Natriuretic Peptides ⊗

Péptidos natriuréticos.

Profile

Natriuretic peptides are endogenous substances that possess diuretic, natriuretic, and vasodilator properties. Three types are known. *Atrial natriuretic peptide* (ANP), also known as atrial natriuretic factor (ANF), atriopeptin, auriculin, or cardionatrin, is produced mainly in the cardiac atria, although another form, ularitide (urodilatin), is produced in the kidney. *Brain natriuretic peptide* (BNP, B-type natriuretic peptide) was originally isolated from brain tissue but is now known to be mainly produced by the cardiac ventricles. *C-type natriuretic peptide* (CNP) is produced by the endothelium and appears to act locally as a vasodilator but has little natriuretic effect.

Natriuretic peptides have an important physiological role in fluid and electrolyte homoeostasis and in the regulation of blood pressure, and they interact closely with other complex systems such as the renin-angiotensin-aldosterone cascade. Plasma concentrations of atrial natriuretic peptide and brain natriuretic peptide are altered in some pathological states and have been used as indicators of cardiac function. Natriuretic peptides that have been investigated for therapeutic use include anaritide, a synthetic form of atrial natriuretic peptide, and ularitide; both have been studied in acute renal failure, and ularitide has also been studied in heart failure. Recombinant forms of atrial natriuretic peptide (carperitide, p.1241) and brain natriuretic peptide (nesiritide, p.1347) are used in the management of acute heart failure.

The currently available natriuretic peptides have short half-lives and have to be given parenterally. Other approaches to manipulating their effects have been investigated, including the use of atriopeptidase inhibitors (neutral endopeptidase inhibitors; neutral metalloendopeptidase inhibitors), such as candoxatrilat and ecadotril (sinorphan) to prolong the half-life of endogenous atrial natriuretic peptide. Compounds such as omapatrilat (p.1361) that inhibit both neutral endopeptidase and angiotensin-converting enzyme are also being studied.

◊ References.

1. Tan ACITL, *et al.* Atrial natriuretic peptide: an overview of clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 1993; **24:** 28–45.
2. Richards AM. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. *Heart* 1996; **76** (suppl 3): 36–44.
3. Wilkins MR, *et al.* The natriuretic-peptide family. *Lancet* 1997; **349:** 1307–10.
4. Levin ER, *et al.* Natriuretic peptides. *N Engl J Med* 1998; **339:** 321–8.
5. Lewis J, *et al.* Atrial natriuretic factor in oliguric acute renal failure: Anaritide Acute Renal Failure Study Group. *Am J Kidney Dis* 2000; **36:** 767–74.
6. Forssmann W, *et al.* The renal urodilatin system: clinical implications. *Cardiovasc Res* 2001; **51:** 450–62.
7. de Lemos JA, *et al.* B-type natriuretic peptide in cardiovascular disease. *Lancet* 2003; **362:** 316–22.
8. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006; **92:** 843–9.
9. Mitrovic V, *et al.* Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006; **27:** 2823–32.
10. Lüss H, *et al.* Renal effects of ularitide in patients with decompensated heart failure. *Am Heart J* 2008; **155:** 1012.e1–8.

Nebivolol *(BAN, USAN, rINN)* ⊗

Narbivolol; Nébivolol; Nebivololi; Nebivololum; R-65824. (1*RS*,1′*RS*)-1,1′-[(2*RS*,2′*SR*)-Bis(6-fluorochroman-2-yl)]-2,2′-iminodiethanol.

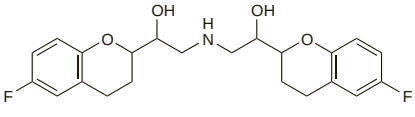
Небиволол

$C_{22}H_{25}F_2NO_4$ = 405.4.

CAS — 99200-09-6; 118457-14-0.

ATC — C07AB12.

ATC Vet — QC07AB12.



Nebivolol Hydrochloride *(BANM, USAN, rINNM)* ⊗

Hidrocloruro de nebivolol; Nébivolol, Chlorhydrate de; Nebivololi Hydrochloridum; R-67555; R-067555.

Небиволола Гидрохлорид

$C_{22}H_{25}F_2NO_4$,HCl = 441.9.

CAS — 169293-50-9; 152520-56-4.

ATC — C07AB12.

ATC Vet — QC07AB12.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Interactions

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

Pharmacokinetics

Nebivolol is rapidly absorbed after oral doses. It is extensively metabolised in the liver by alicyclic and aromatic hydroxylation, *N*-dealkylation, and glucuronidation; the hydroxy metabolites are reported to be active. The rate of aromatic hydroxylation by cytochrome P450 isoenzyme CYP2D6 is subject to genetic polymorphism, and bioavailability and half-life vary widely. In fast metabolisers the elimination half-life of nebivolol is about 10 hours and that of the hydroxy metabolites is about 24 hours. Peak plasma concentrations of unchanged drug plus active metabolites are 1.3 to 1.4 times higher in slow metabolisers and the half-lives of nebivolol and its hydroxy metabolites are prolonged.

Nebivolol is about 98% bound to plasma proteins. It has high lipid solubility. It is excreted in the urine and faeces, almost entirely as metabolites. Nebivolol is distributed into breast milk in *animals*.

Uses and Administration

Nebivolol is a cardioselective beta blocker (p.1225). It has vasodilating activity, which appears to be due to a direct action on the endothelium, possibly involving nitric oxide release. It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Nebivolol is used in the management of hypertension (p.1171), and as an adjunct to standard therapy in patients aged 70 years and older with stable chronic heart failure (p.1165). It is given orally as the hydrochloride although doses are expressed in terms of the base; 5.45 mg of nebivolol hydrochloride is equivalent to about 5 mg of base.

In **hypertension** the usual initial dose of nebivolol is 5 mg once daily. US licensed product information allows the dose to be increased, if necessary, at intervals of 2 weeks, to a maximum dose of 40 mg once daily. Dosage reduction may be necessary in the elderly and in patients with hepatic or renal impairment (see below).

In **heart failure** the initial dose of nebivolol is 1.25 mg once daily. If tolerated, the dose should be doubled every 1 to 2 weeks up to a maximum of 10 mg once daily.

◊ Reviews.

1. Moen MD, Wagstaff AJ. Nebivolol: a review of its use in the management of hypertension and chronic heart failure. *Drugs* 2006; **66:** 1389–1409.
2. Veverka A, *et al.* Nebivolol: a third-generation β-adrenergic blocker. *Ann Pharmacother* 2006; **40:** 1353–60.
3. Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a β-adrenoceptor antagonist with unique characteristics. *Drugs* 2007; **67:** 1097–1107.
4. Prisant LM. Nebivolol: pharmacologic profile of an ultraselective, vasodilatory β -blocker. *J Clin Pharmacol* 2008; **48:** 225–39.

Administration in the elderly. UK licensed product information states that, for hypertension, patients over 65 years of age should be given an initial dose of 2.5 mg of nebivolol once daily, increased to 5 mg once daily if required.

Administration in hepatic impairment. UK licensed product information contra-indicates the use of nebivolol in patients with hepatic impairment. In the USA, licensed product information also contra-indicates nebivolol in severe hepatic impairment (Child-Pugh higher than class B) but patients with moderate hepatic impairment may be given nebivolol for hypertension in an initial oral dose of 2.5 mg once daily, increased with caution if required.

Administration in renal impairment. UK licensed product information states that in hypertension the initial dose of nebivolol should be reduced to 2.5 mg once daily in patients with renal impairment, increased to 5 mg once daily for maintenance if required. US licensed product information similarly recommends an initial dose of 2.5 mg once daily in patients with severe renal impairment (creatinine clearance below 30 mL/minute); the dose may be increased cautiously if required.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nebilet; ***Austria:*** Nomexor; ***Belg.:*** Nobiten; ***Chile:*** Nebilet; ***Cz.:*** Nebilet; Nebispes; ***Fr.:*** Nebilox; Temerit; ***Ger.:*** Nebilet; ***Gr.:*** Lobivon; ***Hung.:*** Nebilet; ***India:*** Nodon; ***Irl.:*** Nebilet; ***Ital.:*** Lobivon; Nebilox; ***Neth.:*** Hypoloc; Lobivon; Nebilet; Nebiloc; ***Pol.:*** Nebilet; ***Port.:*** Hypoloc; Nebilet; ***Rus.:*** Nebilet (Небилет); ***S.Afr.:*** Nebilet; ***Singapore:*** Nebilet; ***Spain:*** Lobivon; Nebilet; Nebilox; Silostar; ***Switz.:*** Nebilet; ***Thai.:*** Nebilet; ***Turk.:*** Vasoxen; ***UK:*** Nebilet; ***USA:*** Bystolic; ***Venez.:*** Nebilet.

Nesiritide Citrate *(USAN, rINNM)* ⊗

Citrato de nesiritida; Nésiritide, Citrate de; Nesiritidi Citras.

Незиритида Цитрат

$C_{143}H_{244}N_{50}O_{42}S_4$,x$C_6H_8O_7$.

CAS — 124584-08-3 (nesiritide); 189032-40-4 (nesiritide citrate).

ATC — C01DX19.

ATC Vet — QC01DX19.

Incompatibility. The manufacturer states that nesiritide injection is physically and/or chemically incompatible with heparin, insulin, sodium etacrynate, bumetanide, enalaprilat, hydralazine, furosemide, and the preservative sodium metabisulfite. Nesiritide binds to heparin and should not be given through heparin-coated central catheters.

Adverse Effects and Precautions

The most common adverse effects of nesiritide relate to vasodilatation and include hypotension, headache, and dizziness. Nausea and vomiting, abdominal pain, back pain, angina pectoris, insomnia, and anxiety, have also been reported. Cardiac arrhythmias have occurred but may be associated with the underlying condition. Adverse effects on renal function have been reported. If hypotension occurs the infusion of nesiritide should be stopped or the dose reduced and general supportive measures should be used; the hypotension may persist for several hours.

Nesiritide should not be used as primary therapy in patients with cardiogenic shock or with hypotension. It is not recommended in patients with low cardiac filling pressures or in those for whom vasodilators are inappropriate, such as those with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, or pericardial tamponade.

Effects on the kidneys. Nesiritide has both haemodynamic and neurohormonal effects on the kidneys and has been reported to worsen renal function. A meta-analysis[1] found that nesiritide significantly increased the risk of worsening renal function in patients with acute heart failure, and there is some evidence[2] that this may be related to the duration of treatment. However, a randomised trial[3] in patients with acute heart failure and pre-existing renal impairment found that the effect of nesiritide on renal function was neutral.

1. Sackner-Bernstein JD, *et al.* Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; **111:** 1487–91. Correction. *ibid.*; 2274.
2. Chow SL, *et al.* Effect of nesiritide infusion duration on renal function in acutely decompensated heart failure patients. *Ann Pharmacother* 2007; **41:** 556–61.
3. Witteles RM, *et al.* Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007; **50:** 1835–40.

Effects on mortality. Although nesiritide improves haemodynamics in patients with acute decompensated heart failure, its effects on mortality are controversial.[1] A retrospective study[2] comparing nesiritide with inotrope therapy or glyceryl trinitrate in patients with acute decompensated heart failure found a similar risk of in-hospital mortality with nesiritide and glyceryl trinitrate, which was significantly lower than the risk with inotrope therapy. However, a meta-analysis[3] of controlled studies comparing nesiritide with non-inotrope control therapy found that there was a trend to higher mortality at 30 days in patients given nesiritide; the results were not statistically significant, but became so after correction of the number of deaths in one of the studies.[4] A later meta-analysis[5] also found a trend towards increased mortality with nesiritide at 30 days, but the results again were not statistically significant, and there was no difference in mortality between nesiritide and control patients at 180 days.

1. Yancy CW. Benefit-risk assessment of nesiritide in the treatment of acute decompensated heart failure. *Drug Safety* 2007; **30:** 765–81.
2. Abraham WT, *et al.* In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46:** 57–64.
3. Sackner-Bernstein JD, *et al.* Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293:** 1900–5.
4. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA* 2006; **296:** 1465–6.
5. Arora RR, *et al.* Short and long-term mortality with nesiritide. *Am Heart J* 2006; **152:** 1084–90.

Interactions

The risk of hypotension may be increased in patients receiving nesiritide with other drugs that lower blood pressure.