7. Mohr JP, *et al.* Meta-analysis of oral nimodipine trials in acute ischemic stroke. *Cerebrovasc Dis* 1994; **4:** 197–203.
8. Horn J, *et al.* Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke* 2001; **32:** 461–5.
9. Roine RO, *et al.* Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial. *JAMA* 1990; **264:** 3171–7.
10. Parnetti L, *et al.* Nimodipine Study Group. Mental deterioration in old age: results of two multicenter, clinical trials with nimodipine. *Clin Ther* 1993; **15:** 394–406.
11. López-Arrieta J, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 12/07/05).

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including nimodipine, in the management of migraine and cluster headache, see under Nifedipine, p.1355.

Preparations

BP 2008: Nimodipine Intravenous Infusion; Nimodipine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: AC Vascular; Acival; Ampina; Aniduv; Cebrofort; Cletonol†; Eugerial; Explaner; Finacilen; Macobal; Nimo-Somazina; Nimodilat; Nimotop; Nivas; Tenocard; ***Austral.:*** Nimotop; ***Austria:*** Nimotop; ***Belg.:*** Nimotop; ***Braz.:*** Eugerial; Neuron; Nimobal; Nimopax; Nimotop; Nimovas†; Noodipina; Norton†; Oxigen; Vasodipina; ***Canad.:*** Nimotop; ***Chile:*** Brainal†; Grifonimod; Neurogeron†; Nimotop; Regental; Vasoflex†; ***Cz.:*** Brainal†; Dilceren; Nimotop; ***Denm.:*** Nimotop; ***Fin.:*** Nimotop; ***Fr.:*** Nimotop; ***Ger.:*** Nim†; Nimotop; ***Gr.:*** Aurodipine; Befimat; Curban; Figozant; Genovox; Myodipine; Naborel; Nelbinex†; Nimodil; Nimotop; Nimovac-V; Nortolan; Rosital; Stigmicarpin; Thrionipen; Vastripine; Ziremex; ***Hong Kong:*** Nimotop; ***Hung.:*** Nimotop; ***India:*** Vasotop; ***Indon.:*** Nimotop; ***Irl.:*** Nimotop; ***Israel:*** Nimotop; ***Ital.:*** Nimotop; Periplum; ***Malaysia:*** Nimotop†; ***Mex.:*** Kenzolol; Nimotop; Vacer; ***Neth.:*** Nimotop; ***Norw.:*** Nimotop; ***NZ:*** Nimotop; ***Philipp.:*** Nimotop; ***Pol.:*** Nimotop; ***Port.:*** Brainox; Genogris; Modibloq; Modina; Nimotop; Sobrepina; Trinalion; ***Rus.:*** Brainal (Брейнал)†; Nemotan (Немотан); Nimotop (Нимотоп); ***S.Afr.:*** Nimotop; ***Singapore:*** Nimotop; ***Spain:*** Admon; Brainal; Calnit; Kenesil; Modus; Nimotop; Remontal; ***Swed.:*** Nimotop; ***Switz.:*** Nimotop; ***Thai.:*** Nimotop; ***Turk.:*** Nimotop; ***UK:*** Nimotop; ***USA:*** Nimotop; ***Venez.:*** Kleren†; Nemodine; Nimotop; Tropocer.

Multi-ingredient: ***Arg.:*** Idesole Plus; Nemocebral Plus; Nimodilat Plus; Nimoreagin; Nivas Plus.

Nisoldipine *(BAN, USAN, rINN)*

Bay-k-5552; Nisoldipiini; Nisoldipin; Nisoldipino; Nisoldipinum. Isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

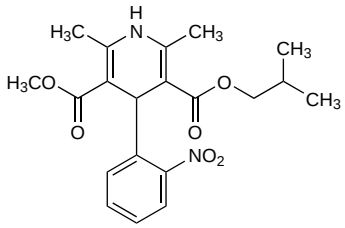
Низольдипин

$C_{20}H_{24}N_2O_6$ = 388.4.

CAS — 63675-72-9.

ATC — C08CA07.

ATC Vet — QC08CA07.



Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nisoldipine is well absorbed from the gastrointestinal tract after oral doses but undergoes rapid and extensive first-pass metabolism in the gut wall and liver and bioavailability has been reported to be only about 4 to 8%. About 60 to 80% of an oral dose is excreted in the urine and the remainder in the faeces, mainly as metabolites. The terminal elimination half-life is about 7 to 12 hours. Nisoldipine is more than 99% bound to plasma proteins.

◊ A study[1] in 11 patients given oral nisoldipine 10 mg once or twice daily indicated that the pharmacokinetics of nisoldipine could best be described by an open 2-compartment model. Peak plasma concentrations occurred 1 hour after a single oral dose, and varied greatly between the patients. The mean plasma elimination half-life was 11.4 hours after a single dose and 14.0 hours after repeated dosing, which was longer than had been previously reported, perhaps reflecting the greater sensitivity of the assay.

In another study oral, but not intravenous, nisoldipine increased liver blood flow in 10 healthy subjects and thus affected its own systemic availability.[2] Variations in liver blood flow may account for the interindividual variation in the pharmacokinetics of nisoldipine.

1. Ottosson A-M, *et al.* Analysis and pharmacokinetics of nisoldipine in hypertensive patients. *Curr Ther Res* 1989; **45:** 347–58.
2. van Harten J, *et al.* Variability in the pharmacokinetics of nisoldipine as caused by differences in liver blood flow response. *J Clin Pharmacol* 1989; **29:** 714–21.

Uses and Administration

Nisoldipine is a dihydropyridine calcium-channel blocker with actions and uses similar to those of nifedipine (p.1354). It is used in the management of hypertension (p.1171) and angina pectoris (p.1157).

Nisoldipine is given orally usually as a modified-release preparation. Absorption is affected by food and the modified-release preparation should be taken on an empty stomach; it should not be taken with high fat meals. Doses are similar for both hypertension and angina. The initial dose is 10 mg once daily and the usual maintenance dose is 20 to 40 mg once daily.

◊ Reviews.

1. Mitchell J, *et al.* Nisoldipine: a new dihydropyridine calcium-channel blocker. *J Clin Pharmacol* 1993; **33:** 46–52.
2. Plosker GL, Faulds D. Nisoldipine coat-core: a review of its pharmacology and therapeutic efficacy in hypertension. *Drugs* 1996; **52:** 232–53.
3. Langtry HD, Spencer CM. Nisoldipine coat-core; a review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of ischaemic heart disease. *Drugs* 1997; **53:** 867–84.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nisodipen†; ***Austria:*** Syscor; ***Belg.:*** Sular; Syscor; ***Braz.:*** Syscor; ***Chile:*** Nivas; ***Cz.:*** Syscor†; ***Fin.:*** Syscor; ***Ger.:*** Baymycard; ***Gr.:*** Syscor; ***Hung.:*** Baymycard; ***Ital.:*** Syscor; ***NZ:*** Syscor; ***S.Afr.:*** Syscor†; ***Spain:*** Cornel†; Sular; Syscor; ***Switz.:*** Syscor†; ***UK:*** Syscor; ***USA:*** Sular.

Nitrendipine *(BAN, USAN, rINN)*

Bay-e-5009; Nitrendipiini; Nitrendipin; Nitrendipinas; Nitrendipino; Nitrendipinum. Ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

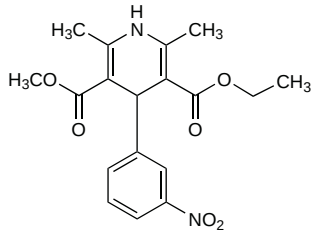
Нитрендипин

$C_{18}H_{20}N_2O_6$ = 360.4.

CAS — 39562-70-4.

ATC — C08CA08.

ATC Vet — QC08CA08.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn*.
Ph. Eur. 6.2 (Nitrendipine). A yellow crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in ethyl acetate. Exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

Adverse Effects, Treatment, and Precautions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1350).

Interactions

As for dihydropyridine calcium-channel blockers (see Nifedipine, p.1352).

Pharmacokinetics

Nitrendipine is reported to be well absorbed after oral doses but undergoes extensive first-pass metabolism; the absolute oral bioavailability is reported to range from about 10 to 20%, depending in part on the dosage form. Nitrendipine is about 98% bound to plasma proteins. It is extensively metabolised in the liver and is excreted as metabolites, mainly in urine, with small amounts in the faeces. Although early studies reported a terminal elimination half-life of about 2 to 4 hours, later studies, using more sensitive assay procedures, have recorded values between about 10 and 22 hours.

◊ References.

1. Soons PA, Breimer DD. Stereoselective pharmacokinetics of oral and intravenous nitrendipine in healthy male subjects. *Br J Clin Pharmacol* 1991; **32:** 11–16.

Uses and Administration

Nitrendipine is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine (p.1354). It is used in the treatment of hypertension (p.1171).

The usual dose is 20 mg daily as a single oral dose or as 2 divided doses. The dose may be increased to 20 mg twice daily if necessary for the control of resistant hypertension. In the elderly, an initial dose of 10 mg daily should be used. The dose should also be reduced in hepatic impairment (see below).

◊ Reviews.

1. Santiago TM, Lopez LM. Nitrendipine: a new dihydropyridine calcium-channel antagonist for the treatment of hypertension. *DICP Ann Pharmacother* 1990; **24:** 167–75.

Administration in hepatic impairment. The initial dose of nitrendipine should be reduced to 5 to 10 mg once daily in patients with hepatic impairment.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nirapel; Nitrendil; Tocrat†; ***Austria:*** Baypress; ***Belg.:*** Baypress; ***Braz.:*** Caltren; Nitrencord; ***Chile:*** Cardiazem; Grifonitren; Nitrendicor†; Presabet†; Tensofar; ***Cz.:*** Baypress; Lusopress; Nitrepress; Nitresan; Unipres; ***Denm.:*** Baypress; ***Fr.:*** Baypress; Nidrel; ***Ger.:*** Bayotensin; Jutapress; Nitre; Nitre-Puren; Nitregamma; Nitren Lich; Nitren†; Nitrendepat†; Nitrendidoc; Nitrendimerck†; Nitrensal; Nitrepress; ***Gr.:*** Aroselin; Baypress; Crivion; G-Press; Lanocardique†; Leonitren; Lisba; Lostradyl; Midonat†; Nelconil; Nifecard; Nivitron; Pallohyman†; Potional; Pressodipin; Spidox; Tepanil†; Ufocard; ***Hong Kong:*** Baypress; ***Hung.:*** Baypress; Unipres; ***Ital.:*** Baypress; Deiten; ***Jpn:*** Baylotensin; ***Mex.:*** Baypress†; ***Neth.:*** Baypress; ***Port.:*** Baypress; Farnitran; Hiperdipina; Hipertenol†; ***Spain:*** Balminil†; Baypresol; Gericin; Niprina; Sub Tensin; Tensogradal; Trendinol†; Vastensium; ***Switz.:*** Baypress; ***Thai.:*** Baypress; Ditrenil; Miniten; ***Turk.:*** Baypress; ***Venez.:*** Baypress; Nitrendil; Retencal†.

Multi-ingredient: ***Ger.:*** Eneas; ***Gr.:*** Eneas; Enit; ***India:*** Cardif Beta; ***Port.:*** Eneas; Enit; ***Spain:*** Eneas; Enit; Vipres; Zorail.

Nitric Oxide *(USAN)*

Azote, monoxyde d'; Azoto oksidas; Azotu(II) tlenek; Kväveoxid; Mononitrogen Monoxide; Nitrogen Monoxide; Nitrogenii oxidum; Nitrogén-monoxid; OHM-11771; Oxid dusnatý; Óxido nítrico; Typpioksidi.

NO = 30.01.

CAS — 10102-43-9.

ATC — R07AX01.

ATC Vet — QR07AX01.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Nitric Oxide). A colourless gas that turns brown when exposed to air. At 20° and at a pressure of 101 kPa, 1 volume dissolves in about 21 volumes of water. Store compressed at a pressure not exceeding 2.5 MPa measured at 15° in suitable containers.

Adverse Effects

Inhaled nitric oxide may lead to the development of methaemoglobinaemia, particularly at higher doses. Although it is a selective pulmonary vasodilator, systemic hypotension may occur. Abrupt withdrawal of therapy may lead to a deterioration in oxygenation and the development of rebound pulmonary hypertension.

Nitrogen dioxide produced when nitric oxide combines with oxygen can cause acute lung injury; high concentrations of inhaled nitric oxide are directly irritant to the lungs.

◊ A potential complication of inhaled nitric oxide is methaemoglobinaemia but this is probably related to the dose; the risk does not appear to be increased during low-dose (20 ppm) therapy.[1] Another possible adverse event is an increased risk of bleeding due to inhibition of platelet aggregation.[2-5] Rebound pulmonary hypertension[6] and deterioration in oxygenation[7,8] have been reported in some children after stopping nitric oxide therapy. Severe systemic hypotension has also been reported[9] after starting therapy in a neonate with severe left ventricular dysfunction. Pulmonary oedema has been associated with the use of nitric oxide in 2 patients with CREST syndrome, a form of systemic sclerosis.[10] Motor neurone disease in a patient with alcoholism has been partly attributed[11] to the use of nitric oxide for pulmonary hypertension.

1. Kinsella JP, Abman SH. Methaemoglobin during nitric oxide therapy with high-frequency ventilation. *Lancet* 1993; **342:** 615.

2. Högman M, *et al.* Bleeding time prolongation and NO inhalation. *Lancet* 1993; **341:** 1664–5.
3. Joannidis M, *et al.* Inhaled nitric oxide. *Lancet* 1996; **348:** 1448–9.
4. Cheung P-Y, *et al.* Inhaled nitric oxide and inhibition of platelet aggregation in critically ill neonates. *Lancet* 1998; **351:** 1181–2.
5. George TN, *et al.* The effect of inhaled nitric oxide therapy on bleeding time and platelet aggregation in neonates. *J Pediatr* 1998; **132:** 731–4.
6. Miller OI, *et al.* Rebound pulmonary hypertension on withdrawal from inhaled nitric oxide. *Lancet* 1995; **346:** 51–2.
7. Aly H, *et al.* Weaning strategy with inhaled nitric oxide treatment in persistent pulmonary hypertension of the newborn. *Arch Dis Child Fetal Neonatal Ed* 1997; **76:** F118–F122.
8. Davidson D, *et al.* Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn. *Pediatrics* 1999; **104:** 231–6.
9. Henrichsen T, *et al.* Inhaled nitric oxide can cause severe systemic hypotension. *J Pediatr* 1996; **129:** 183.
10. Preston IR, *et al.* Pulmonary edema caused by inhaled nitric oxide therapy in two patients with pulmonary hypertension associated with the CREST syndrome. *Chest* 2002; **121:** 656–9.
11. Tsai GE, Gastfriend DR. Nitric oxide-induced motor neuron disease in a patient with alcoholism. *N Engl J Med* 1995; **332:** 1036.

Precautions

Patients given inhaled nitric oxide should be monitored for methaemoglobinaemia and oxygenation. Inhaled nitric oxide and nitrogen dioxide levels should also be monitored. Treatment should not be stopped abruptly since rebound pulmonary hypertension and deterioration in oxygenation may occur.

The exposure of workers to nitric oxide and nitrogen dioxide should be limited.

◊ References.

1. CSM/MCA. Inhaled nitric oxide. *Current Problems* 1996; **22:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 02/06/08)
2. Cuthbertson BH, *et al.* Use of inhaled nitric oxide in British intensive therapy units. *Br J Anaesth* 1997; **78:** 696–700.
3. Phillips ML, *et al.* Assessment of medical personnel exposure to nitrogen oxides during inhaled nitric oxide treatment of neonatal and pediatric patients. *Pediatrics* 1999; **104:** 1095–1100.

Pharmacokinetics

Nitric oxide is absorbed systemically after inhalation but is rapidly inactivated by reaction with haemoglobin to form methaemoglobin and nitrate; it has a half-life of only a few seconds. It is excreted mainly in the urine as nitrate.

Uses and Administration

Nitric oxide is an endogenous chemical messenger that acts mainly by stimulating guanylate cyclase in smooth muscle to cause vasodilatation. It is also involved in platelet aggregation, neurotransmission, and the immune system, and possesses antimicrobial, antitumour, and antiviral activity.

Endogenous nitric oxide is now recognised to be the same substance as endothelium-derived relaxing factor (EDRF). It is synthesised from L-arginine by the enzyme, nitric oxide synthase, of which three isoforms have been identified. Constitutive isoforms occur in endothelial cells (such as in vascular endothelium, platelets, and the heart) and neuronal cells (in some central and peripheral neurones). Small amounts of nitric oxide are regularly produced by these systems. In contrast, an inducible isoform producing larger amounts of nitric oxide is expressed only after activation by external stimuli such as infection or inflammation. This inducible nitric oxide synthase may be expressed in many cells, including macrophages and cells in vascular smooth muscle, the heart, gastrointestinal tract, and liver.

Inhaled nitric oxide is a highly selective pulmonary vasodilator. It is used in the management of term and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. It is also used as a diagnostic tool to test acute vasoreactivity in patients with pulmonary hypertension of various aetiologies, and is being studied in other bronchopulmonary disorders and in different age groups.

In the management of hypoxic respiratory failure in neonates, nitric oxide is given by inhalation in a usual concentration of 20 ppm. Doses have been titrated above and below this concentration but due to the risk of methaemoglobinaemia, doses above 20 ppm are not generally recommended. The concentration should be reduced gradually before stopping treatment.

◊ General reviews.

1. Hart CM. Nitric oxide in adult lung disease. *Chest* 1999; **115:** 1407–17.
2. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. *Heart* 2001; **85:** 342–50.
3. Ichinose F, *et al.* Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation* 2004; **109:** 3106–11.
4. Griffiths MJD, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; **353:** 2683–95.

Respiratory disorders. Inhaled nitric oxide is a potent and highly selective pulmonary vasodilator used in the management of persistent pulmonary hypertension of the newborn (below) and other conditions leading to hypoxic respiratory failure in neonates.

Nitric oxide has also been tried in acute respiratory distress syndrome (below), severe acute respiratory syndrome,[1] respiratory failure,[2] acute severe asthma,[3] primary pulmonary hypertension[4,5] including that in pregnancy,[6,7] and in pulmonary hypertension associated with a wide range of conditions including chronic obstructive pulmonary disease,[8] heart failure,[9] post-cardiac surgery,[10-12] heart or lung transplantation,[13] and high-altitude disorders.[14]

1. Chen L, *et al.* Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004; **39:** 1531–5.
2. Dobyns EL, *et al.* Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 1999; **134:** 406–12.
3. Nakagawa TA, *et al.* Life-threatening status asthmaticus treated with inhaled nitric oxide. *J Pediatr* 2000; **137:** 119–22.
4. Kinsella JP, *et al.* Selective and sustained pulmonary vasodilation with inhalational nitric oxide therapy in a child with idiopathic pulmonary hypertension. *J Pediatr* 1993; **122:** 803–6.
5. Goldman AP, *et al.* Is it time to consider domiciliary nitric oxide? *Lancet* 1995; **345:** 199–200.
6. Lam GK, *et al.* Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. *Obstet Gynecol* 2001; **98:** 895–8.
7. Decoene C, *et al.* Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. *Can J Anaesth* 2001; **48:** 584–7.
8. Vonbank K, *et al.* Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 2003; **58:** 289–93.
9. Matsumoto A, *et al.* Inhaled nitric oxide and exercise capacity in congestive heart failure. *Lancet* 1997; **349:** 999–1000. Correction. *ibid.*; **350:** 818.
10. Haydar A, *et al.* Inhaled nitric oxide for postoperative pulmonary hypertension in patients with congenital heart defects. *Lancet* 1992; **340:** 1545.
11. Miller OI, *et al.* Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet* 2000; **356:** 1464–9.
12. Journois D, *et al.* Effects of inhaled nitric oxide administration on early postoperative mortality in patients operated for correction of atrioventricular canal defects. *Chest* 2005; **128:** 3537–44.
13. Rea RS, *et al.* Role of inhaled nitric oxide in adult heart or lung transplant recipients. *Ann Pharmacother* 2005; **39:** 913–17.
14. Scherrer U, *et al.* Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996; **334:** 624–9.

Acute respiratory distress syndrome. Although inhalation of nitric oxide has been reported to improve oxygenation in patients with acute respiratory distress syndrome (p.1498), meta-analyses[1,2] have failed to confirm any significant mortality benefit, and there is some evidence[2] that nitric oxide increases the risk of renal dysfunction.

1. Sokol J, *et al.* Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 26/09/05).
2. Adhikari NKJ, *et al.* Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. Abridged version: *BMJ* 2007; **334:** 779–82. Full version: http://www.bmj.com/cgi/reprint/334/7597/779 (accessed 31/07/08)

Respiratory disorders in neonates. Inhaled nitric oxide is used in the management of hypoxic respiratory failure in term and near-term neonates.[1-3] It has also been studied in premature neonates.

Most studies have been in neonates with persistent pulmonary hypertension of the newborn (p.1179), although varying definitions have been used. A systematic review[4] of controlled studies in term and near-term neonates with hypoxic respiratory failure found that oxygenation was improved with inhaled nitric oxide, with a reduction in the need for extracorporeal membrane oxygenation, but no effect on mortality has been shown. A randomised trial[5] also found no mortality benefit when nitric oxide was started early in the disease process, although progression was slowed. Neonates with congenital diaphragmatic hernia (CDH), however, have not been shown to benefit,[6,7] and nitric oxide is not recommended in such patients,[4] although the optimal treatment of this condition is controversial; one study[8] suggested that inhaled nitric oxide may have a role in patients with CDH who develop late pulmonary hypertension. Another study[9] suggested that the improvement in oxygenation may not be sustained, and that neonates with pulmonary hypoplasia and dysplasia are less sensitive to nitric oxide.

The dose of nitric oxide found to be effective in most studies has been from 20 to 80 ppm. However, since nitric oxide is associated with dose-related toxicity, lower doses (1 to 2 ppm) have also been studied. One study[10] found no significant difference between high and low doses, but another study[11] found that low doses did not improve oxygenation and diminished the response to subsequent higher doses.

Inhaled nitric oxide has also been reported to improve oxygenation in premature neonates with hypoxic respiratory failure, but its use is not yet established.[12,13] A study[14] in premature infants with respiratory distress syndrome suggested that the incidence of chronic lung disease and death was reduced by nitric oxide, and an open study[15] in very premature infants who had already developed chronic lung disease also found an improvement in oxygenation with nitric oxide therapy. However, a systematic review[16] found that use of rescue nitric oxide therapy in severely ill infants was ineffective, and that late use to prevent chronic lung disease also had no effect. There was some evidence that early routine use in mildly sick infants might improve outcomes, but further studies were needed to identify those infants who were most likely to benefit.

There have been concerns that use of inhaled nitric oxide might adversely affect neurodevelopmental outcome more than conventional therapy particularly in premature infants, but follow-up studies have reported mixed results. Studies in term and near-term infants,[17-19] and in premature infants,[20] have found that use of nitric oxide has no effect on neurodevelopment, but there have also been reports of poor neurodevelopmental outcome[21] and of improved outcome.[22,23] Differences in study design make comparisons between studies difficult, and the effect on neurodevelopment remains to be confirmed.

1. American Academy of Pediatrics Committee on Fetus and Newborn. Use of inhaled nitric oxide. *Pediatrics* 2000; **106:** 344–5.
2. Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. *J Pediatr* 2000; **136:** 717–26.
3. Hoehn T, Krause MF. Response to inhaled nitric oxide in premature and term neonates. *Drugs* 2001; **61:** 27–39.
4. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 04/06/08).
5. Konduri GG, *et al.* A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. *Pediatrics* 2004; **113:** 559–64.
6. Clark RH, *et al.* Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med* 2000; **342:** 469–74.
7. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics* 1997; **99:** 838–45.
8. Kinsella JP, *et al.* Noninvasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. *J Pediatr* 2003; **142:** 397–401.
9. Goldman AP, *et al.* Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics* 1996; **98:** 706–13.
10. Finer NN, *et al.* Randomized, prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. *Pediatrics* 2001; **108:** 949–55.
11. Cornfield DN, *et al.* Randomized, controlled trial of low-dose inhaled nitric oxide in the treatment of term and near-term infants with respiratory failure and pulmonary hypertension. *Pediatrics* 1999; **104:** 1089–94.
12. Subhedar N, Dewhurst C. Is nitric oxide effective in preterm infants? *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F337–F341.
13. Kinsella JP, Abman SH. Inhaled nitric oxide in the premature newborn. *J Pediatr* 2007; **151:** 10–15.
14. Schreiber MD, *et al.* Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med* 2003; **349:** 2099–2107.
15. Clark PL, *et al.* Safety and efficacy of nitric oxide in chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2002; **86:** F41–F45.
16. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 04/06/08).
17. Rosenberg AA, *et al.* Longitudinal follow-up of a cohort of newborn infants treated with inhaled nitric oxide for persistent pulmonary hypertension. *J Pediatr* 1997; **131:** 70–5.
18. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the Neonatal Inhaled Nitric Oxide Study Group (NINOS). *J Pediatr* 2000; **136:** 611–17.
19. Konduri GG, *et al.* Neonatal Inhaled Nitric Oxide Study Group. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. *J Pediatr* 2007; **150:** 235–40.
20. Hintz SR, *et al.* NICHD Neonatal Research Network. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. *J Pediatr* 2007; **151:** 16–22.

21. Cheung P-Y, *et al.* The outcome of very low birth weight neonates (≤1500g) rescued by inhaled nitric oxide: neurodevelopment in early childhood. *J Pediatr* 1998; **133:** 735–9.
22. Mestan KKL, *et al.* Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med* 2005; **353:** 23–32.
23. Tanaka Y, *et al.* Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; **119:** 1159–64.

Sickle-cell disease. Sickle-cell crisis due to vaso-occlusion is an acute complication of sickle-cell disease (p.1044), requiring hospitalisation, with the use of large volumes of intravenous fluids for dehydration, and analgesia including opioids for pain. Concentrations of nitric oxide metabolites and L-arginine have been found to be low in vaso-occlusive crisis and a study[1] in paediatric patients showed that inhaled nitric oxide may be of benefit.

1. Weiner DL, *et al.* Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* 2003; **289:** 1136–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: INOmax; ***Denm.:*** INOmax; ***Gr.:*** INOmax; ***Neth.:*** INOmax; ***Pol.:*** INOmax; ***Port.:*** INOmax; ***Spain:*** INOmax; ***Switz.:*** INOmax; ***USA:*** INOmax.

Noradrenaline *(BAN)* ⊗

Norepinephrine *(BAN, rINN)*; Levarterenol; Noradrenaliini; Noradrenalin; Noradrenalinum; Norepinefriini; Norepinefrin; Norepinefrina; Norépinéphrine; Norepinephrinum; Norepirenamine. (*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol.

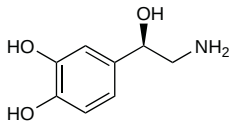
Норэпинефрин

$C_8H_{11}NO_3$ = 169.2.

CAS — 51-41-2.

ATC — C01CA03.

ATC Vet — QC01CA03.



Pharmacopoeias. *Jpn* includes the racemic form.

Noradrenaline Acid Tartrate *(BANM)* ⊗

Norepinephrine Bitartrate *(USAN, rINNM)*; Arterenol Acid Tartrate; *l*-Arterenol Bitartrate; Bitartrato de norepinefrina; Levarterenol Acid Tartrate; Levarterenol Bitartrate; Levarterenoli Bitartras; Noradrenaliinitartraatti; Noradrenaline Bitartrate; Noradrenaline Tartrate; Noradrénaline, tartrate de; Noradrenalini tartras; Noradrenalino tartratas; Noradrenalin-tartarát; Noradrenalintartrat; Norepinefrin tartarát monohydrát; Norepinefryny wodorowinian; Norepinephrine Acid Tartrate *(BANM)*; *l*-Norepinephrine Bitartrate; Norépinéphrine, Bitartrate de; Norepinephrini Bitartras; Norepinephrini Tartras Monohydricus.

Норэпинефрина Битартрат

$C_8H_{11}NO_3,C_4H_6O_6,H_2O$ = 337.3.

CAS — 51-40-1 (anhydrous noradrenaline acid tartrate); 69815-49-2 (noradrenaline acid tartrate monohydrate).

ATC — C01CA03.

ATC Vet — QC01CA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Noradrenaline Tartrate; Noradrenaline Acid Tartrate BP 2008; Norepinephrine Acid Tartrate BP 2008). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.
USP 31 (Norepinephrine Bitartrate). A white or faintly grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 2.5 of water and 1 in 300 of alcohol; practically insoluble in chloroform and in ether. Its solutions in water have a pH of about 3.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Noradrenaline acid tartrate is strongly acidic in solution, and would be expected to be incompatible with drugs having an alkaline pH. Licensed product information in the UK states that solutions are reportedly incompatible with alkalis and oxidising agents, barbiturates, chlorphenamine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, and streptomycin. Incompatibility with insulin has also been reported.[1]

1. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.

Noradrenaline Hydrochloride *(BANM)* ⊗

Norepinephrine Hydrochloride *(BANM, rINNM)*; Hidrocloruro de norepinefrina; Noradrenaliinihydrokloridi; Noradrénaline, chlorhydrate de; Noradrenalin-hidroklorid; Noradrenalinhydroklorid; Noradrenalini hydrochloridum; Noradrenalino hidrochloridas; Norepinefrin hydrochlorid; Norépinéphrine, Chlorhydrate de; Norepinephrini Hydrochloridum.

Норэпинефрина Гидрохлорид

$C_8H_{11}NO_3$,HCl = 205.6.

CAS — 329-56-6.

ATC — C01CA03.

ATC Vet — QC01CA03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Noradrenaline Hydrochloride; Norepinephrine Hydrochloride BP 2008). A white or brownish-white, crystalline powder. It becomes coloured on exposure to air and light. Very soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.5 to 4.5. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

Adverse Effects

As for Sympathomimetics, p.1407. Noradrenaline is an extremely potent peripheral vasoconstrictor and its adverse effects include hypertension (possibly associated with reflex bradycardia), headache, and peripheral ischaemia, which may be severe enough to result in gangrene of the extremities. Extravasation may lead to severe phlebitis and sloughing.

Dental use. Severe headache,[1,2] including fatal cerebral haemorrhage,[1,3] has been reported after the use of lidocaine with noradrenaline 1 in 25 000 for dental anaesthesia. It was suggested[1-3] that preparations containing noradrenaline 1 in 25 000 should not be used, and that a concentration of 1 in 80 000 was to be preferred. However, in the UK the *Dental Practitioners' Formulary*[4] had stated that noradrenaline should not be used as a vasoconstrictor in local anaesthetic solutions since it presented no advantage over adrenaline and carried additional hazard.

1. Boakes AJ, *et al.* Adverse reactions to local anaesthetic/vasoconstrictor preparations: a study of the cardiovascular responses to Xylestesin and Hostacain-with-Noradrenaline. *Br Dent J* 1972; **133:** 137–40.
2. van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anesthesia. *Anesth Prog* 1992; **39:** 87–9.
3. Okada Y, *et al.* Fatal subarachnoid haemorrhage associated with dental local anaesthesia. *Aust Dent J* 1989; **34:** 323–5.
4. *Dental Practitioners' Formulary.* 2002–2004. London: British Dental Association, British Medical Association, and the Royal Pharmaceutical Society of Great Britain; 2002. D6.

Treatment of Adverse Effects

As for Sympathomimetics, p.1407. If extravasation occurs, infiltration with phentolamine (see p.1370) as soon as possible, and certainly within 12 hours, may relieve pain and prevent tissue necrosis.

Precautions

As for Sympathomimetics, p.1407. Noradrenaline has mainly alpha-agonist properties and must be avoided in the presence of hypertension; blood pressure and infusion rate must be monitored frequently. Noradrenaline-induced cardiac arrhythmias are more likely in patients with hypoxia or hypercapnia.

Noradrenaline is a severe tissue irritant and only very dilute solutions should be used. It should be infused centrally or into a large vein if possible, and care should be taken to avoid extravasation.

Noradrenaline may reduce placental perfusion throughout pregnancy and some consider that it and similar vasoconstrictor sympathomimetics are best avoided; also in late pregnancy noradrenaline provokes uterine contractions which can result in fetal asphyxia.

Interactions

As for Sympathomimetics, p.1407. Severe hypertension may occur if noradrenaline is given to patients taking tricyclic antidepressants since tricyclics block the uptake of noradrenaline into nerve endings.

Pharmacokinetics

Like adrenaline (p.1204), noradrenaline is inactive when given orally, and it is rapidly inactivated in the body by similar processes. When given intravenously it is extensively metabolised and only small amounts are excreted unchanged in the urine.

Uses and Administration

Noradrenaline is a direct-acting catecholamine sympathomimetic (p.1408) with pronounced effects on alpha-adrenergic receptors; it also stimulates $beta_1$ receptors but has little effect on $beta_2$ receptors. It is the major neurotransmitter in postganglionic adrenergic neurones, and is stored in granules in the nerve axons. Some is also present in the adrenal medulla and is released with adrenaline.

The major effects of noradrenaline relate to its alpha-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. Beta-stimulant effects of noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the CNS.

Noradrenaline is used for the emergency restoration of blood pressure in acute hypotensive states such as shock (p.1183). It has also been used in the management of cardiac arrest. Noradrenaline has been used in local anaesthesia to diminish the absorption and localise the effect of the local anaesthetic (p.1852) but adrenaline is now preferred (see also Dental use under Adverse Effects, above). Locally applied solutions have been used to control bleeding in upper gastrointestinal haemorrhage and similar disorders.

In **acute hypotensive states**, noradrenaline is used as the acid tartrate, or occasionally as the hydrochloride, but doses are expressed in terms of the base; noradrenaline acid tartrate 2 micrograms or noradrenaline hydrochloride 1.2 micrograms are equivalent to about 1 microgram of noradrenaline. It is given by intravenous infusion of a solution containing the equivalent of 4 micrograms of the base per mL in glucose 5%, or sodium chloride 0.9% and glucose 5%. To avoid tissue necrosis the infusion should be given through a central venous catheter or into a large vein high up in a limb, preferably the arm. Some sources have suggested that addition of phentolamine 5 to 10 mg/litre to the infusion may prevent sloughing, should extravasation occur, without affecting the vasopressor action. The infusion is usually given initially at a rate of 2 to 3 mL/minute (8 to 12 micrograms/minute) and adjusted according to the blood pressure response. Blood pressure is initially recorded every 2 minutes and the rate of infusion continuously monitored. The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure. The average maintenance dose is 0.5 to 1 mL/minute (2 to 4 micrograms/minute), but there is a wide variation and higher doses may be required. The concentration of the infusion may be altered according to clinical needs. Alternatively a solution containing the equivalent of 40 micrograms of the base per mL may be given at an initial rate of 0.16 to 0.33 mL/minute via a central venous catheter, using a syringe pump or drip counter.

Preparations

BP 2008: Noradrenaline Injection;
USP 31: Norepinephrine Bitartrate Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.