Administration in hepatic impairment. The plasma half-life of disopyramide may be increased in hepatic impairment and dosage reduction should be considered; US licensed product information recommends an oral dose of 400 mg daily in divided doses. In patients with liver cirrhosis there is also a significant reduction in the plasma concentration of α_1-acid glycoprotein;[1,2] in addition, its binding capacity for disopyramide is reduced.[1] This is associated with an increase in the free fraction of disopyramide such that measurement of total disopyramide in plasma may not be a safe indicator for dosing, and a therapeutic range 50% lower than in patients with normal hepatic function should be considered.[2]

1. Bonde J, *et al.* Kinetics of disopyramide in decreased hepatic function. *Eur J Clin Pharmacol* 1986; **31:** 73–7.
2. Echizen H, *et al.* Protein binding of disopyramide in liver cirrhosis and in nephrotic syndrome. *Clin Pharmacol Ther* 1986; **40:** 274–80.

Administration in renal impairment. Disopyramide is excreted mainly in the urine and a reduction in clearance with an increase in elimination half-life has been reported[1] in patients with renal impairment. Dosage reduction should therefore be considered. US licensed product information recommends the following oral doses based on creatinine clearance (CC):

- CC greater than 40 mL/minute: 400 mg daily in divided doses
- CC 30 to 40 mL/minute: 100 mg every 8 hours
- CC 15 to 30 mL/minute: 100 mg every 12 hours
- CC less than 15 mL/minute: 100 mg every 24 hours

Modified-release preparations should be avoided in patients with CC less than 40 mL/minute.

At therapeutic concentrations disopyramide is not significantly removed by haemodialysis;[2] the half-life is similar both on and off dialysis (16.8 versus 16.1 hours). An increased free fraction of disopyramide has been seen[3] during haemodialysis associated with an elevation in free fatty acids in plasma and in such cases free plasma-disopyramide concentrations should be monitored.

1. Francois B, *et al.* Pharmacokinetics of disopyramide in patients with chronic renal failure. *Eur J Drug Metab Pharmacokinet* 1983; **8:** 85–92.
2. Sevka MJ, *et al.* Disopyramide hemodialysis and kinetics in patients requiring long-term hemodialysis. *Clin Pharmacol Ther* 1981; **29:** 322–6.
3. Horiuchi T, *et al.* Inhibitory effect of free fatty acids on plasma protein binding of disopyramide in haemodialysis patients. *Eur J Clin Pharmacol* 1989; **36:** 175–80.

Hypertrophic cardiomyopathy. Patients with hypertrophic cardiomyopathy (p.1163) may have exercise intolerance due to left ventricular outflow obstruction. Beta blockers are usually used when symptoms are associated with exercise or emotional factors, but may not be effective in patients with symptoms at rest. Disopyramide has been used for its negative inotropic effect in such patients and a retrospective study[1] found that it improved symptoms without having a proarrhythmic effect.

1. Sherrid MV, *et al.* Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; **45:** 1251–8.

Hypotension. Disopyramide has been widely used in the management of neurally mediated hypotension (p.1174) but there is limited evidence to support its use. Although some reports[1,2] have suggested benefit, a controlled study[3] found that it was no more effective than placebo in preventing tilt-induced syncope. Adverse effects also limit the use of disopyramide, and it is generally no longer considered first line.

1. Milstein S, *et al.* Usefulness of disopyramide for prevention of upright tilt-induced hypotension-bradycardia. *Am J Cardiol* 1990; **65:** 1339–44.
2. Bhaumick SK, *et al.* Oral disopyramide in the treatment of recurrent neurocardiogenic syncope. *Int J Clin Pract* 1997; **51:** 342.
3. Morillo CA, *et al.* A placebo-controlled trial of intravenous and oral disopyramide for prevention of neurally mediated syncope induced by head-up tilt. *J Am Coll Cardiol* 1993; **22:** 1843–8.

Preparations

BP 2008: Disopyramide Capsules; Disopyramide Phosphate Capsules; ***USP 31:*** Disopyramide Phosphate Capsules; Disopyramide Phosphate Extended-release Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Rythmodan; ***Austria:*** Rythmodan; ***Belg.:*** Rythmodan; ***Braz.:*** Dicorantil; ***Canad.:*** Rythmodan; ***Cz.:*** Rythmodan†; ***Denm.:*** Durbis†; ***Fin.:*** Disomet; ***Fr.:*** Isorythm; Rythmodan; ***Ger.:*** Diso-Duriles†; Norpace†; Rythmodul†; ***Gr.:*** Dicorynan; Ritmodan†; Rythmodan; Rythmodul†; ***Hung.:*** Palpitin-PP; ***India:*** Norpace; ***Irl.:*** Rythmodan; ***Israel:*** Rythmical; ***Ital.:*** Ritmodan; ***Jpn:*** Rythmodan; ***Mex.:*** Dimodan; ***Neth.:*** Ritmoforine; Rythmodan†; ***Norw.:*** Durbis; ***NZ:*** Rythmodan; ***Port.:*** Ritmodan†; ***S.Afr.:*** Norpace; Rythmodan; ***Spain:*** Dicorynan; ***Swed.:*** Dirytmin†; Durbis; ***Switz.:*** Norpace†; ***Turk.:*** Norpace; ***UK:*** Rythmodan; ***USA:*** Norpace.

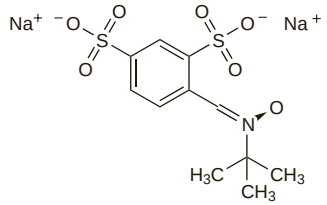
Disufenton Sodium *(USAN, rINN)*

ARL-16556; CPI-22; CXY-059; Disufentón de sodio; Disufenton Sodique; Disufentonum Natricum; NXY-059. Disodium 4-(*tert*-butyliminomethyl)benzene-1,3-disulfonate *N*-oxide.

Дисуфентон Натрия

$C_{11}H_{13}NNa_2O_7S_2$ = 381.3.

CAS — 168021-79-2.



Profile

Disufenton sodium traps free radicals. It has been investigated as a neuroprotectant for acute ischaemic and haemorrhagic stroke but results have been disappointing.

◊ References.

1. Lees KR, *et al.* The Stroke-Acute Ischemic NXY Treatment (Saint I) Trial Investigators. NXY-059 for acute ischemic stroke. *N Engl J Med* 2006; **354:** 588–600.
2. Shuaib A, *et al.* SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med* 2007; **357:** 562–71.
3. Lyden PD, *et al.* Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT trial. *Stroke* 2007; **38:** 2262–9.

Ditazole *(rINN)*

Diethamphenazole; Ditazol; Ditazolum; S-222. 2,2′-[(4,5-Diphenyloxazol-2-yl)imino]diethanol.

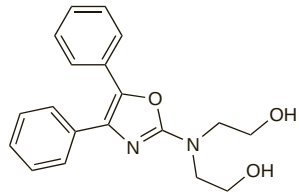
Дитазол

$C_{19}H_{20}N_2O_3$ = 324.4.

CAS — 18471-20-0.

ATC — B01AC01.

ATC Vet — QB01AC01.



Profile

Ditazole is an inhibitor of platelet aggregation used in the management of thromboembolic disorders (p.1187) in doses of 400 mg two or three times daily by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Fendazol†; ***Spain:*** Ageroplas.

Dobutamine Hydrochloride

(BANM, USAN, rINNM)

46236; Compound 81929 (dobutamine); Dobutamiinihydrokloridi; Dobutamine, chlorhydrate de; Dobutamin-hidroklorid; Dobutamin-hydrochlorid; Dobutaminhydroklorid; Dobutamini hydrochloridum; Dobutamino hidrochloridas; Hidrocloruro de dobutamina; LY-174008 (dobutamine tartrate). (±)-4-(2-{[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino}ethyl)pyrocatechol hydrochloride.

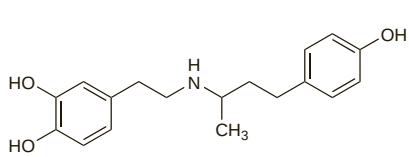
Добутамина Гидрохлорид

$C_{18}H_{23}NO_3$,HCl = 337.8.

CAS — 34368-04-2 (dobutamine); 49745-95-1 (dobutamine hydrochloride); 101626-66-8 (dobutamine tartrate).

ATC — C01CA07.

ATC Vet — QC01CA07.



(dobutamine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Dobutamine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; soluble in methyl alcohol. Protect from light.

USP 31 (Dobutamine Hydrochloride). A white to practically white crystalline powder. Sparingly soluble in water and in methyl alcohol; soluble in alcohol and in pyridine. Store in airtight containers at a temperature of 15° to 30°.

Incompatibility. Dobutamine is incompatible with alkaline solutions such as sodium bicarbonate 5% and alkaline drugs such as aminophylline, furosemide,[1] and thiopental sodium;[1] physical incompatibility with bumetanide, calcium gluconate, insulin, diazepam, and phenytoin has also been suggested. There have also been reports of incompatibility with alteplase,[2] heparin,[3] and warfarin sodium.[4]

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.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
4. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; **54:** 2599–2600.

Adverse Effects and Treatment

As for Sympathomimetics, p.1407. Dobutamine has mainly beta$_1$-agonist properties and its principal adverse effects include dose-related increases in heart rate and blood pressure, ectopic beats, angina or chest pain, and palpitations; dosage should be reduced or temporarily stopped if they occur. Ventricular tachycardia may occur rarely; cardiac rupture has been reported rarely during dobutamine stress testing.

Effects on body temperature. A 71-year-old woman with heart failure developed a fever on 2 separate occasions 8 to 12 hours after starting an infusion of dobutamine.[1]

1. Robison-Strane SR, Bubik JS. Dobutamine-induced fever. *Ann Pharmacother* 1992; **26:** 1523–4.

Effects on the cardiovascular system. For reference to severe cardiovascular complications of dobutamine stress echocardiography, see Diagnosis and Testing under Uses and Administration, below.

For reference to fatalities occurring in patients given dobutamine, see Heart Failure under Uses and Administration, below.

Effects on the neuromuscular system. Myoclonus has been reported[1,2] in patients with renal impairment given dobutamine infusion for heart failure.

1. Wierre L, *et al.* Dobutamine-induced myoclonia in severe renal failure. *Nephrol Dial Transplant* 2004; **19:** 1336–7.
2. Boord A, Benson B. Myoclonus associated with continuous dobutamine infusion in a patient with end-stage renal disease. *Am J Health-Syst Pharm* 2007; **64:** 2241–3.

Effects on the skin. Troublesome pruritus of the scalp has been reported[1] in a patient receiving dobutamine infusions. It was suggested that this might be a direct effect of dobutamine since the reaction was so localised.

1. McCauley CS, Blumenthal MS. Dobutamine and pruritus of the scalp. *Ann Intern Med* 1986; **105:** 966.

Hypersensitivity. Hypersensitivity reactions have been reported in patients receiving dobutamine infusions, possibly due to sodium sulfite in the formulation. Redness, swelling, itching, and a sensation of warmth developed[1] around the infusion site in a patient receiving dobutamine; the reaction recurred when the infusion was repeated a week later. Eosinophilic reactions have also been reported, including hypersensitivity myocarditis[2-4] and asthma.[5]

1. Cernek PK. Dermal cellulitis—a hypersensitivity reaction from dobutamine hydrochloride. *Ann Pharmacother* 1994; **28:** 964.
2. Spear GS. Eosinophilic explant carditis with eosinophilia: ?hypersensitivity to dobutamine infusion. *J Heart Lung Transplant* 1995; **14:** 755–60.
3. Takkenberg JJM, *et al.* Eosinophilic myocarditis in patients awaiting heart transplantation. *Crit Care Med* 2004; **32:** 714–21.
4. Butany J, *et al.* Hypersensitivity myocarditis complicating hypertrophic cardiomyopathy heart. *Can J Cardiol* 2004; **20:** 911–14.
5. Aranda JM, *et al.* Dobutamine-related asthma in a patient awaiting cardiac transplantation: the eosinophilic dilemma. *J Heart Lung Transplant* 2004; **23:** 260–1.

Overdosage. A patient received an accidental overdose[1] of dobutamine when given an intravenous infusion at a rate of more than 130 micrograms/kg per minute for 30 minutes, this being three times the recommended maximum. Characteristic adverse effects such as emesis, palpitations, chest pain, dyspnoea, and paraesthesia developed, together with urinary incontinence, an effect not previously associated with dobutamine.

1. Paulman PM, *et al.* Dobutamine overdose. *JAMA* 1990; **264:** 2386–7.

Precautions

As for Sympathomimetics, p.1407. Dobutamine has primarily inotropic effects and should be avoided or used only with great caution in patients with marked