may be due to bias in prescribing.[3] (Prevalence may also be reduced in patients taking fibrates.[2]) Some longitudinal studies have reported[4,5] that statins also reduce the incidence of dementia, but others have found no evidence of a reduction in risk,[6-8] and it has been suggested[6] that inappropriate analysis may explain the positive results. Prospective, randomised trials are therefore needed to determine their role, if any, in the prevention of dementia.[3]

There is also some evidence that statins[9-11] and other lipid regulating drugs[11] may reduce the progression of cognitive decline in patients with dementia, although the effect has generally been small. However, negative effects on mental function have been reported with some statins (see under Adverse Effects, above) and their use in the management of dementia is not established.

1. Wolozin B, *et al.* Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 2000; **57:** 1439–43.
2. Dufouil C, *et al.* APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. *Neurology* 2005; **64:** 1531–8.
3. Scott HD, Laake K. Statins for the prevention of Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 30/05/08).
4. Jick H, *et al.* Statins and the risk of dementia. *Lancet* 2000; **356:** 1627–31. Correction. *ibid.*; **357:** 562.
5. Wolozin B, *et al.* Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med* 2007; **5:** 20.
6. Li G, *et al.* Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology* 2004; **63:** 1624–8.
7. Zandi PP, *et al.* Cache County Study investigators. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry* 2005; **62:** 217–24.
8. Rea TD, *et al.* Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Arch Neurol* 2005; **62:** 1047–51.
9. Sparks DL, *et al.* Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. *Arch Neurol* 2005; **62:** 753–7.
10. Bernick C, *et al.* Cardiovascular Health Study Collaborative Research Group. Statins and cognitive function in the elderly: the Cardiovascular Health Study. *Neurology* 2005; **65:** 1388–94.
11. Masse I, *et al.* Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2005; **76:** 1624–9.

Kidney disorders. Although proteinuria has been reported with statins (see Effects on the Kidney under Adverse Effects, above) there is also some evidence that statins modestly reduce the progression of proteinuria and loss of renal function.[1-4] However, further studies are required to confirm these effects.

1. Sandhu S, *et al.* Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006; **17:** 2006–16.
2. Douglas K, *et al.* Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med* 2006; **145:** 117–24.
3. Agarwal R. Effects of statins on renal function. *Mayo Clin Proc* 2007; **82:** 1381–90.
4. Strippoli GFM, *et al.* Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ* 2008; **336:** 645–51.

Malignant neoplasms. Although studies in *animals* suggest[1] that statins could be carcinogenic, evidence for a detrimental effect in humans is limited, and some studies have suggested that statins may be protective. Low plasma-cholesterol concentrations have been associated with cancer, and an increased incidence of cancer was reported in a randomised study of pravastatin for cardiovascular risk reduction in elderly patients,[2] although this was attributed to chance. Conversely, several observational studies have reported[3-7] that statins reduce the incidence of cancer, although the effect has generally been small. A number of meta-analyses have been performed and have generally found no association between the use of statins and the incidence of cancer. Analyses including only randomised studies[8,9] have found no significant effect on overall risk, although follow-up may not have been long enough in most studies to be conclusive; there is also little evidence of a protective effect for specific cancers.[10-12] However, another large cohort study[13] in elderly patients found no evidence that statins either increased or reduced the risk, and longer follow-up in a randomised study[14] using simvastatin also found no significant effect.

1. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996; **275:** 55–60.
2. Shepherd J, *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360:** 1623–30.
3. Blais L, *et al.* 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. *Arch Intern Med* 2000; **160:** 2363–8.
4. Graaf MR, *et al.* The risk of cancer in users of statins. *J Clin Oncol* 2004; **22:** 2388–94.
5. Poynter JN, *et al.* Statins and the risk of colorectal cancer. *N Engl J Med* 2005; **352:** 2184–92.
6. Khurana V, *et al.* Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans. *Chest* 2007; **131:** 1282–8.
7. Karp I, *et al.* Statins and cancer risk. *Am J Med* 2008; **121:** 302–9.
8. Dale KM, *et al.* Statins and cancer risk: a meta-analysis. *JAMA* 2006; **295:** 74–80.
9. Bonovas S, *et al.* Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006; **24:** 4808–17.
10. Bonovas S, *et al.* Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005; **23:** 8606–12.
11. Bonovas S, *et al.* Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol* 2007; **25:** 3462–8.
12. Bonovas S, *et al.* Use of statins and risk of haematological malignancies: a meta-analysis of six randomized clinical trials and eight observational studies. *Br J Clin Pharmacol* 2007; **64:** 255–62.
13. Setoguchi S, *et al.* Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation* 2007; **115:** 27–33.
14. Strandberg TE, *et al.* Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004; **364:** 771–7.

Organ and tissue transplantation. Cardiovascular disease is an important cause of morbidity and mortality after organ transplantation and statins are useful for cardiovascular risk reduction in these patients. They may also have immunomodulatory effects and have reduced the risk of rejection in some studies.[1] A meta-analysis of patients who had undergone heart transplantation (p.1812) considered that treatment with a statin within 3 months of transplantation reduced allograft rejection with haemodynamic compromise and reduced 1-year mortality;[2] it was calculated that one life was saved for every 8.5 treated heart transplant patients. There is some tentative evidence that statin therapy may also reduce acute rejection and the development of obliterative bronchiolitis in patients who have undergone lung transplantation (p.1815),[3] although prospective controlled studies are lacking.

1. Paraskevas KI. Applications of statins in cardiothoracic surgery: more than just lipid-lowering. *Eur J Cardiothorac Surg* 2008; **33:** 377–90.
2. Mehra MR, Raval NY. Metaanalysis of statins and survival in de novo cardiac transplantation. *Transplant Proc* 2004; **36:** 1539–41.
3. Johnson BA, *et al.* Statin use is associated with improved function and survival of lung allografts. *Am J Respir Crit Care Med* 2003; **167:** 1271–8.

Osteoporosis. Statins appear to have effects on bone metabolism and preliminary studies[1,2] have suggested that some statins may increase bone mineral density. However, the clinical relevance of any effect is unclear.[3] Several case-control studies[4-6] have also suggested that use of statins may protect against fractures, but another case-control study[7] and an observational study[8] failed to support such an association. A review[9] of 4 further observational studies found that the risk of fracture was lower in women taking statins, but analysis of data from randomised studies of statins for cardiovascular disease[10,11] failed to confirm any effect, and controlled studies are needed[3,12] to confirm the role of statins in the management of osteoporosis (p.1084).

1. Edwards CJ, *et al.* Oral statins and increased bone-mineral density in postmenopausal women. *Lancet* 2000; **355:** 2218–9.
2. Watanabe S, *et al.* Effects of 1-year treatment with fluvastatin or pravastatin on bone. *Am J Med* 2001; **110:** 584–7.
3. Jadhav SB, Jain GK. Statins and osteoporosis: new role for old drugs. *J Pharm Pharmacol* 2006; **58:** 3–18.
4. Chan KA, *et al.* Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 2000; **355:** 2185–8.
5. Meier CR, *et al.* HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 2000; **283:** 3205–10.
6. Wang PS, *et al.* HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 2000; **283:** 3211–16.
7. van Staa T-P, *et al.* Use of statins and risk of fractures. *JAMA* 2001; **285:** 1850–55. Correction. *ibid.*; **286:** 674.
8. LaCroix AZ, *et al.* Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med* 2003; **139:** 97–104.
9. Bauer DC, *et al.* Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med* 2004; **164:** 146–52.
10. Reid IR, *et al.* Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. *Lancet* 2001; **357:** 509–12.
11. Pedersen TR, Kjekshus J. 4S Study Group. Statin drugs and the risk of fracture. *JAMA* 2000; **284:** 1921–2.
12. Coons JC. Hydroxymethylglutaryl-coenzyme A reductase inhibitors in osteoporosis management. *Ann Pharmacother* 2002; **36:** 326–30.

Preparations

BP 2008: Simvastatin Tablets;
USP 31: Simvastatin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Coledis†; Colesterminol; Dosavastatin; Gemistatin; Klonastin; Labistatin; Lipimibe; Lisac; Nivelipol; Nosterol; Redusterol; Sevacol; Several; Tanavat; Vasotenal; Zocor; ***Austral.:*** Lipex; Ransim†; Simvabell; Simvahexal; Simvar; Zimstat; Zocor; ***Austria:*** Gerosim; Nyzoc; SimcorHexal†; Simstin†; Simvarcana; Simvastad; Simvatin; Zocord; ***Belg.:*** Cholemed; Docsimvasta; Simvafour; Simvastamed; Zocor; ***Braz.:*** Androlip†; Clinfar; Cordiron†; Lipotex; Liptrat; Lovacor†; Menocol; Mivalen; Revastin; Sinvalip; Sinvascor; Sinvastacor†; Sinvastamed; Sinvastin†; Sinvatrox; Sinvax; Sinvaz†; Sivastin†; Vaslip; Vastatil; Zocor; ***Canad.:*** Zocor; ***Chile:*** Arterosan†; Nimicor; Simvass; Vasomed; Vasotenal; Zocor; ***Cz.:*** Apo-Simva; Corsim; Egilipid; Sim; Simbela; Simgal; Simirex; Simva; Simvacard; Simvax; Simvor; Vasilip; Zocor; ***Denm.:*** Perichol; Zocolip; Zocor; ***Fin.:*** Corolin†; Lipcut; Zocor; ***Fr.:*** Lodales; Zocor; ***Ger.:*** BeL; Denan†; Simva; SimvaAPS; Simvabeta; Simvacard; Simvacor; Simvadoc; Simvadura; Simvagamma; Simvalip; Zemox†; Zocor; ***Gr.:*** Antichol; Arstatin; Avatratin; Bevostatin; Christatin; Doctiverine; Extrastatin; Glipal; Goldastatin; Iamastatin; Ipramid; Kymazol; Lepur; Lip-Down; Lipomin; Lipopress; Liporex; Lipozid; Lowcholid; Lusimva; Medistatin; Nitastin; Normotherin; Placol; Prelon; Priacin; Prizelip; Raptor; Ravostan; Redusterol; Simplaqor; Simvachol†; Simvacor; Simvalark; Simvalid; Simvaprol; Simvatin; Sivinar; Sotovastin; Starezin; Stasiva; Statinal; Statinum; Stativer; Statosan; Stazor; Sterylip; Vassor; Vastatin; Velkastatin; Zocor; Zurocid; ***Hong Kong:*** Avastinee; Corstat; Covastin; Qualicor; Simcard; Simtin; Vasilip; Vidastat; Zocor; ***Hung.:*** Awestatin; Sicor; Simvacol; Simvagamma; Simvep; Simvor; Vasilip; Zocor; ***India:*** Biosim†; Simcard; Simchol; Simlo; Simvotin; ***Indon.:*** Cholestat; Detrovel; Esvat; Ethicol; Lipinorm; Mersivas; Normofat; Pontizoc; Rechol; Rendapid; Simbado; Simchol; Simcor; Sinova; Valemia; Vazim; Vidastat; Zocor; Zovast; ***Irl.:*** Ritechol; Simator; Simtan; Simzor; Sivatin; Zocor; ***Israel:*** Simovil; Simvacor; Simvaxon; ***Ital.:*** Liponorm; Medipo; Sinvacor; Sivastin; Zocor; ***Malaysia:*** Covastin; Simcard; Simtin; Simvacor; Simvor; Stavid; Vascor; Zocor; ***Mex.:*** Apomastina; Colesken; Fansia; Imbistad; Josken†; Pulsar-AT Dual; Simplaqor; Tulip; Zeid; Zocor; Zorced; ***Neth.:*** Altercor†; Simva†; Zocor; ***Norw.:*** Zocor; ***NZ:*** Lipex; Sim-Statin; ***Philipp.:*** Cholestad; Eurocor; Euvasten; Forcad; Ivast; Lipivas; Normastin; Orovas; Simtin; Simvahex; Uni-Per; Vastilan; Vidastat; Wilsim; Zivas; Zocor; Zolvastin; Zovast; ***Pol.:*** Cardin; Simgal; Simratio; Simredin; Simvacard; Simvachol; Simvacor; Simvahexal; Simvasterol; Vasilip; Vastan; Ximve; Zocor; ***Port.:*** Colvastina; Dislipina; Jabastatina; Lipaz; Simvacol; Simvasim; Sinpor; Sintar; Sinvastil; Sumaclina†; Tavitan; Vascorim; Zera; Zocor; ***Rus.:*** Actalipid (Акталипид); Aterostat (Атеростат); Simgal (Симгал); Simlo (Симло); Simvacard (Симвакард); Simvahexal (Симвагексал); Simvalimit (Симвалимит); Simvastol (Симвастол); Simvor (Симвор); Vasilip (Вазилип); Zocor (Зокор); Zorstat (Зорстат); Zovatin (Зоватин); ***S.Afr.:*** Lipidex; Simaspen; Simcard; Simvacor; Simvotin; Zocor; ***Singapore:*** Covastin; Ifistatin; Simtin; Simvacor; Simvor; Vascor†; Zocor; ***Spain:*** Arudel; Belmalip; Colemin; Glutasey; Histop; Lipociden; Pantok; Simvasten†; Simvastur†; Teylor; Zocor; ***Swed.:*** Zocord; ***Switz.:*** Adipur; Simcora; Simvasine; Simvast; Simvastin; Zocor; ***Thai.:*** Bestatin; Eucor; Lochol; Simvor; Torio; Vascor; Zimmex; Zocor; ***Turk.:*** Lipovas; Simvakol; Zocor; Zovatin; ***UAE:*** Simvast; ***UK:*** Simvador; Zocor; ***USA:*** Zocor; ***Venez.:*** Cynt; Hisplenil†; Kavelor; Rowestin†; Simplaqor; Sinvaz; Tavor; Tinasin; Vasotenal; Vastan; Zocor.

Multi-ingredient: ***Arg.:*** Alipas Duo; Labistatin Duo; Redusterol Duo; Vasotenal EZ; Vytorin; ***Austral.:*** Vytorin; ***Austria:*** Inegy; Vytorin; ***Braz.:*** Diocomb Sl; Prevencor; Vytorin; Zetsim; ***Chile:*** Adacai; Vytorin; Zintrepid; ***Cz.:*** Inegy; ***Fr.:*** Inegy; ***Ger.:*** Inegy; ***Gr.:*** Inegy; Vytorin; ***Hong Kong:*** Vytorin; ***Hung.:*** Inegy; ***Indon.:*** Vytorin; ***Irl.:*** Inegy; ***Ital.:*** Inegy; Vytorin; ***Malaysia:*** Vytorin; ***Mex.:*** Amlidual; Vytorin; Zintrepid; ***Neth.:*** Inegy; Vytorin; ***Norw.:*** Inegy; ***NZ:*** Vytorin; ***Philipp.:*** Vytorin; ***Port.:*** Inegy; ***Singapore:*** Vytorin; ***Swed.:*** Zocord/ASA†; ***UK:*** Inegy; ***USA:*** Simcor; Vytorin; ***Venez.:*** Adacai; Vytorin; Zintrepid.

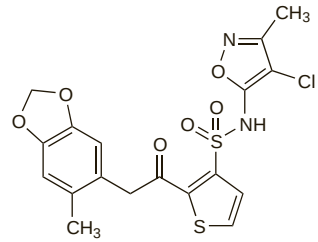
Sitaxentan Sodium *(rINNM)*

Natrii Sitaxentanum; Sitaxentán sódico; Sitaxentan Sodique; Sitaxsentan Sodium; TBC-11251 (sitaxentan or sitaxentan sodium). *N*-(4-Chloro-3-methyl-5-isoxazolyl)-2-{[4,5-(methylenedioxy)-*o*-tolyl]acetyl}-3-thiophenesulfonamide sodium.

Натрий Ситаксентан

$C_{18}H_{14}ClN_2NaO_6S_2$ = 476.9.

CAS — 184036-34-8 (sitaxentan); 210421-74-2 (sitaxentan sodium).



(sitaxentan)

Adverse Effects

As for Bosentan, p.1235. Increases in INR and prolongation of the prothrombin time have also been reported.

Sitaxentan is teratogenic in *rats.*

Precautions

As for Bosentan, p.1235. Sitaxentan is contra-indicated in patients with mild to severe hepatic impairment (Child-Pugh Class A to C).

Although, like bosentan, sitaxentan is teratogenic in *rats* and similar precautions apply, its effects on combined oral contraceptives may differ (see Interactions below).

Interactions

Sitaxentan is both an inhibitor of and a substrate for the cytochrome P450 isoenzyme CYP2C9 and interactions may therefore occur with other drugs that are either metabolised by, or inhibit, this isoenzyme. Plasma concentrations of oral anticoagulants such as warfarin may be increased.

Use with ciclosporin is contra-indicated as plasma concentrations of sitaxentan are greatly increased (see below).

Sitaxentan has increased exposure to ethinylestradiol and norethisterone in those taking oral contraceptives and may possibly increase the associated risk of thromboembolism.

Ciclosporin. Licensed product information for sitaxentan states that its concentration was increased sixfold when given with ciclosporin 3.5 mg/kg twice daily. Although the mechanism of action is unknown it has been postulated that sitaxentan sodium is a substrate for the organic anion transporting polypeptide (OATP) transporter protein and should therefore be used with caution with other, more potent, OATP inhibitors.

Pharmacokinetics

Sitaxentan sodium is absorbed after oral doses with peak plasma concentrations being achieved within 1 to 4 hours. Its absolute bioavailability is 70 to 100%. A high-fat meal delays the rate of absorption but does not affect the extent. Sitaxentan is more than 99% bound to plasma proteins, mainly albumin.

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).

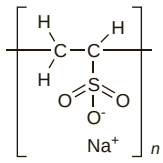
Натрия Аполат

$(C_2H_3NaO_3S)_n$.

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

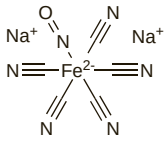
Disodium (*OC*-6-22)-Pentakis(cyano-*C*)nitrosylferrate Dihydrate; Natrii nitroprussias; Natrii Nitroprussias Dihydricus; Natrii Nitroprussicum; Natrio nitroprusidas; Natriumnitroprussid; Natriumnitroprussidi; Nitroprusiato sódico; Nitroprussid sodný dihydrát; Nitroprusszid-nátrium; Sodium Nitroferricyanide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