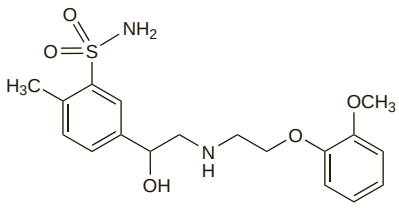
Amosulalol Hydrochloride *(rINNM)* ⊗

Amosulalol, Chlorhydrate d'; Amosulaloli Hydrochloridum; Hidrocloruro de amosulalol; YM-09538. (±)-5-(1-Hydroxy-2-{[2-(*o*-methoxyphenoxy)ethyl]amino}ethyl)-*o*-toluenesulphonamide hydrochloride.

Амосулалола Гидрохлорид

$C_{18}H_{24}N_2O_5S,HCl$ = 416.9.

CAS — 85320-68-9 (amosulalol); 70958-86-0 (amosulalol hydrochloride); 93633-92-2 (amosulalol hydrochloride).



(amosulalol)

Profile

Amosulalol is a beta blocker (p.1225); it also has alpha-blocking activity. It has been given orally as the hydrochloride in the management of hypertension.

Amrinone *(BAN, rINN)*

Amrinon; Amrinona; Amrinoni; Amrinonum; Inamrinone *(USAN)*; Win-40680. 5-Amino-3,4′-bipyridyl-6(1*H*)-one.

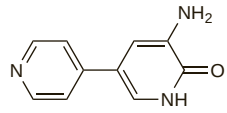
Амринон

$C_{10}H_9N_3O$ = 187.2.

CAS — 60719-84-8.

ATC — C01CE01.

ATC Vet — QC01CE01.



Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Inamrinone). A pale yellow to tan powder; odourless or with a faint odour. Practically insoluble in water and in chloroform; slightly soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Amrinone Lactate *(BANM, rINNM)*

Amrinone, Lactate d'; Amrinoni Lactas; Lactato de amrinona.

Амринона Лактат

$C_{10}H_9N_3O,C_3H_6O_3$ = 277.3.

CAS — 75898-90-7.

ATC — C01CE01.

ATC Vet — QC01CE01.

Incompatibility. The manufacturer has reported that amrinone lactate injection is physically incompatible with glucose-containing solutions and with furosemide.

Precipitation occurred[1] when amrinone was mixed with sodium bicarbonate injection, probably because of the reduced solubility of amrinone in alkaline solutions.

1. Riley CM, Junkin P. Stability of amrinone and digoxin, procainamide hydrochloride, propranolol hydrochloride, sodium bicarbonate, potassium chloride, or verapamil hydrochloride in intravenous admixtures. *Am J Hosp Pharm* 1991; **48:** 1245–52.

Adverse Effects

Amrinone produces gastrointestinal disturbances that may necessitate withdrawal of treatment. It produces dose-dependent thrombocytopenia. Hepatotoxicity may occur, particularly during long-term oral treatment. Hypotension and cardiac arrhythmias have been reported. Other adverse effects include headache, fever, chest pain, nail discoloration, and decreased tear production. Hypersensitivity reactions including myositis and vasculitis have been reported. Local pain and burning may occur at the site of intravenous injection.

The adverse effects associated with oral use have made this route unacceptable and amrinone is now only given intravenously for short-term use. Studies with other inotropic phosphodiesterase inhibitors have shown that their prolonged oral use can increase the mortality rate.

◊ References.

1. Wynne J, *et al.* Oral amrinone in refractory congestive heart failure. *Am J Cardiol* 1980; **45:** 1245–9.
2. Wilmshurst PT, Webb-Peploe MM. Side effects of amrinone therapy. *Br Heart J* 1983; **49:** 447–51.
3. Wilmshurst PT, *et al.* The effects of amrinone on platelet count, survival and function in patients with congestive cardiac failure. *Br J Clin Pharmacol* 1984; **17:** 317–24.
4. Silverman BD, *et al.* Clinical effects and side effects of amrinone: a study of 24 patients with chronic congestive heart failure. *Arch Intern Med* 1985; **145:** 825–9.
5. Webster MWI, Sharpe DN. Adverse effects associated with the newer inotropic agents. *Med Toxicol* 1986; **1:** 335–42.
6. Mattingly PM, *et al.* Pancytopenia secondary to short-term, high-dose intravenous infusion of amrinone. *DICP Ann Pharmacother* 1990; **24:** 1172–4.
7. Ross MP, *et al.* Amrinone-associated thrombocytopenia: pharmacokinetic analysis. *Clin Pharmacol Ther* 1993; **53:** 661–7.

Precautions

Amrinone should be used with caution in severe obstructive aortic or pulmonary valvular disease or in hypertrophic cardiomyopathy. Blood pressure and heart rate should be monitored during parenteral use. The fluid and electrolyte balance should be maintained. Platelet counts and liver function should also be monitored.

Pharmacokinetics

Although amrinone is rapidly absorbed from the gastrointestinal tract it is no longer given orally. The half-life is variable and after intravenous injection has been reported to be about 4 hours in healthy subjects and about 6 hours in patients with heart failure. Binding to plasma proteins is generally low. Amrinone is partially metabolised in the liver and excreted in the urine as unchanged drug and metabolites; up to about 40% is excreted as unchanged drug after intravenous use. About 18% of an oral dose has been detected in the faeces over 72 hours.

◊ General references.

1. Rocci ML, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13:** 91–109. Correction. *ibid.* 1988; **14:** (contents page).

Infants. For reference to the pharmacokinetics of amrinone in neonates and infants, see under Uses and Administration, below.

Renal impairment. Studies in a child with multi-organ failure and anuria[1] and in 3 adults with anuria after cardiac surgery[2] have shown that amrinone is effectively removed by haemofiltration but clearance varies widely between patients. Non-renal clearance may also be altered in critically ill patients and monitoring of plasma-amrinone concentrations has been suggested.[2]

1. Lawless S, *et al.* Effect of continuous arteriovenous haemofiltration on pharmacokinetics of amrinone. *Clin Pharmacokinet* 1993; **25:** 80–2.
2. Hellinger A, *et al.* Elimination of amrinone during continuous veno-venous haemofiltration after cardiac surgery. *Eur J Clin Pharmacol* 1995; **48:** 57–9.

Uses and Administration

Amrinone is a phosphodiesterase inhibitor that has vasodilator and positive inotropic properties. It is used in the management of heart failure (p.1165). Although amrinone is effective when given orally this route has been associated with an unacceptable level of adverse effects, and the drug is now only given intravenously for the short-term management of heart failure unresponsive to other forms of therapy.

The mode of action is not fully known, but appears to involve an increase in cyclic adenosine monophosphate concentration secondary to inhibition of phosphodiesterase, leading to an increased contractile force in cardiac muscle.

Amrinone is given intravenously as the lactate and doses are expressed in terms of the base. Amrinone lactate 1.48 mg is equivalent to about 1 mg of amrinone. The initial loading dose is 750 micrograms/kg by slow intravenous injection over 2 to 3 minutes. This is followed by a maintenance infusion, although the loading dose may be repeated after 30 minutes if necessary. Maintenance doses are 5 to 10 micrograms/kg per minute by infusion to a usual maximum total dose (including loading doses) of 10 mg/kg in 24 hours. Doses of up to 18 mg/kg daily have been used for short periods in a limited number of patients.

Administration in infants. Pharmacokinetic and pharmacodynamic studies[1,2] in infants undergoing cardiac surgery indicated that the dose needed for infants to achieve a plasma-amrinone concentration of 2 to 7 micrograms/mL was an initial intravenous bolus of 3 to 4.5 mg/kg in divided doses followed by a continuous infusion of 10 micrograms/kg per minute. Neonates appear to eliminate amrinone more slowly than infants, possibly due to their immature renal function;[1,3] it was therefore suggested[1] that neonates should receive a similar bolus dose to infants, followed by a continuous infusion of 3 to 5 micrograms/kg per minute. In a further study[4] that included mainly infants and older children, amrinone clearance and volume of distribution varied widely between patients but did not appear to be related to age.

1. Lawless S, *et al.* Amrinone in neonates and infants after cardiac surgery. *Crit Care Med* 1989; **17:** 751–4.
2. Lawless ST, *et al.* The acute pharmacokinetics and pharmacodynamics of amrinone in pediatric patients. *J Clin Pharmacol* 1991; **31:** 800–3.
3. Laitinen P, *et al.* Pharmacokinetics of amrinone in neonates and infants. *J Cardiothorac Vasc Anesth* 2000; **14:** 378–82.
4. Allen-Webb EM, *et al.* Age-related amrinone pharmacokinetics in a pediatric population. *Crit Care Med* 1994; **22:** 1016–24.

Preparations

USP 31: Inamrinone Injection.

Proprietary Preparations (details are given in Part 3)
Cz.: Wincoram†; ***Ger.:*** Wincoram†; ***India:*** Amicor; Cardiotone†; ***Israel:*** Inocor; ***Ital.:*** Inocor†; ***Jpn:*** Amcoral†; Cartonic†; ***Malaysia:*** Inocor†; ***Mex.:*** Inocor; ***Port.:*** Inocor†; ***Spain:*** Wincoram†; ***USA:*** Inocor.

Ancrod *(BAN, USAN, rINN)*

Ancrodum.

Анкрод

CAS — 9046-56-4.

ATC — B01AD09.

ATC Vet — QB01AD09.

Description. Ancrod is an enzyme obtained from the venom of the Malayan pit-viper (*Calloselasma rhodostoma* = *Agkistrodon rhodostoma*).

Adverse Effects and Treatment

Haemorrhage may occur during treatment with ancrod and usually responds to its withdrawal. If haemorrhage is severe, cryoprecipitate can be used to raise plasma fibrinogen concentrations; plasma may be used if cryoprecipitate is not available. An antivenom has been used to neutralise ancrod.

Skin rash, transient chills, and fever have been reported with the use of ancrod.

Precautions

As for Heparin, p.1303.

Ancrod should not be given to patients with severe infections or disseminated intravascular coagulation. It should be used cautiously in patients with cardiovascular disorders that may be complicated by defibrination. It is very important that when ancrod is given by intravenous infusion it should be given slowly to prevent the formation of large amounts of unstable fibrin.

Ancrod is not recommended during pregnancy; high doses in *animals* have caused placental haemorrhage and fetal death.

Interactions

Ancrod should not be used with antifibrinolytics such as aminocaproic acid or with plasma volume expanders such as dextrans.

Uses and Administration

Ancrod is an anticoagulant. It reduces the blood concentration of fibrinogen by the cleavage of microparticles of fibrin which are rapidly removed from the circulation by fibrinolysis or phagocytosis. It reduces blood viscosity but has no effect on established thrombi. Haemostatic concentrations of fibrinogen are normally restored in about 12 hours and normal concentrations in 10 to 20 days.

Ancrod has been used in the treatment of thromboembolic disorders, particularly in deep-vein thrombosis and to prevent thrombosis after surgery in patients requiring anticoagulation but who have developed heparin-induced thrombocytopenia or thrombosis (see Venous Thromboembolism, p.1189). It is under investigation in the treatment of ischaemic stroke and has also been given for priapism.

◊ References.

1. Sherman DG, *et al.* Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. *JAMA* 2000; **283:** 2395–2403.
2. Hennerici MG, *et al.* ESTAT investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial. *Lancet* 2006; **368:** 1871–8.