used a low dose of aspirin and a modified-release formulation of dipyridamole, which may explain the discrepancy with earlier studies.[3] Subsequent meta-analyses[3-6] have confirmed that dipyridamole, alone or with aspirin, reduces the risk of recurrent stroke, but have been based mainly on the ESPS-2, which may be a limitation.[3] However, a further large study[7] comparing aspirin alone with aspirin and dipyridamole also found that the incidence of vascular events (including stroke) was lower in those receiving both drugs. Most guidelines[8,9] therefore now recommend aspirin with dipyridamole as one of the preferred options for long-term management of ischaemic stroke.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106. Correction. *ibid.*; 1540.
2. Diener HC, *et al.* European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; **143:** 1–13.
3. Wilterdink JL, Easton JD. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 1999; **56:** 1087–92.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86. Correction. *ibid.*; 141.
5. Leonardi-Bee J, *et al.* Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke* 2005; **36:** 162–8.
6. De Schryver ELLM, *et al.* Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 19/03/08).
7. Halkes PH, *et al.* ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006; **367:** 1665–73. Correction. *ibid.* 2007; **369:** 274.
8. European Stroke Organisation (ESO) Executive Committee. ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25:** 457–507. Also available at: http://www.eso-stroke.org/pdf/ESO08_Guidelines_English.pdf (accessed 11/07/08)
9. Albers GW, *et al.* Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 630S–669S.

Preparations

BP 2008: Dipyridamole Tablets;
USP 31: Dipyridamole Injection; Dipyridamole Oral Suspension; Dipyridamole Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Maxicardil; Persantin; Sedangor; ***Austral.:*** Persantin; ***Austria:*** Persantin; ***Belg.:*** Coronair; Dipyridan†; Docdipyri; Persantine; ***Braz.:*** Persantin; ***Canad.:*** Novo-Dipiradol†; Persantine; ***Chile:*** Persantin; ***Cz.:*** Curantyl N†; Persantin†; ***Denm.:*** Persantin; ***Fin.:*** Atrombin; Dipyrin; Persantin; ***Fr.:*** Cleridium†; Persantine; ***Ger.:*** Curantyl N†; ***Gr.:*** Adezan; Persantin; ***Hong Kong:*** Persantin; Procardin; ***India:*** Persantin; ***Indon.:*** Cardial; Persantin; Vasokor; Vasotin; ***Irl.:*** Persantin; ***Israel:*** Cardoxin; ***Ital.:*** Corosan; Novodil; Persantin; ***Jpn:*** Persantin; ***Malaysia:*** Persantin†; ***Mex.:*** Digal; Dipres; Dirinol; Lodimol; Persantin; Pracem; Trepol; Trompersantin†; Vadinar; ***Neth.:*** Persantin; ***Norw.:*** Persantin; ***NZ:*** Persantin; Pytazen; ***Philipp.:*** Persantin; ***Port.:*** Persantin; ***Rus.:*** Curantyl (Курантил); Persantin (Персантин); ***S.Afr.:*** Persantin; Plato; ***Singapore:*** Persantin; Procardin; ***Spain:*** Persantin; ***Swed.:*** Persantin; ***Thai.:*** Agremol; Persantin; Posanin; ***Turk.:*** Drisentin; Kardisentin; Tromboliz; ***UK:*** Persantin; ***USA:*** Persantine; ***Venez.:*** Megalis†; Meranol†; Persantin; Precar†.

Multi-ingredient: ***Arg.:*** Agrenox; Licuamon; ***Austral.:*** Asasantin; ***Austria:*** Asasantin; Thrombohexal; ***Belg.:*** Aggrenox; ***Canad.:*** Aggrenox; ***Cz.:*** Aggrenox; ***Denm.:*** Asasantin; ***Fin.:*** Asasantin; ***Fr.:*** Asasantine; ***Ger.:*** Aggrenox; Asasantin†; ***Gr.:*** Aggrenox; ***Hong Kong:*** Aggrenox; ***Hung.:*** Asasantin; ***India:*** Dynasprin; ***Indon.:*** Aggrenox; ***Irl.:*** Asasantin; ***Mex.:*** Asasantin†; ***Neth.:*** Asasantin; ***Norw.:*** Asasantin; ***Philipp.:*** Aggrenox; ***Port.:*** Aggrenox; ***S.Afr.:*** Asasantin; ***Swed.:*** Asasantin; ***Switz.:*** Asasantine; ***Thai.:*** Aggrenox; ***UK:*** Asasantin; ***USA:*** Aggrenox.

Disopyramide *(BAN, USAN, rINN)*

Disopiramida; Disopyramid; Disopyramidi; Disopyramidum; Dizopiramid; Dizopiramidas; SC-7031. 4-Di-isopropylamino-2-phenyl-2-(2-pyridyl)butyramide.

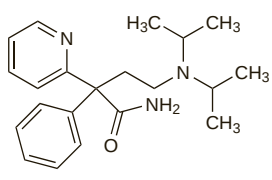
Дизопирамид

$C_{21}H_{29}N_3O$ = 339.5.

CAS — 3737-09-5.

ATC — C01BA03.

ATC Vet — QC01BA03.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*
Ph. Eur. 6.2 (Disopyramide). A white or almost white powder. Slightly soluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

Disopyramide Phosphate *(BANM, USAN, rINNM)*

Disopyramide, phosphate de; Disopyramidfosfat; Disopyramidfosfát; Disopyramidi phosphas; Disopyramidifosfaatti; Dizopiramid Fosfata; Dizopiramid-foszfát; Dizopiramido fosfatas; Dyzopiramidu fosforan; Fosfato de disopiramida; SC-13957.

Дизопирамида Фосфат

$C_{21}H_{29}N_3O,H_3PO_4$ = 437.5.

CAS — 22059-60-5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Disopyramide Phosphate). A white or almost white powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.
USP 31 (Disopyramide Phosphate). A white or practically white, odourless powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 4.0 and 5.0. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

The adverse effects most commonly associated with disopyramide relate to its antimuscarinic properties and are dose-related. They include dry mouth, blurred vision, urinary hesitancy, impotence, and constipation; the most serious effect is urinary retention. Gastrointestinal effects, which are less common, include nausea, bloating, and abdominal pain. Other adverse effects reported include skin rashes, hypoglycaemia, dizziness, fatigue, muscle weakness, headache, and urinary frequency. Insomnia and depression have also been associated with disopyramide. There have been rare reports of psychosis, cholestatic jaundice, elevated liver enzymes, thrombocytopenia, and agranulocytosis. Disopyramide prolongs the QT interval and may induce or worsen arrhythmias, particularly ventricular tachycardia and fibrillation; heart block and conduction disturbances may occur. It is also a negative inotrope and may cause heart failure, and hypotension.

Over-rapid intravenous injection of disopyramide may cause profuse sweating and severe cardiovascular depression.

In overdose cardiovascular and antimuscarinic effects are pronounced, and there may be apnoea, loss of consciousness, loss of spontaneous respiration, and asystole. Treatment of overdosage is symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion.

◊ A review of the adverse effects associated with the class Ia antiarrhythmic drugs disopyramide, procainamide, and quinidine, and their clinical management.[1]

1. Kim SY, Benowitz NL. Poisoning due to class IA antiarrhythmic drugs quinidine, procainamide and disopyramide. *Drug Safety* 1990; **5:** 393–420.

Incidence of adverse effects. During long-term therapy with disopyramide 400 to 1600 mg daily in 40 patients, 28 (70%) had one or more adverse effects.[1] Dry mouth occurred in 15 (38%), constipation in 12 (30%), blurred vision in 11 (28%), urinary hesitancy in 9 (23%), nausea in 9 (23%), impotence in 2 (5%), and dyspareunia in one patient (3%). In addition 3 of the 9 patients with pre-existing heart failure had worsening of their condition due to disopyramide. Adverse effects were sufficiently severe for disopyramide to be stopped in 7 patients, and for dosage reductions in another 7.

1. Bauman JL, *et al.* Long-term therapy with disopyramide phosphate: side effects and effectiveness. *Am Heart J* 1986; **111:** 654–60.

Effects on the blood. Granulocytopenia was associated on 2 occasions with the use of disopyramide phosphate in a 61-year-old man.[1]

1. Conrad ME, *et al.* Agranulocytosis associated with disopyramide therapy. *JAMA* 1978; **240:** 1857–8.

Effects on the eyes. The antimuscarinic activity of disopyramide may cause adverse effects such as dilated pupils,[1] severe blurring of vision,[1] and acute glaucoma.[2,3] Disopyramide should be avoided in patients with glaucoma and used with caution if there is a family history of glaucoma.

1. Frucht J, *et al.* Ocular side effects of disopyramide. *Br J Ophthalmol* 1984; **68:** 890–1.
2. Trope GE, Hind VMD. Closed-angle glaucoma in patient on disopyramide. *Lancet* 1978, **i:** 329.
3. Ahmad S. Disopyramide: pulmonary complications and glaucoma. *Mayo Clin Proc* 1990; **65:** 1030–1.

Effects on the heart. Disopyramide has a strong negative inotropic effect and reversible heart failure has been reported[1] after its use. As many as 50% of patients with a history of heart failure may have a recurrence of the disease with an incidence of less than 5% in other patients.

As disopyramide can prolong the QT interval it can induce ventricular tachyarrhythmias. A case of fatal torsade de pointes has been reported.[2]

1. Podrid PJ, *et al.* Congestive heart failure caused by oral disopyramide. *N Engl J Med* 1980; **302:** 614–17.
2. Schattner A, *et al.* Fatal torsade de pointes following jaundice in a patient treated with disopyramide. *Postgrad Med J* 1989; **65:** 333–4.

Effects on the liver. Cholestatic jaundice with raised liver enzyme values has been associated with disopyramide.[1-3] Laboratory and clinical abnormalities disappear on withdrawal although liver enzyme values may remain elevated for several months.

Severe hepatocellular damage with disseminated intravascular coagulation[4] has also been reported.

1. Craxi A, *et al.* Disopyramide and cholestasis. *Ann Intern Med* 1980; **93:** 150–1.
2. Edmonds ME, Hayler AM. *Eur J Clin Pharmacol* 1980; **18:** 285–6.
3. Bakris GL, *et al.* Disopyramide-associated liver dysfunction. *Mayo Clin Proc* 1983; **58:** 265–7.
4. Doody PT. Disopyramide hepatotoxicity and disseminated intravascular coagulation. *South Med J* 1982; **75:** 496–8.

Effects on mental state. Agitation and distress leading to paranoia and auditory and visual hallucinations have been reported[1,2] in patients shortly after starting disopyramide therapy. Complete recovery occurred on withdrawal.

1. Falk RH, *et al.* Mental distress in patient on disopyramide. *Lancet* 1977; **i:** 858–9.
2. Padfield PL, *et al.* Disopyramide and acute psychosis. *Lancet* 1977; **i:** 1152.

Effects on the nervous system. Peripheral neuropathy affecting the feet and severe enough to prevent walking was associated with disopyramide in a 72-year-old patient.[1] There was gradual improvement on withdrawal of disopyramide with the patient being symptom-free after 4 months. Another patient[2] developed a peripheral polyneuropathy 4 years after starting disopyramide; symptoms improved over a number of months after disopyramide was stopped.

A 75-year-old woman with atrial fibrillation suffered a tonic-clonic seizure followed by respiratory arrest after receiving disopyramide 150 mg intravenously over a period of 10 minutes.[3] On recovery she complained of a dry mouth and blurred vision and it was considered that the seizure was caused by the antimuscarinic action of disopyramide, although it may have been due to a direct stimulant action.

1. Dawkins KD, Gibson J. Peripheral neuropathy with disopyramide. *Lancet* 1978; **i:** 329.
2. Briani C, *et al.* Disopyramide-induced neuropathy. *Neurology* 2002; **58:** 663.
3. Johnson NM, *et al.* Epileptiform convulsion with intravenous disopyramide. *Lancet* 1978; **ii:** 848.

Effects on sexual function. Impotence has been reported[1-3] in patients receiving disopyramide, and is usually attributed to its antimuscarinic effects, although other antimuscarinic symptoms may not be apparent. In one patient[1] full recovery of sexual function occurred when the dose was reduced (plasma concentration reduced from 14 to 3 micrograms/mL); another patient[3] developed impotence shortly after starting disopyramide, despite a low plasma concentration (1.5 micrograms/mL), but the condition resolved without changing therapy.

1. McHaffie DJ, *et al.* Impotence in patient on disopyramide. *Lancet* 1977; **i:** 859.
2. Ahmad S. Disopyramide and impotence. *South Med J* 1980; **73:** 958.
3. Hasegawa J, Mashiba H. Transient sexual dysfunction observed during antiarrhythmic therapy by long-acting disopyramide in a male Wolff-Parkinson-White patient. *Cardiovasc Drugs Ther* 1994; **8:** 277.

Effects on the urinary tract. In a report of 9 cases of urinary retention associated with disopyramide and a review of the literature,[1] it was noted that urinary retention secondary to disopyramide use was most likely to develop in male patients over the age of 65 in whom there was some pre-existing renal dysfunction; there was an increased risk in patients with evidence of prostatic hyperplasia.

1. Danziger LH, Horn JR. Disopyramide-induced urinary retention. *Arch Intern Med* 1983; **143:** 1683–6.

Hypersensitivity. Worsening of ventricular arrhythmia and an anaphylactoid reaction occurred in a 58-year-old man after a single oral dose of disopyramide 300 mg.[1] Two hours later he complained of a swollen tongue and difficulty in breathing. He became cyanotic but his respiratory status improved when given diphenhydramine 25 mg intravenously.

1. Porterfield JG, *et al.* Respiratory difficulty after use of disopyramide. *N Engl J Med* 1980; **303:** 584.

Hypoglycaemia. After the manufacturer received reports of hypoglycaemia associated with disopyramide, 2 controlled studies were conducted in healthy subjects.[1] Disopyramide produced a small decrease in blood-glucose concentration but there were no symptoms of hypoglycaemia, although it was considered that the glucose-lowering effect might be clinically significant in patients with hepatic or renal impairment. A review[2] found that renal impairment, advanced age, and malnutrition were the main risk factors for hypoglycaemia, and hypoglycaemia with reduced insulin requirements has also been reported[3] in a patient with type 2 diabetes mellitus. An interaction with clarithromycin has also been reported as a possible cause (see Antibacterials under

Interactions, below). However, the overall incidence appears to be low[2] and a case-control study[4] in 91 patients with hypoglycaemia failed to confirm an association with disopyramide.

1. Strathman I, *et al.* Hypoglycemia in patients receiving disopyramide phosphate. *Drug Intell Clin Pharm* 1983; **17:** 635–8.
2. Cacoub P, *et al.* Disopyramide-induced hypoglycemia: case report and review of the literature. *Fundam Clin Pharmacol* 1989; **3:** 527–35.
3. Reynolds RM, Walker JD. Hypoglycaemia induced by disopyramide in a patient with type 2 diabetes mellitus. *Diabet Med* 2001; **18:** 1009–10.
4. Takada M, *et al.* The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; **56:** 335–42.

Overdosage. A 2-year-old boy suffered hypotension, cardiac arrhythmias, and convulsions and died 28 hours after ingestion of 600 mg of disopyramide.[1] In a report[2] of 5 cases of fatal overdosage with disopyramide the most common clinical finding appeared to be an early loss of consciousness after an episode of respiratory arrest. Four of the patients responded to resuscitation at first but then deteriorated rapidly, with cardiac arrhythmias and loss of spontaneous respiration; in 4 of the cases post-mortem examination found pulmonary congestion secondary to left ventricular failure.

1. Hutchison A, Kilham H. Fatal overdosage of disopyramide in a child. *Med J Aust* 1978; **2:** 335–6.
2. Hayler AM, *et al.* Fatal overdosage with disopyramide. *Lancet* 1978; **i:** 968–9.

Precautions

Disopyramide is contra-indicated in complete heart block (unless the patient has a pacemaker) and in cardiogenic shock. It should be used with extreme caution in patients with other conduction disorders or uncompensated heart failure. As for quinidine (see Precautions for Quinidine, p.1384), if disopyramide is used to treat atrial tachycardia it may be necessary to pre-treat with digoxin. Hypokalaemia should be corrected before disopyramide is started. Care should be taken in patients susceptible to hypoglycaemia, including those with heart failure, hepatic or renal impairment, and patients taking drugs that affect glucose metabolism.

Intravenous injections of disopyramide should be given slowly to avoid hypotension and it is recommended that facilities for cardiac monitoring and defibrillation should be available when the injection is used.

Dosage reduction may be necessary in patients with hepatic or renal impairment and in patients with heart failure.

Owing to its antimuscarinic properties, disopyramide should be avoided in patients with glaucoma or a tendency to urinary retention, as in benign prostatic hyperplasia, and also in patients with myasthenia gravis because of the risk of precipitating a myasthenic crisis. It should be used with caution in patients with a family history of glaucoma.

◊ For dosage adjustments in the elderly and in patients with hepatic or renal impairment, see under Uses and Administration, below.

Breast feeding. Disopyramide is distributed into breast milk and milk to plasma ratios of 0.4, about 0.5, and 0.9 have been reported.[1-3] Disopyramide has been detected in the plasma of breast-fed infants, but was not associated with adverse effects. The American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding. However, the infant should be monitored for adverse effects, especially antimuscarinic effects.

1. MacKintosh D, Buchanan N. Excretion of disopyramide in human breast milk. *Br J Clin Pharmacol* 1985; **19:** 856–7.
2. Hoppu K, *et al.* Disopyramide and breast feeding. *Br J Clin Pharmacol* 1986; **21:** 553.
3. Barnett DB, *et al.* Disopyramide and its N-monodesalkyl metabolite in breast milk. *Br J Clin Pharmacol* 1982; **14:** 310–12.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Pregnancy. Disopyramide is not usually recommended in pregnancy since it may induce uterine contractions. Although no adverse effects were noted in a patient given disopyramide 200 mg every 8 hours from 26 weeks of gestation until delivery,[1] another patient who was given 4 oral doses of disopyramide 100 to 300 mg at six-hourly intervals in week 32 of pregnancy had uterine contractions 1 to 2 hours after each dose.[2] A further patient[3] given disopyramide at 36 weeks of gestation developed painful uterine contractions 40 minutes after a single 150-mg dose orally; active labour and haemorrhage developed after a second dose was given, and an emergency caesarean section was required. A double-blind, placebo-controlled study[4] involving 20 women hospitalised for induction of labour confirmed that disopyramide induces uterine contractions. All 10 women given disopyramide 150 mg every 6 hours for 48 hours began contractions and in 8 delivery was induced.

1. Shaxted EJ, Milton PJ. Disopyramide in pregnancy: a case report. *Curr Med Res Opin* 1979; **6:** 70–2.
2. Leonard RF, *et al.* Initiation of uterine contractions by disopyramide during pregnancy. *N Engl J Med* 1978; **299:** 84–5.
3. Abbi M, *et al.* Preterm labor and accidental hemorrhage after disopyramide therapy in pregnancy: a case report. *J Reprod Med* 1999; **44:** 653–5.
4. Tadmor OP, *et al.* The effect of disopyramide on uterine contractions during pregnancy. *Am J Obstet Gynecol* 1990; **162:** 482–6.

Interactions

Disopyramide should be used cautiously with drugs that have negative inotropic effects or that affect conduction, including beta blockers and other class I antiarrhythmics; it prolongs the QT interval and should not be given with other arrhythmogenic drugs. Disopyramide is metabolised by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with inhibitors or inducers of this enzyme and with other drugs metabolised by CYP3A4. Use of disopyramide with other antimuscarinic drugs produces enhanced antimuscarinic effects.

Anti-anginals. For reference to disopyramide reducing the effectiveness of sublingual *isosorbide dinitrate*, see p.1318.

Antiarrhythmics. The effects of disopyramide on cardiac conduction are additive to those of other class I antiarrhythmic drugs.[1] Disopyramide may prolong the QT interval, a factor associated with torsade de pointes, particularly when given with drugs that have a similar effect; this effect was noted in a few patients given *amiodarone* with disopyramide.[2] Also the serum concentration of disopyramide has been increased by *quinidine*;[3] there was a reciprocal decrease in the serum-quinidine concentration but this was less important clinically.

1. Ellrodt G, Singh BN. Adverse effects of disopyramide (Norpace): toxic interactions with other antiarrhythmic agents. *Heart Lung* 1980; **9:** 469–74.
2. Tartini R, *et al.* Dangerous interaction between amiodarone and quinidine. *Lancet* 1982; **i:** 1327–9.
3. Baker BJ, *et al.* Concurrent use of quinidine and disopyramide: evaluation of serum concentrations and electrocardiographic effects. *Am Heart J* 1983; **105:** 12–15.

Antibacterials. The metabolism of disopyramide may be increased by enzyme inducers such as *rifampicin*;[1,2] the increased clearance of disopyramide may lead to subtherapeutic plasma concentrations.

Conversely, enzyme inhibitors may increase serum-disopyramide concentrations[3] and ventricular arrhythmias have been noted in patients given azithromycin,[4] clarithromycin,[5-7] and erythromycin.[3] Hypoglycaemia attributed to increased disopyramide concentrations has also been reported[8,9] with clarithromycin.

1. Aitio M-L, *et al.* The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; **11:** 279–85.
2. Staum JM. Enzyme induction: rifampin-disopyramide interaction. *DICP Ann Pharmacother* 1990; **24:** 701–3.
3. Ragosta M, *et al.* Potentially fatal interaction between erythromycin and disopyramide. *Am J Med* 1989; **86:** 465–6.
4. Granowitz EV, *et al.* Potentially fatal interaction between azithromycin and disopyramide. *Pacing Clin Electrophysiol* 2000; **23:** 1433–5.
5. Paar D, *et al.* Life-threatening interaction between clarithromycin and disopyramide. *Lancet* 1997; **349:** 326–7.
6. Hayashi Y, *et al.* Torsades de pointes ventricular tachycardia induced by clarithromycin and disopyramide in the presence of hypokalemia. *Pacing Clin Electrophysiol* 1999; **22:** 672–4.
7. Choudhury L, *et al.* Torsades de pointes due to drug interaction between disopyramide and clarithromycin. *Heart Dis* 1999; **1:** 206–7.
8. Iida H, *et al.* Hypoglycemia induced by interaction between clarithromycin and disopyramide. *Jpn Heart J* 1999; **40:** 91–96.
9. Morlet-Barla N, *et al.* Hypoglycémie grave et récidivante secondaire à l'interaction disopyramide-clarithromicine. *Presse Med* 2000; **29:** 1351.

Antiepileptics. The clearance of disopyramide may be increased by enzyme inducers such as *phenytoin* and *phenobarbital*, and a small study[1] found that phenytoin reduced serum-disopyramide concentrations.

1. Aitio M-L, *et al.* The effect of enzyme induction on the metabolism of disopyramide in man. *Br J Clin Pharmacol* 1981; **11:** 279–85.

Beta blockers. Beta blockers have negative inotropic effects that may be potentiated if they are given with disopyramide. A pharmacokinetic interaction may also occur with beta blockers since the clearance of disopyramide has been reported[1] to be reduced by about 16% during *atenolol* therapy.

1. Bonde J, *et al.* Atenolol inhibits the elimination of disopyramide. *Eur J Clin Pharmacol* 1985; **28:** 41–3.

Pharmacokinetics

Disopyramide is readily and almost completely absorbed from the gastrointestinal tract, peak plasma concentrations being attained about 0.5 to 3 hours after oral doses.

Disopyramide is partially metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4. The major metabolite is mono-*N*-dealkylated disopyramide which retains some antiarrhythmic and antimuscarinic activity. The major route of excretion is through the kidney, about 50% as the unchanged drug, 20% as the *N*-dealkylated metabolite, and 10% as other metabolites. About 10% is excreted in the faeces. The clearance of disopyramide does not appear to be influenced by urinary pH.

Disopyramide protein binding varies with the plasma concentration, limiting the usefulness of plasma concentration monitoring as a guide to therapy; protein binding is reported to be 50 to 65% at therapeutic plasma concentrations (about 2 to 4 micrograms/mL). Estimations of the plasma half-life of disopyramide range from about 4 to 10 hours. The half-life is increased in hepatic and renal impairment, and in heart failure.

Disopyramide crosses the placental barrier and is distributed into breast milk.

◊ Reviews.

1. Siddoway LA, Woosley RL. Clinical pharmacokinetics of disopyramide. *Clin Pharmacokinet* 1986; **11:** 214–22.

Uses and Administration

Disopyramide is a class Ia antiarrhythmic (p.1153) with an action on the heart similar to that of quinidine (p.1385). It also has antimuscarinic and negative inotropic properties.

Disopyramide is used in the management of supraventricular and ventricular arrhythmias (p.1160).

It may be given orally as either the base or the phosphate or intravenously as the phosphate; doses are expressed in terms of the base. Disopyramide phosphate 1.3 g is equivalent to about 1 g of disopyramide. The usual oral dose is 300 to 800 mg daily in divided doses adjusted according to response. A modified-release preparation can be used, enabling 12-hourly dosage intervals.

Disopyramide may be given by slow intravenous injection in a dose of 2 mg/kg to a maximum of 150 mg, at a rate not exceeding 30 mg/minute; this is followed by 200 mg orally immediately on completion of the injection and every 8 hours for 24 hours. If the arrhythmia recurs the intravenous injection may be repeated, but a total intravenous dose of 4 mg/kg (maximum 300 mg) should not be exceeded in the first hour, nor should the total by both intravenous and oral routes exceed 800 mg in 24 hours. Alternatively, the initial intravenous injection may be followed by intravenous infusion of 400 micrograms/kg per hour (or 20 to 30 mg/hour) to a maximum of 800 mg daily. Patients receiving disopyramide intravenously or in high oral doses should be monitored by ECG.

Dosage reduction and/or increased dosage interval may be necessary in patients with hepatic or renal impairment (see below) and in some elderly patients (see, below). Doses should also be adjusted in patients with heart failure to compensate for the prolonged half-life.

For the dosage of disopyramide in children, see below.

Action. A study in 6 patients with atrial flutter suggested that the antiarrhythmic activity of racemic disopyramide resides in the S(+)-enantiomer.[1]

1. Lima JJ, *et al.* Antiarrhythmic activity and unbound concentrations of disopyramide enantiomers in patients. *Ther Drug Monit* 1990; **12:** 23–8.

Administration in children. An optimum dosage regimen for children has not been fully established, but US product information suggests the following oral doses:

- under 1 year: 10 to 30 mg/kg daily
- age 1 to 4 years: 10 to 20 mg/kg daily
- age 4 to 12 years: 10 to 15 mg/kg daily
- age 12 to 18 years: 6 to 15 mg/kg daily

Administration in the elderly. The clearance of disopyramide was reduced in elderly non-smoking patients compared with young subjects, but the reduction was less marked in elderly patients who smoked more than 20 cigarettes daily.[1] It was recommended that the dose of disopyramide should be reduced by about 30% in elderly non-smokers.

1. Bonde J, *et al.* The influence of age and smoking on the elimination of disopyramide. *Br J Clin Pharmacol* 1985; **20:** 453–8.

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.

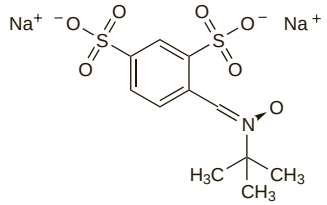
Disufenton Sodium *(USAN, rINN)*

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.

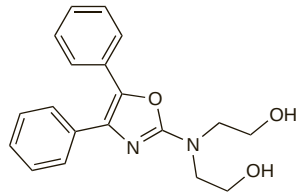
Дитазол

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

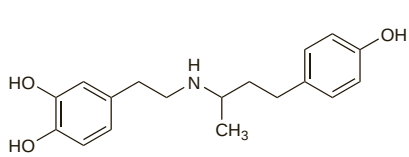
Добутамина Гидрохлорид

$C_{18}H_{23}NO_3$,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