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.

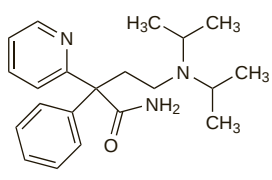
Дизопирамид

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