Pharmacokinetics

Nesiritide is cleared from the circulation by 3 mechanisms: uptake into cells; proteolytic cleavage by endopeptidases; and excretion by the kidneys. It has a biphasic elimination, with a terminal elimination half-life of 18 minutes.

Uses and Administration

Nesiritide is a recombinant brain natriuretic peptide (see p.1347) used in the management of acutely decompensated heart failure (p.1165). It is given intravenously as the citrate, but dosage is expressed in terms of the base. The initial dose of nesiritide is 2 micrograms/kg by intravenous injection over 1 minute, followed by a maintenance infusion of 10 nanograms/kg per minute.

Heart failure. The use of nesiritide in acute decompensated heart failure (p.1165) has been reviewed.[1,2] It may be used for short-term treatment as an alternative to standard intravenous therapy with vasodilators, inotropes, or diuretics, and appears to have no proarrhythmic effects; however, its effects on mortality are controversial (see under Adverse Effects and Precautions, above) and its role in therapy remains unclear. There is some evidence from retrospective studies that it may be safely used in addition to standard therapy[3,4] and may have a role as a more prolonged treatment in patients awaiting cardiac transplantation.[5] Although nesiritide has also been given intermittently for outpatient management of chronic heart failure, this use is not currently recommended.[6]

1. Vichiendilokkul A, *et al.* Nesiritide: a novel approach for acute heart failure. *Ann Pharmacother* 2003; **37:** 247–58.
2. Keating GM, Goa KL. Nesiritide: a review of its use in acute decompensated heart failure. *Drugs* 2003; **63:** 47–70.
3. O'Dell KM, *et al.* Nesiritide for secondary pulmonary hypertension in patients with end-stage heart failure. *Am J Health-Syst Pharm* 2005; **62:** 606–9.
4. Smull DL, Jorde UP. Concomitant use of nesiritide and milrinone in decompensated congestive heart failure. *Am J Health-Syst Pharm* 2005; **62:** 291–5.
5. Witteles R, *et al.* B-type natriuretic peptide is effective therapy before care. *Ann Intern Med* 2004; **141:** 895.
6. Bauer JB, Randazzo MA. Nesiritide for outpatient treatment of heart failure. *Am J Health-Syst Pharm* 2005; **62:** 2639–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Natrecor; ***Indon.:*** Natrecor; ***Israel:*** Noratak; ***Switz.:*** Noratak; ***USA:*** Natrecor; ***Venez.:*** Natrecor.

Nicardipine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de nicardipino; Nicardipine, Chlorhydrate de; Nicardipini Hydrochloridum; Nikardipiinihydrokloridi; Nikardipin Hidroklorür; Nikardipinhydroklorid; RS-69216; RS-69216-XX-07-0; YC-93. 2-[Benzyl(methyl)amino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate hydrochloride.

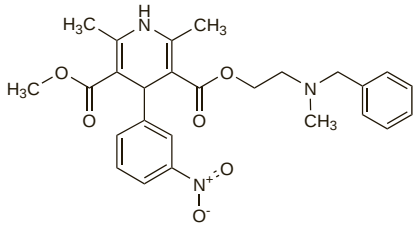
Никардипина Гидрохлорид

$C_{26}H_{29}N_3O_6$,HCl = 516.0.

CAS — 55985-32-5 (nicardipine); 54527-84-3 (nicardipine hydrochloride).

ATC — C08CA04.

ATC Vet — QC08CA04.



(nicardipine)

Pharmacopoeias. In *Chin.* and *Jpn.*

Incompatibility. The manufacturers recommend that a solution containing nicardipine hydrochloride 100 micrograms/mL is used for intravenous infusion. Suitable diluents are solutions of glucose or sodium chloride. Sodium bicarbonate and lactated Ringer's are incompatible with nicardipine infusion. Nicardipine hydrochloride (1 mg/mL in glucose 5%) has also been reported[1] to be visually incompatible with furosemide, heparin, and thiopental.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.

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

Nicardipine is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first-pass hepatic metabolism. Bioavailability of about 35% has been reported after a 30-mg dose at steady state. The pharmacokinetics of nicardipine are non-linear due to the saturable first-pass hepatic metabolism and an increase in dose may produce a disproportionate increase in plasma concentration. There is also considerable interindividual variation in plasma-nicardipine concentrations. Nicardipine is more than 95% bound to plasma proteins. Nicardipine is extensively metabolised in the liver and is excreted in the urine and faeces, mainly as inactive metabolites. The terminal plasma half-life is about 8.6 hours, thus steady-state plasma concentrations are achieved after 2 to 3 days of dosing three times daily.

◊ References.

1. Graham DJM, *et al.* Pharmacokinetics of nicardipine following oral and intravenous administration in man. *Postgrad Med J* 1984; **60** (suppl 4): 7–10.
2. Graham DJM, *et al.* The metabolism and pharmacokinetics of nicardipine hydrochloride in man. *Br J Clin Pharmacol* 1985; **20:** 23S–28S.
3. Razak TA, *et al.* The effect of hepatic cirrhosis on the pharmacokinetics and blood pressure response to nicardipine. *Clin Pharmacol Ther* 1990; **47:** 463–9.
4. Porchet HC, Dayer P. Serum concentrations and effects of (±)-nicardipine compared with nifedipine in a population of healthy subjects. *Clin Pharmacol Ther* 1990; **48:** 155–60.

Uses and Administration

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

Nicardipine hydrochloride is generally given orally although the intravenous route has been used for the short-term treatment of hypertension.

Oral doses of nicardipine hydrochloride are similar for both **hypertension** and **angina**. The initial dose is 20 mg three times daily and may be increased at intervals of at least 3 days until the required effect is achieved. The usual maintenance dose is 30 mg three times daily, but daily doses of between 60 and 120 mg in divided doses may be given. Modified-release preparations of nicardipine hydrochloride for dosage twice daily are also available.

Nicardipine hydrochloride may be given by slow intravenous infusion as a 100 micrograms/mL solution in the short-term treatment of hypertension. An initial infusion rate of 5 mg/hour is recommended, increased, as necessary, up to a maximum of 15 mg/hour and subsequently reduced to 3 mg/hour. For use in children, see below.

Reduced doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment (see below).

◊ Reviews.

1. Curran MP, *et al.* Intravenous nicardipine: its use in the short-term treatment of hypertension and various other indications. *Drugs* 2006; **66:** 1755–82.

Administration in children. Intravenous infusion of nicardipine has been used in both infants and children for the management of hypertension. In studies[1-4] in children aged between 2 days and 17 years, initial doses ranged from 0.2 to 5 micrograms/kg per minute, with maintenance infusions of 0.15 to 6 micrograms/kg per minute. Adverse effects were rare; one study[4] reported adverse effects in 5 of 31 treatment courses, including tachycardia, flushing, palpitations, and hypotension. There has also been a report[5] of the successful use of intravenous infusion of nicardipine in 8 preterm infants (gestational age 28 to 36 weeks). Infusions were given at a dose of 0.5 to 2 micrograms/kg per minute and continued for periods of 3 to 36 days. No hypotension, oedema, or tachycardia were observed.

The *BNFC* suggests that neonates and children up to age 18 years may be given nicardipine hydrochloride by continuous intravenous infusion for the management of hypertensive crises. The initial dose is 500 nanograms/kg per minute, adjusted according to response; the usual maintenance dose is 1 to 4 micrograms/kg per minute, with a maximum dose of 250 micrograms/minute.

1. Treluyer JM, *et al.* Intravenous nicardipine in hypertensive children. *Eur J Pediatr* 1993; **152:** 712–4.
2. Sartori SC, *et al.* Intravenous nicardipine for treatment of systemic hypertension in children. *Pediatrics* 1999; **104** (suppl): 676–7.
3. Tobias JD. Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children. *Am J Ther* 2001; **8:** 3–6.
4. Flynn JT, *et al.* Intravenous nicardipine for treatment of severe hypertension in children. *J Pediatr* 2001; **139:** 38–43.
5. Gouyon JB, *et al.* Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child* 1997; **76:** F126–F127.

Administration in hepatic or renal impairment. Reduced doses of nicardipine hydrochloride and longer dosing intervals may be necessary in patients with hepatic or renal impairment. The US manufacturers recommend an initial dose of 20 mg twice daily by mouth in patients with hepatic impairment.

Cerebrovascular disorders. Nicardipine has been reported to increase cerebral blood flow[1] and use by various routes has been investigated for possible benefit in haemorrhagic[2-5] and ischaemic stroke[6,7] (p.1185), although nimodipine (p.1357) is the dihydropyridine calcium-channel blocker usually used. Nicardipine has also been tried[8] in patients with cerebrovascular insufficiency. However, studies have produced inconclusive results.

1. Savage I, James I. The effect of nicardipine hydrochloride on cerebral blood flow in normotensive volunteers. *Br J Clin Pharmacol* 1986; **21:** 591P–592P.
2. Suzuki M, *et al.* Intrathecal administration of nicardipine hydrochloride to prevent vasospasm in patients with subarachnoid hemorrhage. *Neurosurg Rev* 2001; **24:** 180–4.
3. Kasuya H, *et al.* Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans. *Stroke* 2002; **33:** 1011–15.
4. Dorhout Mees SM, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/07/08).
5. Barth M, *et al.* Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa study. *Stroke* 2007; **38:** 330–6.
6. Yao L, Ding D. Effect of nicardipine on somatosensory evoked potentials in patients with acute cerebral infarction. *J Neurol Neurosurg Psychiatry* 1990; **53:** 844–6.
7. Rosenbaum D, *et al.* Early treatment of ischemic stroke with a calcium antagonist. *Stroke* 1991; **22:** 437–41.
8. Silva APE, Diament CK. Nicardipine versus cinnarizine in cerebrovascular insufficiency. *Curr Ther Res* 1988; **43:** 888–99.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Karden; ***Belg.:*** Rydene; ***Fr.:*** Loxen; ***Ger.:*** Antagonil; ***Indon.:*** Perdipine; ***Irl.:*** Cardene†; ***Ital.:*** Bionicard; Cardioten; Cardip; Cordisol†; Lisanirc; Neucor; Nicant†; Nicapress; Nicardal; Nicarpin; Nicaven; Nimicor; Niven†; Perdipina; Ranvil†; Vasodin; ***Jpn:*** Perdipine; ***Malaysia:*** Cardepine; ***Neth.:*** Cardene; ***Philipp.:*** Cardepine; ***Port.:*** Nerdipina; ***Singapore:*** Cardibloc; ***Spain:*** Dagan; Flusemide; Lecibral; Lincil; Lucenfal; Nerdipina; Vasonase; ***Thai.:*** Cardepine; Nerdipine†; ***Turk.:*** Loxen; ***UK:*** Cardene; ***USA:*** Cardene.

Niceritrol *(BAN, rINN)*

Nicéritrol; Niceritrolum; Nikeritroli; PETN. Pentaerythritol tetranicotinate; 2,2-Bis(hydroxymethyl)propane-1,3-diol tetranicotinate.

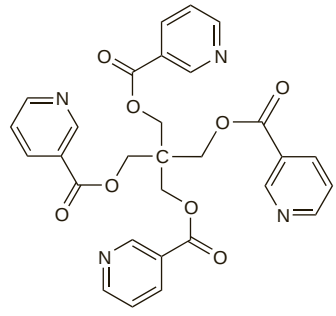
Ницеритрол

$C_{29}H_{24}N_4O_8$ = 556.5.

CAS — 5868-05-3.

ATC — C10AD01.

ATC Vet — QC10AD01.



NOTE. The synonym PETN has been applied to both niceritrol and pentaerithrityl tetranitrate.