusside solutions, including dimethyl sulfoxide,[6] glycerol,[1] sodium citrate,[1] and other salts with anionic chelating potential such as sodium acetate or phosphate.[1] In contrast sodium bisulfite and the hydroxybenzoates are reported to reduce stability.[1]

1. Schumacher GE. Sodium nitroprusside injection. *Am J Hosp Pharm* 1966; **23:** 532.
2. Hargrave RE. Degradation of solutions of sodium nitroprusside. *J Hosp Pharm* 1974; **32:** 188–91.
3. Mahony C, *et al.* In vitro stability of sodium nitroprusside solutions for intravenous administration. *J Pharm Sci* 1984; **73:** 838–9.
4. Davidson SW, Lyall D. Sodium nitroprusside stability in light-protective administration sets. *Pharm J* 1987; **239:** 599–601.
5. Lyall D. Sodium nitroprusside stability. *Pharm J* 1988; **240:** 5.
6. Asker AF, Gragg R. Dimethyl sulfoxide as a photoprotective agent for sodium nitroprusside solutions. *Drug Dev Ind Pharm* 1983; **9:** 837–48.

Adverse Effects

Sodium nitroprusside rapidly reduces blood pressure and is converted in the body to cyanide and then thiocyanate. Its adverse effects can be attributed mainly to excessive hypotension and excessive cyanide accumulation; thiocyanate toxicity may also occur, especially in patients with renal impairment. Intravenous infusion of sodium nitroprusside may produce nausea and vomiting, apprehension, headache, dizziness, restlessness, perspiration, palpitations, retrosternal discomfort, abdominal pain, and muscle twitching, but these effects may be reduced by slowing the infusion rate.

An excessive amount of cyanide in plasma (more than 80 nanograms/mL), because of overdosage or depletion of endogenous thiosulfate (which converts cyanide to thiocyanate *in vivo*), may result in tachycardia, sweating, hyperventilation, arrhythmias, and profound metabolic acidosis. Metabolic acidosis may be the first sign of cyanide toxicity. Methaemoglobinaemia may also occur.

Adverse effects attributed to thiocyanate include tinnitus, miosis, and hyperreflexia; confusion, hallucinations, and convulsions have also been reported.

Other adverse effects include thrombocytopenia and phlebitis.

Effects on the blood. ***THROMBOCYTOPENIA.*** Platelet counts decreased in 7 of 8 patients with heart failure 1 to 6 hours after intravenous infusion of nitroprusside was started.[1] The counts began to return to normal 24 hours after the infusion was stopped.

1. Mehta P, *et al.* Nitroprusside lowers platelet count. *N Engl J Med* 1978; **299:** 1134.

Effects on the gastrointestinal tract. Five out of 38 patients who were given sodium nitroprusside intravenously for controlled hypotension during surgery developed symptoms of adynamic ileus postoperatively.[1] The symptoms could have been secondary to intestinal ischaemia due to diminished mesenteric arterial blood flow. However, other explanations have been proposed including sympathetic stimulation[2,3] or the concomitant use of opioid analgesics.[4]

1. Chen JW, *et al.* Adynamic ileus following induced hypotension. *JAMA* 1985; **253:** 633.
2. Gelman S. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.
3. Lampert BA. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.
4. Lemmo J, Karnes J. Adynamic ileus following induced hypotension. *JAMA* 1985; **254:** 1721.

Effects on intracranial pressure. A significant increase in intracranial pressure while the mean blood pressure was 80 or 90% of initial values was reported[1] in 14 normocapnic patients given an infusion of sodium nitroprusside to produce controlled hypotension prior to neurosurgery; values reverted towards normal at mean blood pressures of 70% of controls. A similar but insignificant trend occurred in 5 hypocapnic patients. In another report[2] a rise in intracranial pressure was noted after the use of nitroprusside in a patient with Reye's syndrome.

1. Turner JM, *et al.* Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 1977; **49:** 419–24.
2. Griswold WR, *et al.* Nitroprusside-induced intracranial hypertension. *JAMA* 1981; **246:** 2679–80.

Phlebitis. Acute transient phlebitis has occurred after infusion of sodium nitroprusside.[1]

1. Miller R, Stark DCC. Acute phlebitis from nitroprusside. *Anesthesiology* 1978; **49:** 372.

Treatment of Adverse Effects

Adverse effects due to excessive hypotension may be treated by slowing or stopping the infusion.

For details of the treatment of cyanide poisoning see Hydrocyanic Acid, p.2045. Thiocyanate can be removed by dialysis.

Precautions

Sodium nitroprusside should not be used in the presence of compensatory hypertension (for example, in arteriovenous shunts or coarctation of the aorta). It should be used with caution, if at all, in patients with hepatic impairment, and in patients with low plasma-cobalamin concentrations or Leber's optic atrophy. It should also be used with caution in patients with impaired renal or pulmonary function and with particular caution in patients with impaired cerebrovascular circulation. Thiocyanate, a metabolite of sodium nitroprusside, inhibits iodine binding and uptake and sodium nitroprusside should be used with caution in patients with hypothyroidism. The blood-thiocyanate concentration should be monitored if treatment continues for more than 3 days and should not exceed 100 micrograms/mL although toxicity may be apparent at lower thiocyanate concentrations. Thiocyanate concentrations do not reflect cyanide toxicity and cyanide concentrations should also be monitored; the blood concentration of cyanide should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. The acid–base balance should also be monitored. Care should be taken to ensure that extravasation does not occur. Sodium nitroprusside should not be withdrawn abruptly due to the risk of rebound effects.

Aortic stenosis. Vasodilators such as sodium nitroprusside are usually contra-indicated in conditions where cardiac outflow is obstructed since cardiac output cannot increase to compensate for the fall in blood pressure. However, a study[1] in patients with aortic stenosis and severe left ventricular dysfunction found that sodium nitroprusside was well tolerated and that it rapidly and markedly improved cardiac function.

1. Khot UN, *et al.* Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003; **348:** 1756–63.

Pregnancy. Although there are concerns that nitroprusside given to the mother might produce cyanide toxicity in the fetus, a systematic review[1] was unable to find sufficient evidence to determine the risk.

1. Sass N, *et al.* Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J* 2007; **125:** 108–11.

Tachyphylaxis. Tachyphylaxis to sodium nitroprusside was associated with high plasma concentrations of cyanide without metabolic acidosis in 3 patients undergoing hypotensive anaesthesia.[1]

1. Cottrell JE, *et al.* Nitroprusside tachyphylaxis without acidosis. *Anesthesiology* 1978; **49:** 141–2.