Preparations

BP 2008: Prazosin Tablets;
USP 31: Prazosin Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Decliten; Minipres†; ***Austral.:*** Minipress; Prasig†; Pratsiol; Prazohexal†; Pressin; ***Austria:*** Minipress; ***Belg.:*** Minipress; ***Braz.:*** Minipress; ***Canad.:*** Apo-Prazo; Minipress; Novo-Prazin; Nu-Prazo; ***Cz.:*** Deprazolin; ***Denm.:*** Hexapress; Peripress†; Prazac; ***Fin.:*** Peripress†; Pratsiol; ***Fr.:*** Alpress; Minipress; ***Ger.:*** Adversuten†; duramipress†; Minipress; ***Hong Kong:*** Apo-Prazo; CP-Prazo; Minipress; Mizosin; ***Hung.:*** Huma-Prazin†; Minipress; ***India:*** Minipress; Prazocip; ***Irl.:*** Hypovase; ***Israel:*** Hypotens; ***Jpn:*** Minipress†; ***Malaysia:*** Atodel; Minipress; Minison; ***Mex.:*** Anapres; Ensibest; Minipres; Sinozzard; ***NZ:*** Apo-Prazo; Hyprosin; Pratsiol; ***Pol.:*** Polpressin†; ***S.Afr.:*** Minipress†; Pratsiol; ***Singapore:*** Apo-Prazo; Minipress; ***Spain:*** Minipres; ***Switz.:*** Minipress†; ***Thai.:*** Atodel; Lopress; Minipress; Parabowl†; Polypress; Pratsiol†; Pressin; ***Turk.:*** Minipress; ***UK:*** Hypovase; Kentovase†; ***USA:*** Minipress; ***Venez.:*** Minpres.

Multi-ingredient: ***Ger.:*** Polypress†; ***USA:*** Minizide†.

Prenalterol Hydrochloride *(BANM, USAN, rINNM)*

C-50005/A-Ba (racemate); CGP-7760B; H133/22; H-80/62 (racemate); Hidrocloruro de prenalterol; Prénaltérol, Chlorhydrate de; Prenalteroli Hydrochloridum. (*S*)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride.

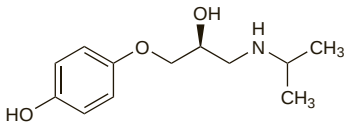
Пренальтерола Гидрохлорид

$C_{12}H_{19}NO_3$,HCl = 261.7.

CAS — 57526-81-5 (prenalterol); 61260-05-7 (prenalterol hydrochloride).

ATC — C01CA13.

ATC Vet — QC01CA13.



(prenalterol)

Profile

Prenalterol is a sympathomimetic (p.1407) with stimulant effects on beta$_1$ adrenoceptors. It has an inotropic action on the heart with relatively little chronotropic effect. Prenalterol hydrochloride has been given parenterally in the treatment of heart failure and shock. It has also been promoted for the reversal of beta blockade.

Probucol *(BAN, USAN, rINN)*

DH-581; Probucolum. 4,4′-(Isopropylidenedithio)bis(2,6-di-*tert*-butylphenol).

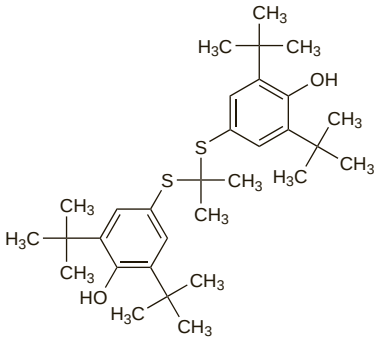
Пробукол

$C_{31}H_{48}O_2S_2$ = 516.8.

CAS — 23288-49-5.

ATC — C10AX02.

ATC Vet — QC10AX02.



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

USP 31 (Probucol). A white to off-white, crystalline powder. Insoluble in water; soluble in alcohol and in petroleum spirit; freely soluble in chloroform and in propyl alcohol. Protect from light.

Profile

Probucol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias (p.1169). It lowers total plasma-cholesterol concentrations, mainly by reducing low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol concentrations but has little effect on triglyceride or very-low-density lipoprotein (VLDL)-cholesterol concentrations. It has also been used to prevent restenosis after reperfusion and revascularisation procedures (below), and in scleroderma.

Probucol prolongs the QT interval and has been associated with cardiac arrhythmias.

Reperfusion and revascularisation procedures. Restenosis is common after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Probucol, started a few weeks before the procedure, has been reported to reduce the rate of restenosis after coronary angioplasty,[1] and to reduce the need for repeat interventions,[1,2] although another study[3] found no effect.

1. Tardif J-C, *et al.* Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1997; **337:** 365–72.
2. Daida H, *et al.* Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). *Am J Cardiol* 2000; **86:** 550–2.
3. Nunes GL, *et al.* Role of probucol in inhibiting intimal hyperplasia after coronary stent implantation: a randomized study. Abstract: *Am Heart J* 2006; **152:** 914. Full version: http://www.ahjonline.com/article/S0002-8703(06)00463-7/pdf (accessed 07/08/07)

Preparations

USP 31: Probucol Tablets.

Proprietary Preparations (details are given in Part 3)
Mex.: Serterol†; ***Port.:*** Lisosterol; ***S.Afr.:*** Lurselle†; ***Spain:*** Superlipid†; ***Thai.:*** Lurselle†.

Procainamide Hydrochloride

(BANM, rINNM)

Hidrocloruro de procainimida; Novocainamidum; Procaïnamide, chlorhydrate de; Procainamidi Chloridum; Procainamidi hydrochloridum; Prokaiinamidihydrokloridi; Prokainamid-hidroklorid; Prokainamid-hydrochlorid; Prokainamidhydroklorid; Prokainamido hidrochloridas; Prokainamidu chlorowodorek. 4-Amino-*N*-(2-diethylaminoethyl)benzamide hydrochloride.

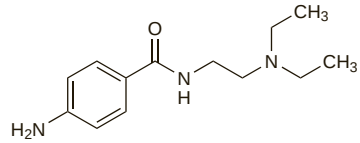
Прокаинамида Гидрохлорид

$C_{13}H_{21}N_3O$,HCl = 271.8.

CAS — 51-06-9 (procainamide); 614-39-1 (procainamide hydrochloride).

ATC — C01BA02.

ATC Vet — QC01BA02.



(procainamide)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 6.2 (Procainamide Hydrochloride). A white or very slightly yellow, hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 5.6 to 6.3. Store in airtight containers. Protect from light.

USP 31 (Procainamide Hydrochloride). A white to tan, odourless, crystalline powder. Very soluble in water; soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether and in benzene. A 10% solution in water has a pH of 5.0 to 6.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. Procainamide is more stable in neutral solutions such as sodium chloride, than in acidic solutions such as glucose, but patients requiring intravenous procainamide often have heart failure and cannot tolerate the sodium load associated with sodium chloride injections. The stability of procainamide in glucose 5% is improved by neutralising the glucose using sodium bicarbonate, or storing the admixture at 5°. The concentration of procainamide remained above 90% of the initial concentration for 24 hours if the glucose was first neutralised and this was considered more practical than refrigeration if extended stability was required.[1]

The compound formed by mixing procainamide hydrochloride with glucose 5% was shown to be a mixture of α- and β-glucosylamines[2] and about 10 to 15% of the procainamide was lost in this way after 10 hours at room temperature.

An oral liquid,[3] prepared from procainamide capsules, containing 5, 50, or 100 mg/mL of the hydrochloride was stable for at least 6 months when stored at 4° to 6°.

1. Raymond GG, *et al.* Stability of procainamide hydrochloride in neutralized 5% dextrose injection. *Am J Hosp Pharm* 1988; **45:** 2513–17.
2. Sianipar A, *et al.* Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994; **46:** 951–5.
3. Metras JI, *et al.* Stability of procainamide hydrochloride in an extemporaneously compounded oral liquid. *Am J Hosp Pharm* 1992; **49:** 1720–4.

Adverse Effects

Cardiac effects occur particularly during intravenous use of procainamide and in overdose. Rapid intravenous dosage may result in severe hypotension, ventricular fibrillation, and asystole. High plasma concentrations are also associated with impaired cardiac conduction.

Hypersensitivity reactions to procainamide are common. Procainamide is a frequent cause of drug-induced SLE and the incidence has been reported to be as high as 30% during long-term use. Antinuclear antibodies may be detected in a high proportion of patients, but they do not necessarily develop the symptoms of SLE, which include arthralgia, arthritis, myalgia, pleural effusion, pericarditis, and fever. Agranulocytosis, eosinophilia, neutropenia, thrombocytopenia, and haemolytic anaemia have been reported. Other symptoms of hypersensitivity not necessarily related to SLE may also occur including hepatomegaly, angioedema, skin rashes, pruritus, urticaria, flushing, and hypergammaglobulinaemia.

Anorexia, nausea, vomiting, a bitter taste, and diarrhoea are more common with higher oral doses. Effects on the CNS such as mental depression, dizziness, and psychosis with hallucinations, have been reported.

Incidence of adverse effects. Out of 488 hospitalised patients in the Boston Collaborative Drug Surveillance Program who had received procainamide, 45 had acute adverse effects attributed to the drug.[1] Life-threatening reactions included heart block (3), tachyarrhythmias (2), and bradycardia and/or hypotension (2). Other reactions included gastrointestinal upsets (19), pyrexia (8), bradycardia and hypotension (5), tachyarrhythmias (3), heart block (1), eosinophilia (1), and urticaria (1).

1. Lawson DH, Jick H. Adverse reactions to procainamide. *Br J Clin Pharmacol* 1977; **4:** 507–11.

Effects on the blood. Adverse haematological effects reported during procainamide therapy include neutropenia,[1-3] agranulocytosis,[2-6] thrombocytopenia,[5] haemolytic anaemia,[7] and pancytopenia.[8] These disorders are usually reversible on withdrawing procainamide although some fatalities have been reported.[3,4] It has been suggested[2,6] that agranulocytosis or severe neutropenia is more likely in patients taking modified-release preparations, but others have found no difference in the incidence between modified-release and conventional-release preparations.[3] An increased risk of agranulocytosis with procainamide has been documented in one large study.[9] Although the precise estimate of excess risk could not be calculated, the order of magnitude was about 3 per million exposed for up to one week. This excess risk was low and of little relevance in the initial choice of therapy.

1. Riker J, *et al.* Bone marrow granulomas and neutropenia associated with procainamide. *Arch Intern Med* 1978; **138:** 1731–2.
2. Ellrodt AG, *et al.* Severe neutropenia associated with sustained-release procainamide. *Ann Intern Med* 1984; **100:** 197–201.
3. Meyers DG, *et al.* Severe neutropenia associated with procainamide: comparison of sustained release and conventional preparations. *Am Heart J* 1985; **109:** 1393–5.
4. Fleet S. Agranulocytosis, procainamide, and phenytoin. *Ann Intern Med* 1984; **100:** 616–17.
5. Christensen DJ, *et al.* Agranulocytosis, thrombocytopenia, and procainamide. *Ann Intern Med* 1984; **100:** 918.
6. Thompson JF, *et al.* Procainamide agranulocytosis: a case report and review of the literature. *Curr Ther Res* 1988; **44:** 872–81.
7. Kleinman S, *et al.* Positive direct antiglobulin tests and immune hemolytic anemia in patients receiving procainamide. *N Engl J Med* 1984; **311:** 809–12.
8. Bluming AZ, *et al.* Severe transient pancytopenia associated with procainamide ingestion. *JAMA* 1976; **236:** 2520–1.
9. Kelly JP, *et al.* Risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs: The International Agranulocytosis and Aplastic Anemia Study. *Clin Pharmacol Ther* 1991; **49:** 330–41.

Effects on the gastrointestinal tract. Pseudo-obstruction of the bowel occurred in a diabetic patient when given procainamide both orally and intravenously. It was believed that the anticholinergic properties of procainamide, together with the diabetic state, contributed to the severe hypomotility of the gastrointestinal tract.[1]

1. Peterson AM, *et al.* Procainamide-induced pseudo-obstruction in a diabetic patient. *DICP Ann Pharmacother* 1991; **25:** 1334–5.

Effects on the heart. Procainamide prolongs the QT interval and has been associated with the development of torsade de pointes,[1,2] and fatal cardiovascular toxicity has been reported[3] in patients with renal impairment. Toxicity appears to be related to accumulation of the major metabolite, *N*-acetylprocainamide, and haemodialysis has been used to reduce plasma concentrations and control symptoms,[1,4] although its benefits have been disputed (see Dialysis, under Treatment of Adverse Effects,

below). However, symptoms developed in 1 patient[2] despite plasma concentrations of both procainamide and *N*-acetylprocainamide being within the therapeutic range.

1. Nguyen KPV, *et al*. N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104:** 283–4.
2. Habbab MA, El-Sherif N. Drug-induced torsades de pointes: role of early afterdepolarizations and dispersion of repolarization. *Am J Med* 1990; **89:** 241–6.
3. Vlasses PH, *et al*. Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.
4. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8:** 528–31.

Effects on the liver. There have been reports of granulomatous hepatitis[1] and intrahepatic cholestasis[2,3] due to hypersensitivity reactions in patients taking procainamide. Fever and elevation of liver enzyme values also occurred. The reactions were reversible on withdrawing procainamide.

1. Rotmensch HH, *et al*. Granulomatous hepatitis: a hypersensitivity response to procainamide. *Ann Intern Med* 1978; **89:** 646–7.
2. Ahn C-S, Tow DE. Intrahepatic cholestasis due to hypersensitivity reaction to procainamide. *Arch Intern Med* 1990; **150:** 2589–90.
3. Chuang LC, *et al*. Possible case of procainamide-induced intrahepatic cholestatic jaundice. *Ann Pharmacother* 1993; **27:** 434–7.

Effects on mental function. Acute psychosis has been reported[1] in patients receiving therapy with procainamide.

1. Bizjak ED, *et al*. Procainamide-induced psychosis: a case report and review of the literature. *Ann Pharmacother* 1999; **33:** 948–51.

Effects on the muscles. Procainamide may affect neuromuscular transmission and there have been reports of severe generalised skeletal muscle weakness[1-3] in patients receiving procainamide. In 2 patients this was associated with respiratory failure[1,2] and developed shortly after starting therapy. Concentrations of procainamide and its *N*-acetyl metabolite exceeded the normal therapeutic ranges and rapid cycling peritoneal dialysis was used to remove the drug in 1 patient.[2] Adverse muscle symptoms are a feature of procainamide-induced lupus erythematosus (see below), but in such instances symptoms usually develop on long-term treatment.

1. Lewis CA, *et al*. Myopathy after short term administration of procainamide. *BMJ* 1986; **292:** 593–4.
2. Javaheri S, *et al*. Diaphragmatic paralysis. *Am J Med* 1989; **86:** 623–4.
3. Sayler DJ, DeJong DJ. Possible procainamide-induced myopathy. *DICP Ann Pharmacother* 1991; **25:** 436.

Lupus erythematosus. Procainamide is a well-known cause of drug-induced lupus erythematosus.[1,2] It occurs in about 20% of patients on long-term therapy,[2] although the majority of patients taking procainamide for more than 1 year have detectable antinuclear antibodies. There is some evidence[3] that slow acetylators are more likely to develop antibodies than rapid acetylators, and that the antibodies appear more rapidly in slow acetylators, but this may not correlate with the development of clinical symptoms.[4] The clinical syndrome may include fever, polyarthritis, arthralgia, myalgia, and pleuropulmonary and pericardial features, and is usually spontaneously reversible on withdrawal of procainamide.

1. Price EJ, Venables PJW. Drug-induced lupus. *Drug Safety* 1995; **12:** 283–90.
2. Rubin RL. Drug-induced lupus. *Toxicology* 2005; **209:** 135–47.
3. Woosley RL, *et al*. Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N Engl J Med* 1978; **298:** 1157–9.
4. Mongey A-B, *et al*. Acetylation status is associated with serological changes but not clinically significant disease in patients receiving procainamide. *J Rheumatol* 1999; **26:** 1721–6.

Treatment of Adverse Effects

In overdosage with procainamide treatment is largely symptomatic and supportive. Activated charcoal may be considered if the patient presents within 1 hour of ingestion. The ECG, blood pressure, and renal function should be monitored. Supportive measures include correction of hypotension, assisted ventilation, and electrical pacing. Haemodialysis or haemoperfusion increase the elimination of procainamide and *N*-acetylprocainamide, see below.

SLE will normally respond to withdrawal of procainamide but corticosteroids may be required.

Dialysis. In the UK, the National Poisons Information Service does not recommend the use of haemodialysis or haemofiltration in the treatment of poisoning with class Ia antiarrhythmics. Nonetheless, both procainamide and *N*-acetylprocainamide are removed by haemodialysis, and there are reports[1-4] of the successful use of haemodialysis in patients with procainamide toxicity. However, toxicity has occurred in patients undergoing regular haemodialysis,[2,5,6] suggesting that some accumulation still takes place, and rebound increases in plasma concentrations have also been reported[4,7] after dialysis. Haemoperfusion[5,7] and haemofiltration[6] have also been used, and may be more effective. Peritoneal dialysis may also remove a small amount of procainamide and *N*-acetylprocainamide,[7] and there has been a report[8] of the successful use of rapid cycling peritoneal dialysis in a patient on maintenance peritoneal dialysis who developed procainamide-induced diaphragmatic paralysis.

1. Atkinson AJ, *et al*. Hemodialysis for severe procainamide toxicity: clinical and pharmacokinetic observations. *Clin Pharmacol Ther* 1976; **20:** 585–92.
2. Stevenson WG, Weiss J. Torsades de pointes due to N-acetylprocainamide. *Pacing Clin Electrophysiol* 1985; **8:** 528–31.
3. Nguyen KPV, *et al*. N-Acetylprocainamide, torsades de pointes, and hemodialysis. *Ann Intern Med* 1986; **104:** 283–4.
4. Rosansky SJ, Brady ME. Procainamide toxicity in a patient with acute renal failure. *Am J Kidney Dis* 1986; **7:** 502–6.
5. Braden GL, *et al*. Hemoperfusion for treatment of N-acetylprocainamide intoxication. *Ann Intern Med* 1986; **105:** 64–5.
6. Domoto DT, *et al*. Removal of toxic levels of N-acetylprocainamide with continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration. *Ann Intern Med* 1987; **106:** 550–2.
7. Low CL, *et al*. Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity. *Nephrol Dial Transplant* 1996; **11:** 881–4.
8. Javaheri S, *et al*. Diaphragmatic paralysis. *Am J Med* 1989; **86:** 623–4.

Precautions

Procainamide is contra-indicated in heart block (unless the patient has a pacemaker) and in SLE, and should be used with caution in patients with myocardial damage or severe organic heart disease. The *BNF* considers that it should not be used in heart failure or hypotension. Patients with torsade de pointes may deteriorate if given procainamide. If procainamide is used to treat atrial tachycardia it may be necessary to pre-treat with digoxin. Procainamide should preferably not be used in patients with myasthenia gravis or digoxin toxicity. There may be cross-sensitivity between procaine and procainamide.

Accumulation of procainamide may occur in patients with heart failure or hepatic or renal impairment and dosage reduction may be necessary.

Blood counts and screening for lupus erythematosus and serum antinuclear factor should be carried out regularly during therapy.

Intravenous use of procainamide may lead to severe hypotension; it should be injected slowly and blood pressure and ECG should be monitored.

Breast feeding. There was evidence of accumulation of procainamide and *N*-acetylprocainamide in the breast milk of a woman taking procainamide 500 mg four times daily.[1] Milk and serum samples were obtained at three-hourly intervals for 15 hours. Mean serum concentrations of the drug and metabolite were found to be 1.1 and 1.6 micrograms/mL respectively; those in the milk were 5.4 and 3.5 micrograms/mL respectively. The mean milk:serum ratios were 4.3 (range 1.0 to 7.3) and 3.8 (range 1.0 to 6.2) respectively. However, it was considered that the amount ingested by the infant would not yield clinically significant serum concentrations. Although licensed product information states that procainamide should be avoided in breast-feeding women, there have been no reports of adverse effects in infants, and the American Academy of Pediatrics considers[2] that its use is therefore usually compatible with breast feeding.

1. Pittard WB, Glazier H. Procainamide excretion in human milk. *J Pediatr* 1983; **102:** 631–3.
2. 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)

Interactions

Procainamide may enhance the effects of antihypertensives, other antiarrhythmics and arrhythmogenic drugs, antimuscarinics, and neuromuscular blockers, and diminish those of parasympathomimetics, such as neostigmine. Procainamide is actively secreted by kidney tubules and interactions may occur with drugs secreted by the same pathway, such as cimetidine and trimethoprim.

Alcohol. The total body clearance of procainamide is increased by alcohol[1] and the elimination half-life reduced. The acetylation rate of procainamide is also increased resulting in a greater proportion of drug present as the active metabolite *N*-acetylprocainamide.

1. Olsen H, Mørland J. Ethanol-induced increase in procainamide acetylation in man. *Br J Clin Pharmacol* 1982; **13:** 203–8.

Antacids. Procainamide is adsorbed by some antacids and reduced bioavailability has been reported[1] in healthy subjects given procainamide with *kaolin-pectin*; the authors recommended that procainamide and adsorbents should not be used together.

1. Al-Shora HI, *et al*. Interactions of procainamide, verapamil, guanethidine and hydralazine with adsorbent antacids and antidiarrhoeal mixtures. *Int J Pharmaceutics* 1988; **47:** 209–13.

Antiarrhythmics. *Amiodarone* given orally alters the pharmacokinetic properties of an intravenous dose of procainamide,[1] decreasing clearance and prolonging the plasma elimination half-life. The dosage of intravenous procainamide should be reduced by 20 to 30% during concurrent use. Increased serum-procainamide concentrations have also been reported[2] in patients stabilised on oral procainamide who had amiodarone added to their therapy; the dosage of procainamide had to be reduced in some patients due to signs of toxicity. *Quinidine* has also been reported[3] to increase plasma-procainamide concentrations.

1. Windle J, *et al*. Pharmacokinetic and electrophysiologic interactions of amiodarone and procainamide. *Clin Pharmacol Ther* 1987; **41:** 603–10.
2. Saal AK, *et al*. Effect of amiodarone on serum quinidine and procainamide levels. *Am J Cardiol* 1984; **53:** 1264–7.
3. Hughes B, *et al*. Increased procainamide plasma concentrations caused by quinidine: a new drug interaction. *Am Heart J* 1987; **114:** 908–9.

Antibacterials. The renal clearance of procainamide and *N*-acetylprocainamide is reduced by *trimethoprim*[1,2] through competition for renal tubular secretion. Serum concentrations may be increased with a resulting increase in pharmacodynamic response. The fluoroquinolones *ciprofloxacin*,[3] *levofloxacin*,[3] and *ofloxacin*[4] have also been reported to reduce the renal clearance of procainamide.

1. Kosoglou T, *et al*. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988; **44:** 467–77.
2. Vlasses PH, *et al*. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* 1989; **149:** 1350–3.
3. Bauer LA, *et al*. Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* 2005; **49:** 1649–51.
4. Martin DE, *et al*. Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* 1996; **36:** 85–91.

Histamine H_2-antagonists. Histamine H_2-antagonists compete with other basic drugs for renal tubular secretion. *Cimetidine* reduces the renal clearance of procainamide and *N*-acetylprocainamide[1,2] and a dosage reduction may be necessary. Increases[3,4] and decreases[4] in renal and metabolic clearances of procainamide have occurred with *ranitidine*.

1. Christian CD, *et al*. Cimetidine inhibits renal procainamide clearance. *Clin Pharmacol Ther* 1984; **36:** 221–7.
2. Somogyi A, *et al*. Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. *Eur J Clin Pharmacol* 1983; **25:** 339–45.
3. Somogyi A, Bochner F. Dose and concentration dependent effect of ranitidine on procainamide disposition and renal clearance in man. *Br J Clin Pharmacol* 1984; **18:** 175–81.
4. Rocci ML, *et al*. Ranitidine-induced changes in the renal and hepatic clearances of procainamide are correlated. *J Pharmacol Exp Ther* 1989; **248:** 923–8.

Pharmacokinetics

Procainamide is readily and almost completely absorbed from the gastrointestinal tract. It is widely distributed throughout the body and is only about 15 to 20% bound to plasma proteins. The therapeutic effect of procainamide has been correlated with plasma concentrations of about 3 to 10 micrograms/mL in most patients; progressively severe toxicity is noted at concentrations above 12 micrograms/mL.

Some procainamide undergoes acetylation in the liver to *N*-acetylprocainamide, which also has antiarrhythmic properties. The rate of acetylation of procainamide is genetically determined, there being slow and fast acetylators. Procainamide also undergoes hydrolysis in plasma to para-aminobenzoic acid.

Procainamide is excreted in the urine by active renal secretion, 30 to 70% as unchanged procainamide, with the remainder as *N*-acetylprocainamide and other metabolites. The elimination half-life of procainamide is 2.5 to 5 hours and that of its acetyl metabolite 6 to 7 hours. *N*-Acetylprocainamide may represent a significant fraction of the total drug in the circulation.

Procainamide crosses the placenta and is distributed into breast milk.

◊ References.

1. Grasela TH, Sheiner LB. Population pharmacokinetics of procainamide from routine clinical data. *Clin Pharmacokinet* 1984; **9:** 545–54.

Bioavailability. Modified-release procainamide preparations have been shown[1] to produce similar steady-state serum concentrations of procainamide and *N*-acetylprocainamide when compared with equivalent total doses of immediate-release capsules. However, tablet matrices of a modified-release preparation have been recovered from the stools of a patient with diarrhoea[2] and 3.5 g of procainamide was recovered in these matrices over an 18-hour collection period; the patient had correspondingly low plasma-procainamide concentrations.

1. Vlasses PH, *et al.* Immediate-release and sustained-release procainamide: bioavailability at steady state in cardiac patients. *Ann Intern Med* 1983; **98:** 613–14.
2. Woosley RL, *et al.* Antiarrhythmic therapy: clinical pharmacology update. *J Clin Pharmacol* 1984; **24:** 295–305.

The elderly. Reduced renal clearance of procainamide has been reported in the elderly.[1,2]

1. Reidenberg MM, *et al.* Aging and renal clearance of procainamide and acetylprocainamide. *Clin Pharmacol Ther* 1980; **28:** 732–5.
2. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.

Hepatic impairment. In 20 healthy subjects and 20 patients with chronic liver disease given a single 500-mg oral dose of procainamide hydrochloride about 64 and 33% respectively of the dose was excreted in the urine within 6 hours.[1] Decreased procainamide acetylation in the patients compared with the control group was not correlated with the severity of liver disease, whereas decreased procainamide hydrolysis and increased procainamide-derived aminobenzoic acid acetylation appeared to be related to the degree of hepatic impairment. It was suggested that the decrease in excretion of procainamide and its metabolites in the urine of the patients with liver disease could be due to an impairment in oral absorption since renal function was within the normal range but the variations in acetylation and hydrolysis were related to hepatic function.

1. du Souich P, Erill S. Metabolism of procainamide and p-aminobenzoic acid in patients with chronic liver disease. *Clin Pharmacol Ther* 1977; **22:** 588–95.

Renal impairment. Procainamide and its active *N*-acetyl metabolite are mainly excreted in the urine and accumulation, particularly of the metabolite, may occur in renal impairment. A study[1] in 20 patients found that procainamide clearance correlated with renal function, and that the ratio of *N*-acetylprocainamide to procainamide in the serum increased as renal function declined. Fatal toxicity in patients with renal impairment and plasma-procainamide concentrations within the therapeutic range has been attributed[2] to accumulation of *N*-acetylprocainamide. Both procainamide and *N*-acetylprocainamide are removed by dialysis, although the benefit of these procedures has been disputed (see Dialysis under Treatment of Adverse Effects, above).

1. Bauer LA, *et al.* Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. *Int J Clin Pharmacol Ther Toxicol* 1989; **27:** 213–16.
2. Vlasses PH, *et al.* Lethal accumulation of procainamide metabolite in severe renal insufficiency. *Am J Nephrol* 1986; **6:** 112–16.

Uses and Administration

Procainamide is a class Ia antiarrhythmic (p.1153); it has properties similar to those of quinidine (p.1385).

Procainamide is usually reserved for the short-term management of severe or symptomatic ventricular arrhythmias (p.1160) such as those following myocardial infarction. It may also be used for cardioversion and management of atrial fibrillation.

Therapeutic effect is generally associated with plasma concentrations of 3 to 10 micrograms/mL. The dose of procainamide hydrochloride required will depend on the age, renal and hepatic function, and underlying cardiac condition of the patient: an adult with normal renal function generally requires up to 50 mg/kg daily in divided oral doses every 3 to 6 hours. Higher doses may be necessary for atrial arrhythmias. Modified-release preparations are available.

In an emergency and under continuous ECG and blood pressure monitoring, procainamide hydrochloride may be given intravenously. The injection should be diluted in glucose 5% to permit better control of the speed of injection, and should be given in doses of 100 mg every 5 minutes at a rate not exceeding 50 mg/minute until the arrhythmia has been suppressed or a maximum dose of 1 g has been reached. A response may be obtained after 100 to 200 mg has been given and more than 500 or 600 mg is not generally required. Alternatively, procainamide hydrochloride may be given by continuous infusion of 500 to 600 mg over 25 to 30 minutes. Therapeutic plasma concentrations may then be maintained by infusion at a rate of 2 to 6 mg/minute. When transferring to oral therapy, a period of about 3 to 4 hours should elapse between the last intravenous dose and the first oral dose.

Procainamide hydrochloride has also been given intramuscularly.

Procainamide hydrochloride may need to be given in reduced doses or at longer dosing intervals in the elderly and in patients with hepatic or renal impairment. For use in children, see below.

Acecainide (*N*-acetylprocainamide), the active metabolite of procainamide, has class III antiarrhythmic activity and has been used in ventricular arrhythmias.

Administration in children. In a study in 5 children treated with procainamide for various cardiac arrhythmias the mean elimination half-life was found to be 1.7 hours, and the plasma clearance was higher than that reported in adults.[1] In contrast the total serum clearance of procainamide in 3 neonates with supraventricular tachycardia was found to be similar to that in adults and the mean elimination half-life was 5.3 hours.[2] A loading dose of 10 to 12 mg/kg intravenously was given followed by a continuous infusion of 20 to 75 micrograms/kg per minute.

An oral dose of 15 to 50 mg/kg daily in 4 divided doses has been used in children.

1. Singh S, *et al.* Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther* 1982; **32:** 607–11.
2. Bryson SM, *et al.* Therapeutic monitoring and pharmacokinetic evaluation of procainamide in neonates. *DICP Ann Pharmacother* 1991; **25:** 68–71.

Preparations

BP 2008: Procainamide Injection; Procainamide Tablets;
USP 31: Procainamide Hydrochloride Capsules; Procainamide Hydrochloride Extended-release Tablets; Procainamide Hydrochloride Injection; Procainamide Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Pronestyl; ***Braz.:*** Procamide; ***Canad.:*** Procan; Pronestyl†; ***Gr.:*** Pronestyl; ***Hong Kong:*** Pronestyl†; ***India:*** Pronestyl; ***Irl.:*** Pronestyl; ***Israel:*** Pronestyl†; ***Neth.:*** Pronestyl; ***NZ:*** Pronestyl; ***S.Afr.:*** Pronestyl; ***Spain:*** Biocoryl; ***UK:*** Pronestyl†; ***USA:*** Procanbid.

Propafenone Hydrochloride

(BANM, USAN, rINNM)

Fenopraine Hydrochloride; Hidrocloruro de propafenona; Propafenon Hidroklorür; Propafénone, chlorhydrate de; Propafenon-hydrochlorid; Propafenonhydroklorid; Propafenoni hydrochloridum; Propafenonihydrokloridi; Propafenono hidrochloridas; SA-79; WZ-884642; WZ-884643. 2′-(2-Hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride.

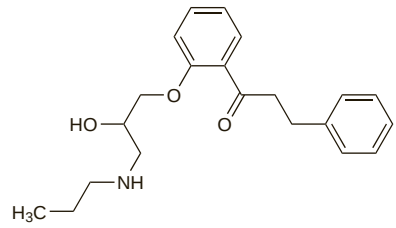
Пропафенона Гидрохлорид

$C_{21}H_{27}NO_3$,HCl = 377.9.

CAS — 54063-53-5 (propafenone); 34183-22-7 (propafenone hydrochloride).

ATC — C01BC03.

ATC Vet — QC01BC03.



(propafenone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Propafenone Hydrochloride). Colourless crystals or a white or almost white powder. Slightly soluble in cold water; soluble in hot water and in methyl alcohol; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.0 to 6.2.
USP 31 (Propafenone Hydrochloride). A white powder. Soluble in hot water and in methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone; insoluble in ether and in toluene. A 0.5% solution in water has a pH of 5.0 to 6.2. Store in airtight containers at a temperature between 15° and 30°. Protect from light.

Adverse Effects

Propafenone can cause disturbances in cardiac conduction which can result in bradycardia, heart block, and sinus arrest. It may aggravate heart failure and may cause hypotension. In common with other antiarrhythmics, propafenone may induce or worsen arrhythmias in some patients.

Among the most common adverse effects are gastrointestinal intolerance, dry mouth, a bitter or metallic taste, dizziness, blurred vision, headache, and fatigue. Convulsions, blood dyscrasias, liver disorders, lupus erythematosus, skin rashes, impotence, and increased breathlessness and worsening of asthma have also been reported.

Effects on the heart. Propafenone may worsen ventricular arrhythmias and there have been reports[1,2] of fatal exacerbations occurring hours to days after starting treatment. Cardiovascular toxicity may also occur in overdosage.[3] Torsade de pointes has been reported[2,4,5] but appears to be less frequent than with class Ia antiarrhythmics.

1. Nathan AW, *et al.* Fatal ventricular tachycardia in association with propafenone, a new class IC antiarrhythmic agent. *Postgrad Med J* 1984; **60:** 155–6.
2. Buss J, *et al.* Malignant ventricular tachyarrhythmias in association with propafenone treatment. *Eur Heart J* 1985; **6:** 424–8.
3. Clarot F, *et al.* Fatal propafenone overdoses: case reports and a review of the literature. *J Anal Toxicol* 2003; **27:** 595–9.
4. Rosengarten M, Brooks R. Torsade de pointes ventricular tachycardia in a hypothyroid patient treated with propafenone. *Can J Cardiol* 1987; **3:** 234–9.
5. Hii JT, *et al.* Propafenone-induced torsade de pointes: cross-reactivity with quinidine. *Pacing Clin Electrophysiol* 1991; **14:** 1568–70.

Effects on the liver. A review of liver injury secondary to propafenone therapy concluded that it is a rare occurrence and appears to be due to hepatocellular injury, cholestasis, or a combination.[1]

1. Spinler SA, *et al.* Propafenone-induced liver injury. *Ann Pharmacother* 1992; **26:** 926–8.

Effects on mental function. Delusions, hallucinations, and paranoia have been reported in an elderly patient after 2 doses of propafenone. The manufacturer had received reports of mania and psychosis.[1] Amnesia developed in a 61-year-old man 6 days after starting treatment with propafenone.[2] Symptoms resolved 6 to 7 hours after stopping the drug.

1. Robinson AJ. Paranoia after propafenone. *Pharm J* 1991; **247:** 556.
2. Jones RJ, *et al.* Probable propafenone-induced transient global amnesia. *Ann Pharmacother* 1995; **29:** 586–90.

Effects on the nervous system. Myoclonus has been reported in a patient receiving propafenone.[1] In another patient peripheral neuropathy developed 10 months after starting treatment but symptoms had resolved 6 months after stopping the drug.[2] There have also been reports of ataxia.[3]

1. Chua TP, *et al.* Myoclonus associated with propafenone. *BMJ* 1994; **308:** 113.
2. Galasso PJ, *et al.* Propafenone-induced peripheral neuropathy. *Mayo Clin Proc* 1995; **70:** 469–72.
3. Odeh M, *et al.* Propafenone-induced ataxia: report of three cases. *Am J Med Sci* 2000; **320:** 151–3.

Lupus erythematosus. Symptoms of lupus erythematosus and raised antinuclear antibody titres were associated with propafenone therapy on 2 occasions in a 63-year-old woman.[1]

1. Guindo J, *et al.* Propafenone and a syndrome of the lupus erythematosus type. *Ann Intern Med* 1986; **104:** 589.

Precautions

Propafenone is contra-indicated in patients with uncontrolled heart failure, conduction disturbances including heart block unless controlled by artificial pacing, cardiogenic shock (unless arrhythmia-induced), severe bradycardia, or pronounced hypotension. It may alter the endocardial pacing threshold and adjustment may be necessary in patients with pacemakers.

Propafenone has beta-blocking activity and may exacerbate obstructive airways disease; it should be used with great caution in such disorders and is contra-indicated in severe disease. Propafenone may aggravate myasthenia gravis and should be avoided in patients with this condition. Electrolyte disturbances should be corrected before beginning treatment. Propafenone should be used with caution in patients with hepatic or renal impairment.

Pregnancy and breast feeding. Experience in a patient given propafenone throughout the last trimester of pregnancy indicated that despite transplacental diffusion propafenone could safely be used at this time without harm to the fetus. Propafenone and its metabolite were detected in breast milk at concentrations considered to represent a markedly subtherapeutic dose to an infant.[1]

1. Libardoni M, *et al.* Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk. *Br J Clin Pharmacol* 1991; **32:** 527–8.