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).

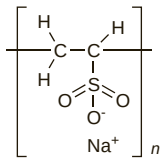
Натрия Аполат

$(C_2H_3NaO_3S)_n$.

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

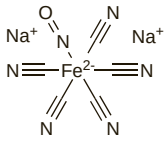
Disodium (*OC*-6-22)-Pentakis(cyano-*C*)nitrosylferrate Dihydrate; Natrii nitroprussias; Natrii Nitroprussias Dihydricus; Natrii Nitroprussicum; Natrio nitroprusidas; Natriumnitroprussid; Natriumnitroprussidi; Nitroprusiato sódico; Nitroprussid sodný dihydrát; Nitroprusszid-nátrium; Sodium Nitroferricyanide 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.

Withdrawal. Rebound haemodynamic changes, including hypertension and increased heart rate, occurred 10 to 30 minutes after stopping intravenous sodium nitroprusside infusion in 20 patients with heart failure.[1] The changes generally resolved spontaneously within 1 to 3 hours and produced only minimal exacerbation of symptoms in most patients, although 3 developed pulmonary oedema 20 to 30 minutes after stopping the infusion, needing restarting of nitroprusside in 2 cases. A study[2] investigating a possible mechanism for this effect found that plasma-renin concentrations were increased during infusion of nitroprusside and remained elevated for 30 minutes after the infusion was stopped. It was suggested that this persistence of elevated plasma-renin concentrations after clearance of short-lived nitroprusside may be responsible for the rebound effects.

1. Packer M, *et al*. Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. *N Engl J Med* 1979; **301:** 1193–7.
2. Cottrell JE, *et al*. Rebound hypertension after sodium nitroprusside-induced hypotension. *Clin Pharmacol Ther* 1980; **27:** 32–6.

Interactions

Enhanced hypotension should be expected if sodium nitroprusside is used with other antihypertensives or drugs that produce hypotension.

Alteplase. Sodium nitroprusside infusion prolonged the fibrinolytic activity of alteplase when given to *animals*; use of nitrovasodilators with alteplase may be responsible for the enhanced bleeding tendency seen in some patients on thrombolytic therapy.[1]

1. Korbut R, *et al*. Prolongation of fibrinolytic activity of tissue plasminogen activator by nitrovasodilators. *Lancet* 1990; **335:** 669.

Pharmacokinetics

Sodium nitroprusside is rapidly metabolised to cyanide in erythrocytes and smooth muscle and, *in vivo*, this is followed by the release of nitric oxide, the active metabolite. Cyanide is further metabolised in the liver to thiocyanate, which is slowly excreted in the urine; this metabolism is mediated by the enzyme rhodanase and requires the presence of thiosulfate. The plasma half-life of thiocyanate is reported to be about 3 days, but may be much longer in patients with renal impairment.

◊ Reviews.

1. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet* 1984; **9:** 239–51.

Uses and Administration

Sodium nitroprusside is a short-acting hypotensive drug with a duration of action of 1 to 10 minutes. It produces peripheral vasodilatation and reduces peripheral resistance by a direct action on both veins and arterioles. It has been termed a nitrovasodilator because it releases nitric oxide *in vivo*. Its effects appear within a few seconds of intravenous infusion. Sodium nitroprusside is used in the treatment of hypertensive crises (p.1171) and to produce controlled hypotension during general anaesthesia. It has also been used to reduce preload and afterload in severe heart failure (p.1165) including that associated with myocardial infarction (p.1175).

It is given by continuous intravenous infusion of a solution containing 50 to 200 micrograms/mL. A controlled infusion device must be used. The solution should be prepared immediately before use by dissolving sodium nitroprusside in glucose 5% and then diluting with glucose 5%; the solution must be protected from light during infusion. Blood pressure should be monitored closely and care should be taken to prevent extravasation. In general, treatment should not continue for more than 72 hours. If required for several days concentrations of cyanide should be monitored; the blood concentration should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. Thiocyanate concentrations in blood should also be measured if infusion continues for more than 72 hours and should not exceed 100 micrograms/mL. Since rebound hypertension has been reported when sodium nitroprusside is withdrawn, the infusion should be tailed off gradually over 10 to 30 minutes.

For **hypertensive crises** in patients not receiving antihypertensive drugs, an initial dose of 0.3 to 1.5 micrograms/kg per minute may be given, increasing gradually under close supervision until the desired reduction in blood pressure is achieved. The average dose required to maintain the blood pressure 30 to 40% below the pretreatment diastolic blood pressure is 3 micrograms/kg per minute and the usual dose range is 0.5 to 6 micrograms/kg per minute. Lower doses should be used in patients already receiving other antihypertensives. The maximum recommended rate is about 8 micrograms/kg per minute in the UK, and 10 micrograms/kg per minute in the USA; infusions at these rates should be used for no longer than 10 minutes and should be stopped after 10 minutes if there is no response. If there is a response, sodium nitroprusside should ideally be given for only a few hours to avoid the risk of cyanide toxicity. Treatment with an oral antihypertensive should be introduced as soon as possible.

For the **induction of hypotension** during anaesthesia a maximum dose of 1.5 micrograms/kg per minute is recommended.

In **heart failure** an initial dose of 10 to 15 micrograms/minute has been used, increasing by 10 to 15 micrograms/minute every 5 to 10 minutes according to response. The usual dosage range is 10 to 200 micrograms/minute and the dose should not exceed 280 micrograms/minute (or 4 micrograms/kg per minute).

Sodium nitroprusside has also been used as a reagent for detecting ketones in urine.

Administration in children. Although experience is more limited than with adults, sodium nitroprusside has been successfully used in infants and children. Continuous infusion of nitroprusside at a rate of 2 to 4 micrograms/kg per minute for 28 days was reported[1] in an 11-year-old child with refractory hypertension, without any signs of thiocyanate toxicity. In a series of 58 neonates with cardiovascular disorders or respiratory distress syndrome,[2] sodium nitroprusside was given in a usual initial dose of 250 to 500 nanograms/kg per minute, and the rate was then repeatedly doubled at intervals of 15 to 20 minutes until the desired effect was achieved, adverse effects supervened, or it was judged ineffective. The maximum rate did not exceed 6 micrograms/kg per minute. Infusion of sodium nitroprusside in doses of 0.5 to 8 micrograms/kg per minute to produce controlled reduction of blood pressure has also been reported[3] in 28 children with hypertensive crises; 16 had also received labetalol.[3]

1. Luderer JR, *et al*. Long-term administration of sodium nitroprusside in childhood. *J Pediatr* 1977; **91:** 490–1.
2. Benitz WE, *et al*. Use of sodium nitroprusside in neonates: efficacy and safety. *J Pediatr* 1985; **106:** 102–10.
3. Deal JE, *et al*. Management of hypertensive emergencies. *Arch Dis Child* 1992; **67:** 1089–92.

Ergotamine poisoning. For the use of sodium nitroprusside in the treatment of cyanosis of the extremities due to ergotamine overdosage, see Cardiovascular Effects, p.620.

Preparations

BP 2008: Sodium Nitroprusside Intravenous Infusion;
USP 31: Sodium Nitroprusside for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Doketrol; Niprusodio; Nitroprus; ***Braz.:*** Nipride; Nitropresabbott; Nitroprus; ***Canad.:*** Nipride; ***Cz.:*** Nipruss; ***Fr.:*** Nitriate; ***Ger.:*** Nipruss; ***Gr.:*** Nitriate; ***India:*** Sonide; ***Irl.:*** Nipride†; ***Israel:*** Nipruss; ***Jpn:*** Nitopro; ***Mex.:*** Nitan†; ***Rus.:*** Naniprus (Нанипрус); ***S.Afr.:*** Hypoten; SNP; ***Spain:*** Nitroprussiat; ***Turk.:*** Nipruss; ***USA:*** Nitropress.

Sotalol Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de sotalol; MJ-1999; Sotalol, chlorhydrate de; Sotalol Hidroklorür; *d,l*-Sotalol Hydrochloride; Sotalol-hydrochlorid; Sotalolhydroklorid; Sotaloli hydrochloridum; Sotalolihydrokloridi; Sotalolio hidrochloridas; Szotalol-hidroklorid. 4′-(1-Hydroxy-2-isopropylaminoethyl)methanesulphonanilide hydrochloride.

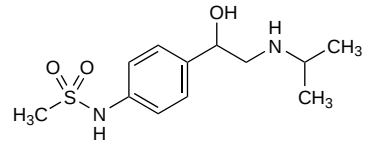
Соталола Гидрохлорид

$C_{12}H_{20}N_2O_3S,HCl$ = 308.8.

CAS — 3930-20-9 (sotalol); 959-24-0 (sotalol hydrochloride).

ATC — C07AA07.

ATC Vet — QC07AA07.



(sotalol)

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

Ph. Eur. 6.2 (Sotalol Hydrochloride). A white or almost white powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 31 (Sotalol Hydrochloride). A white to off-white powder. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform.

Stability. Suspensions of sotalol hydrochloride 5 mg/mL made using either commercially available or extemporaneously prepared vehicles were found[1] to be stable for up to 3 months when stored at 4° or 25°. Prolonged storage at 25° was not recommended, however, because of the risk of microbial growth.

1. Nahata MC, Morosco RS. Stability of sotalol in two liquid formulations at two temperatures. *Ann Pharmacother* 2003; **37:** 506–9.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Torsade de pointes has been reported in patients given sotalol, usually due to prolongation of the QT interval. The QT interval should be monitored: extreme caution is required if the QT interval exceeds 500 milliseconds and sotalol should be stopped or the dose reduced if the QT interval exceeds 550 milliseconds. As hypokalaemia or hypomagnesaemia may predispose patients to arrhythmias, serum-electrolyte concentrations should be monitored before and during treatment with sotalol.

Sotalol should be used with caution in renal impairment (see under Uses and Administration, below) and is contra-indicated in patients whose creatinine clearance is less than 10 mL/minute.

Breast feeding. Sotalol is distributed into breast milk and milk to serum ratios have been reported[1-3] to range from 2.2 to 8.8. In one report[2] it was calculated that a breast-fed infant might ingest 20 to 23% of a maternal dose; however, no bradycardia was noted in the infant in this study. The American Academy of Pediatrics states[4] that there have been no reports of clinical effects in breast-fed infants whose mothers were receiving sotalol and that therefore it may be considered to be usually compatible with breast feeding.

1. O'Hare MF, *et al*. Sotalol as a hypotensive agent in pregnancy. *Br J Obstet Gynaecol* 1980; **87:** 814–20.
2. Hackett LP, *et al*. Excretion of sotalol in breast milk. *Br J Clin Pharmacol* 1990; **29:** 277–8.
3. Wagner X, *et al*. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119:** 700–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Interactions

There is an increased risk of precipitating ventricular arrhythmias if sotalol is given with other drugs that prolong the QT interval, and use with the following drugs is therefore not recommended: class Ia antiarrhythmics (including disopyramide, procainamide, and quinidine), amiodarone, phenothiazine antipsychotics, tricyclic antidepressants, certain antihistamines (astemizole or terfenadine), cisapride, erythromycin, halofantrine, pentamidine, quinolones, sultopride, and vincamine. Caution is required if sotalol is given with drugs that cause electrolyte disturbances, such as diuretics, since this also increases the risk of arrhythmias.

Other interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Sotalol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are