Interactions

Propafenone is extensively metabolised by the cytochrome P450 enzyme system, mainly by the isoenzyme CYP2D6, although CYP1A2 and CYP3A4 are also involved. Interactions may therefore occur with other drugs that are metabolised by these enzymes. Plasma-propafenone concentrations may be reduced by enzyme inducers such as rifampicin; enzyme inhibitors, such as cimetidine, fluoxetine, quinidine, and HIV-protease inhibitors, may increase plasma-propafenone concentrations. Propafenone itself may alter the plasma concentrations of other drugs, including beta blockers, ciclosporin, desipramine, digoxin, theophylline, venlafaxine, and warfarin. The absorption of propafenone may be reduced by orlistat. There may be an increased risk of arrhythmias if propafenone is given with other antiarrhythmics or arrhythmogenic drugs.

Antiarrhythmics. *Quinidine* inhibits the hepatic metabolism of propafenone and has been reported[1] to increase plasma-propafenone concentrations in extensive metabolisers;[1] the plasma concentration of the active 5-hydroxy metabolite was reduced and that of the *N*-depropyl metabolite increased but there was no change in the clinical response. Another study,[2] however, found that quinidine increased the beta-blocking effect of propafenone in extensive metabolisers, and a study[3] in patients with refractory atrial fibrillation found that addition of quinidine to propafenone was as effective and possibly better tolerated than increasing the propafenone dose.

1. Funck-Brentano C, *et al.* Genetically-determined interaction between propafenone and low dose quinidine: role of active metabolites in modulating net drug effect. *Br J Clin Pharmacol* 1989; **27:** 435–44.
2. Mörike KE, Roden DM. Quinidine-enhanced beta-blockade during treatment with propafenone in extensive metabolizer human subjects. *Clin Pharmacol Ther* 1994; **55:** 28–34.
3. Lau C-P, *et al.* Control of paroxysmal atrial fibrillation recurrence using combined administration of propafenone and quinidine. *Am J Cardiol* 2000; **86:** 1327–32.

Antibacterials. *Rifampicin* has lowered steady-state plasma concentrations of propafenone with the reappearance of arrhythmia.[1]

1. Castel JM, *et al.* Rifampicin lowers plasma concentrations of propafenone and its antiarrhythmic effect. *Br J Clin Pharmacol* 1990; **30:** 155–6.

Histamine H_2-antagonists. *Cimetidine* has been reported[1] to raise plasma-propafenone concentrations. The mean steady-state concentration increased by 22% but the wide interindividual variability meant this change was not significant.

1. Pritchett ELC, *et al.* Pharmacokinetic and pharmacodynamic interactions of propafenone and cimetidine. *J Clin Pharmacol* 1988; **28:** 619–24.

Pharmacokinetics

Propafenone is readily and almost completely absorbed from the gastrointestinal tract. It is metabolised in the liver, largely by the cytochrome P450 isoenzyme CYP2D6, but also to a small extent by CYP1A2 and CYP3A4; the extent of metabolism is genetically determined. In subjects with the extensive metaboliser phenotype there is extensive first-pass metabolism to two active metabolites, 5-hydroxypropafenone and *N*-depropylpropafenone, and to other minor inactive metabolites. In the small proportion of subjects with the slow metaboliser phenotype (lacking CYP2D6) little or no 5-hydroxypropafenone is formed. The bioavailability of propafenone is dependent upon metaboliser phenotype but more importantly on dosage as the first-pass metabolism is saturable. In practice doses are high enough to compensate for differences in phenotype. Propafenone and its metabolites also undergo glucuronidation.

Propafenone is more than 95% protein bound.

Propafenone is excreted in the urine and faeces mainly in the form of conjugated metabolites. The elimination half-life is reported to be 2 to 10 hours in extensive metabolisers and 10 to 32 hours in slow metabolisers.

Propafenone crosses the placenta and is distributed into breast milk.

◊ General references.

1. Hii JTY, *et al.* Clinical pharmacokinetics of propafenone. *Clin Pharmacokinet* 1991; **21:** 1–10.

Uses and Administration

Propafenone is a class Ic antiarrhythmic (p.1153) with some negative inotropic and beta-adrenoceptor blocking activity. It is used in the management of supraventricular and ventricular arrhythmias.

Treatment should be started under close monitoring of the ECG and blood pressure. The usual initial oral dose of propafenone hydrochloride is 150 mg three times daily and this may be increased, if necessary, at intervals of 3 to 4 days up to a maximum of 300 mg three times daily. Reduced doses may be appropriate in patients weighing less than 70 kg and in the elderly; dose reduction may also be necessary in hepatic impairment (see below).

Propafenone hydrochloride is available in some countries as a modified-release preparation. It has also been given by slow intravenous injection or by infusion.

Administration in hepatic impairment. The clearance of propafenone may be reduced in hepatic impairment; careful monitoring is required and lower doses should be considered. US licensed product information states that the dose should be only 20 to 30% of that given in normal hepatic function.

Administration in renal impairment. A study[1] of the disposition of propafenone found that renal function did not affect the pharmacokinetics of propafenone or 5-hydroxypropafenone, and another study[2] suggested that propafenone could be used safely for atrial fibrillation in patients with chronic renal failure. Nevertheless, UK and US licensed product information states that caution is necessary if propafenone is given to patients with renal impairment.

Propafenone does not appear to be removed by haemofiltration.[3]

1. Fromm MF, *et al.* Influence of renal function on the steady-state pharmacokinetics of the antiarrhythmic propafenone and its phase I and phase II metabolites. *Eur J Clin Pharmacol* 1995; **48:** 279–83.
2. Napoli C, *et al.* Propafenone in the conversion of atrial fibrillation in patients suffering from chronic renal failure. *Am J Ther* 1997; **4:** 130–3.
3. Seto W, *et al.* Propafenone disposition during continuous venovenous hemofiltration. *Ann Pharmacother* 1999; **33:** 957–9.

Cardiac arrhythmias. Propafenone is effective in many cardiac arrhythmias.[1,2] It may have a role in the management of supraventricular arrhythmias (see p.1160), including as a single oral loading dose for recent-onset atrial fibrillation.[3,4] It may also be used in ventricular arrhythmias, although in many cases non-pharmacological therapy is preferred. Successful use in children with various arrhythmias has also been reported.[5,6]

1. Capucci A, Boriani G. Propafenone in the treatment of cardiac arrhythmias: a risk-benefit appraisal. *Drug Safety* 1995; **12:** 55–72.
2. Reimold SC, *et al.* Propafenone for the treatment of supraventricular tachycardia and atrial fibrillation: a meta-analysis. *Am J Cardiol* 1998; **82:** 66N–71N.
3. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001; **37:** 542–7.
4. Boriani G, *et al.* Oral loading with propafenone for conversion of recent-onset atrial fibrillation: a review on in-hospital treatment. *Drugs* 2002; **62:** 415–23.
5. Heusch A, *et al.* Clinical experience with propafenone for cardiac arrhythmias in the young. *Eur Heart J* 1994; **15:** 1050–6.
6. Janoušek J, Paul T. Safety of oral propafenone in the treatment of arrhythmias in infants and children (European Retrospective Multicenter Study). *Am J Cardiol* 1998; **81:** 1121–4.

Preparations

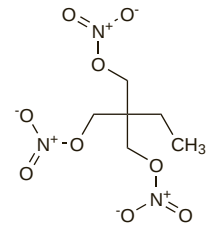
Proprietary Preparations (details are given in Part 3)
Arg.: Normorytmin; ***Austria:*** Asonacor†; Rhythmocor; Rytmonorma; ***Belg.:*** Rytmonorm; ***Braz.:*** Ritmonorm; ***Canad.:*** Rythmol; ***Chile:*** Ritmocor; Rytmonorm†; ***Cz.:*** Prolekofen; Propa-Tabletten†; Propanorm; Rytmonorm; ***Denm.:*** Rytmonorm; ***Fin.:*** Rytmonorm; ***Fr.:*** Rythmol; ***Ger.:*** Cuxafenon; Jutanorm†; Propamerck†; Rytmo-Puren; Rytmogenat†; Rytmonorm; ***Gr.:*** Rythmonorm; ***Hong Kong:*** Rytmonorm; ***Hung.:*** Rytmonorm; ***Indon.:*** Rytmonorm; ***Irl.:*** Arythmol; ***Israel:*** Profex; Rythmex; ***Ital.:*** Cardiofenone; Fenorit; Rytmonorm; ***Malaysia:*** Rytmonorm†; ***Mex.:*** Biopafen; Homopafen†; Nistaken; Norfenon; ***Neth.:*** Rytmonorm; ***NZ:*** Rytmonorm; ***Philipp.:*** Rytmocard; ***Pol.:*** Polfenon; Rytmonorm; ***Port.:*** Arythmol; Rytmonorm; ***Rus.:*** Propanorm (Пропанорм); Rytmonorm (Ритмонорм); ***S.Afr.:*** Rythmol; ***Singapore:*** Rytmonorm; ***Spain:*** Rytmonorm; ***Swed.:*** Rytmonorm; ***Switz.:*** Rytmonorm; ***Thai.:*** Rytmonorm; ***Turk.:*** Rytmonorm; ***UK:*** Arythmol; ***USA:*** Rythmol; ***Venez.:*** Rytmonorm.

Propatylnitrate *(BAN, rINN)*

ETTN; Ettriol Trinitrate; Propatilnitrato; Propatyl Nitrate *(USAN)*; Propatylnitrat; Propatylnitratum; Propatyylinitraatti; Trinettriol; Win-9317. 2-Ethyl-2-hydroxymethylpropane-1,3-diol trinitrate.

Пропатилнитрат

$C_6H_{11}N_3O_9$ = 269.2.
CAS — 2921-92-8.
ATC — C01DA07.
ATC Vet — QC01DA07.



Profile

Propatylnitrate is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296) that has been used in angina pectoris.

Preparations

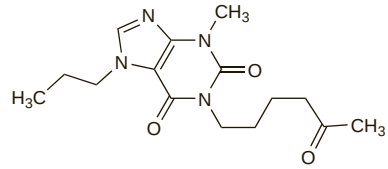
Proprietary Preparations (details are given in Part 3)
Braz.: Sustrate.

Propentofylline *(BAN, rINN)*

HWA-285; Propentofilina; Propentofylliini; Propentofyllin; Propentofyllinum. 3-Methyl-1-(5-oxohexyl)-7-propylxanthine.

Пропентофиллин

$C_{15}H_{22}N_4O_3$ = 306.4.
CAS — 55242-55-2.
ATC — N06BC02.
ATC Vet — QC04AD90; QN06BC02; QR03DA90.



Profile

Propentofylline is a xanthine derivative that has been investigated in cerebrovascular disorders including dementia. It is also used in veterinary medicine.

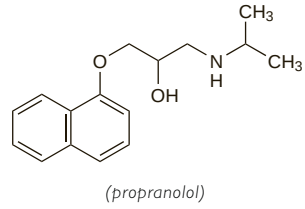
Propranolol Hydrochloride

(BANM, USAN, rINNM) ⊗

AY-64043; Hidrocloruro de propranolol; ICI-45520; NSC-91523; Propanolol-hidroklorid; Propanololi Hydrochloridum; Propranolol, chlorhydrate de; Propranolol Hidroklorür; Propranolol-hydrochlorid; Propranololhydroklorid; Propranololi hydrochloridum; Propranololihydrokloridi; Propranololio hidrochloridas; Propranololu chlorowodorek. (±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride.

Пропранолола Гидрохлорид

$C_{16}H_{21}NO_2$,HCl = 295.8.
CAS — 525-66-6 (propranolol); 13013-17-7 (propranolol); 318-98-9 (propranolol hydrochloride); 3506-09-0 (propranolol hydrochloride).
ATC — C07AA05.
ATC Vet — QC07AA05.



(propranolol)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Propranolol Hydrochloride). A white or almost white powder. Soluble in water and in alcohol.
USP 31 (Propranolol Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. In aqueous solutions propranolol decomposes with oxidation of the isopropylamine side-chain, accompanied by a

reduction in pH and discoloration of the solution. Solutions are most stable at pH 3 and decompose rapidly when alkaline.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Propranolol is distributed into breast milk. A milk/plasma ratio range of 0.33 to 1.65 was reported in a study of 3 women.[1] It was calculated that the maximum dose likely to be ingested by a breast-fed infant would be less than 0.1% of the maternal dose. Other small studies[2,3] have reported similar results. No adverse effects have been seen in breast-fed infants whose mothers were given propranolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Smith MT, *et al.* Propranolol, propranolol glucuronide, and naphthoxylactic acid in breast milk and plasma. *Ther Drug Monit* 1983; **5:** 87–93.
2. Karlberg B, *et al.* Excretion of propranolol in human breast milk. *Acta Pharmacol Toxicol (Copenh)* 1974; **34:** 222–4.
3. Bauer JH, *et al.* Propranolol in human plasma and breast milk. *Am J Cardiol* 1979; **43:** 860–2.
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 10/01/08)

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Propranolol is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic-tissue binding and first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma concentrations vary greatly between individuals. Propranolol has high lipid solubility. It crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is about 90% bound to plasma proteins. It is metabolised in the liver and at least one of its metabolites (4-hydroxypropranolol) is considered to be active, but the contribution of metabolites to its overall activity is uncertain. The metabolites and small amounts of unchanged drug are excreted in the urine. The plasma half-life of propranolol is about 3 to 6 hours. Propranolol is reported not to be significantly dialysable.

Pregnancy. A study in 6 pregnant patients (32 to 36 weeks' gestation) showed that the disposition of propranolol 120 mg orally and 10 mg intravenously was not altered in pregnancy compared with the postnatal period.[1] Another study[2] in 13 pregnant patients given propranolol to control hypertension showed that the pharmacokinetics of propranolol and most of its major metabolites were not altered during pregnancy. Samples at term[3] in 10 of the women showed that propranolol and all of its known metabolites were present in maternal plasma, cord plasma, and neonatal plasma. At delivery plasma protein binding of propranolol was reported as 87.5% in maternal plasma and 67.2% in cord plasma. Similar results for maternal and cord plasma protein binding have been reported by others.[4]

1. O'Hare MFO, *et al.* Pharmacokinetics of propranolol during pregnancy. *Eur J Clin Pharmacol* 1984; **27:** 583–7.
2. Smith MT, *et al.* Chronic propranolol administration during pregnancy: maternal pharmacokinetics. *Eur J Clin Pharmacol* 1983; **25:** 481–90.
3. Smith MT, *et al.* Metabolism of propranolol in the human maternal-placental-foetal unit. *Eur J Clin Pharmacol* 1983; **24:** 727–32.
4. Wood M, Wood AJJ. Changes in plasma drug binding and α-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981; **29:** 522–6.

Uses and Administration

Propranolol is a non-cardioselective beta blocker (p.1225). It is reported to have membrane-stabilising properties, but does not possess intrinsic sympathomimetic activity.

Propranolol is used as the hydrochloride in the management of hypertension (p.1171), phaeochromocytoma (p.1179), angina pectoris (p.1157), myocardial infarction (p.1175), and cardiac arrhythmias (p.1160). It is also used in hypertrophic cardiomyopathy (p.1163). It is used to control symptoms of sympathetic overactivity in the management of hyperthyroidism (p.2165), anxiety disorders (p.952), and tremor (p.1231). Other indications include the prophylaxis of migraine (p.616) and of upper gastrointestinal bleeding in patients with portal hypertension (see Variceal Haemorrhage under Monoethanolamine Oleate, p.2346).

Propranolol hydrochloride is usually given orally. In **hypertension** it is given in initial doses of 40 to 80 mg twice daily increased as required to a usual range of 160 to 320 mg daily; some patients may require up to 640 mg daily. Propranolol is *not* suitable for the emergency treatment of hypertension; it should not be given intravenously in hypertension.

In **phaeochromocytoma**, patients treated surgically may be given 60 mg daily on the 3 days before the operation, always with alpha blockade. If the tumour is inoperable prolonged treatment may be given with a daily dose of 30 mg.

In **angina,** initial doses of propranolol hydrochloride 40 mg given 2 or 3 times daily are increased as required to a usual range of 120 to 240 mg daily. Some patients may require up to 320 mg daily.

Propranolol hydrochloride is given within 5 to 21 days of **myocardial infarction** in doses of 40 mg given four times daily for 2 or 3 days followed by 80 mg twice daily. Another regimen is to give 180 to 240 mg daily in divided doses.

Propranolol may be given in doses of 30 to 160 mg daily in divided doses in the long-term management of **cardiac arrhythmias**. For the emergency treatment of cardiac arrhythmias, propranolol hydrochloride may be given by slow intravenous injection over a period of 1 minute, in a dose of 1 mg, repeated if necessary every 2 minutes until a maximum total of 10 mg has been given in conscious patients and 5 mg in patients under anaesthesia. Patients receiving propranolol intravenously should be carefully monitored.

In **hypertrophic cardiomyopathy** the usual dose of propranolol hydrochloride is 10 to 40 mg given three or four times daily.

In **hyperthyroidism** propranolol hydrochloride is given in doses of 10 to 40 mg three or four times daily. If intravenous administration is necessary 1 mg is given over 1 minute, repeated at 2-minute intervals until a response is seen or to a maximum dose of 10 mg in conscious patients or 5 mg in patients under anaesthesia.

The dose for **anxiety** is 40 mg daily; this may be increased to 40 mg two or three times daily.

Essential tremor may be treated with 40 mg given two or three times daily; the dose can be increased at weekly intervals to 160 mg daily although doses up to 320 mg daily may be necessary.

An initial dose of 40 mg two or three times daily is used in **migraine** prophylaxis; the dose can be increased at weekly intervals up to 160 mg daily. Some patients have been given 240 mg daily.

In **portal hypertension,** propranolol hydrochloride should be given in initial doses of 40 mg twice daily; the dose may be increased as required up to 160 mg twice daily.

For the use of propranolol in children, see below.

Administration in children. Propranolol hydrochloride has been used both orally and intravenously in children, although it is not licensed for all indications. Suggested doses are:

for **hypertension**:

- neonates: 250 micrograms/kg orally three times daily, increased as required to a maximum of 2 mg/kg three times daily
- 1 month to 12 years: 0.25 to 1 mg/kg orally three times daily, increased as required to a maximum of 5 mg/kg daily in divided doses
- over 12 years: an adult dose (see above)

for **arrhythmias, phaeochromocytoma, and hyperthyroidism**:

- neonates: 250 to 500 micrograms/kg orally three times daily. *Alternatively* 20 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring
- 1 month to 18 years: 250 to 500 micrograms/kg orally three or four times daily, adjusted according to response, to a maximum of 1 mg/kg four times daily or a total daily dose of 160 mg. *Alternatively* 25 to 50 micrograms/kg may be given intravenously three or four times daily, injected slowly with appropriate monitoring

for **prophylaxis of migraine**:

- children up to 12 years: 10 to 20 mg orally two or three times daily
- over 12 years: an adult dose (see above)

for **tetralogy of Fallot**, see below

Administration in hepatic impairment. A study of the disposition of oral propranolol at steady state in 9 normal subjects and 7 with cirrhosis found a mean threefold increase in unbound blood-propranolol concentrations in patients with cirrhosis when compared with the controls. Mean half-lives for the 2 groups were 11.2 and 4 hours respectively.[1] Another study of propranolol given as a single dose of a 20-mg tablet and as a 160-mg modified-release preparation daily for 7 days in 10 patients with cirrhosis and portal hypertension found higher plasma concentrations in patients with severe liver disease compared with those reported in normal controls.[2] Others have reported similar findings.[3]

In patients with severe liver disease, it has been suggested that propranolol therapy be started at a low dose such as 20 mg three times daily,[2] 80 mg of a modified-release preparation given once daily,[2] or 160 mg of a modified-release preparation given every other day.[3] Monitoring of beta blockade is essential; checking the heart rate[2] or exercise testing[3] have been suggested as suitable methods to assess the extent of beta blockade in patients with cirrhosis.

1. Wood AJJ, *et al.* The influence of cirrhosis on steady-state blood concentrations of unbound propranolol after oral administration. *Clin Pharmacokinet* 1978; **3:** 478–87.
2. Arthur MJP, *et al.* Pharmacology of propranolol in patients with cirrhosis and portal hypertension. *Gut* 1985; **26:** 14–19.
3. Calès P, *et al.* Pharmacodynamic and pharmacokinetic study of propranolol in patients with cirrhosis and portal hypertension. *Br J Clin Pharmacol* 1989; **27:** 763–70.

Administration in renal impairment. A study of the pharmacokinetics of propranolol in 11 patients with chronic renal insufficiency showed no impairment in the elimination kinetics of propranolol compared with 8 subjects with normal renal function.[1] Peak concentrations of propranolol reported in patients with chronic renal failure have been 2 to 3 times higher than those in patients receiving dialysis or in normal subjects.[1,2] Additional studies indicate that there is no pharmacokinetic reason to amend the dosage of propranolol in patients with renal impairment.[3]

Findings from a study in 8 patients on haemodialysis include a slight elevation of plasma-propranolol concentrations, no elevation of plasma concentration of 4-hydroxypropranolol, but extremely high plasma concentrations of other propranolol metabolites.[4]

1. Lowenthal DT, *et al.* Pharmacokinetics of oral propranolol in chronic renal disease. *Clin Pharmacol Ther* 1974; **16:** 761–9.
2. Bianchetti G, *et al.* Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin Pharmacokinet* 1976; **1:** 373–84.
3. Wood AJJ, *et al.* Propranolol disposition in renal failure. *Br J Clin Pharmacol* 1980; **10:** 561–6.
4. Stone WJ, Walle T. Massive propranolol metabolite retention during maintenance hemodialysis. *Clin Pharmacol Ther* 1980; **28:** 449–55.

Tetralogy of Fallot. Beta blockers, particularly propranolol, have been used for the treatment[1] and prophylaxis[1-3] of cyanotic attacks in infants and children with tetralogy of Fallot and reversible right-ventricular outflow tract obstruction, although caution is required since bradycardia may develop.[4] Esmolol may be preferred during surgery.[5-7]

In the UK, licensed prescribing information allows an oral dose of propranolol hydrochloride of up to 1 mg/kg given 3 or 4 times daily. It may also be given intravenously in a dose of up to 100 micrograms/kg 3 or 4 times daily, injected slowly under ECG control.

The *BNFC* recommends the following doses:

- Neonates: 0.25 to 1 mg/kg orally 2 or 3 times daily, to a maximum of 2 mg/kg 3 times daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 12 hours if necessary
- Children aged 1 month to 12 years: 0.25 to 1 mg/kg orally 3 or 4 times daily, to a maximum of 5 mg/kg daily, or 15 to 20 micrograms/kg (maximum 100 micrograms/kg) intravenously, repeated every 6 to 8 hours if necessary.

1. Cumming GR. Propranolol in tetralogy of Fallot. *Circulation* 1970; **41:** 13–15.
2. Eriksson BO, *et al.* Long-term treatment with propranolol in selected cases of Fallot's tetralogy. *Br Heart J* 1969; **31:** 37–44.
3. Ponce FE, *et al.* Propranolol palliation of tetralogy of Fallot: experience with long-term drug treatment in pediatric patients. *Pediatrics* 1973; **52:** 100–108.
4. Clark DJ, *et al.* Propranolol induced bradycardia in tetralogy of Fallot. *Br Heart J* 1989; **61:** 378–9.
5. Nussbaum J, *et al.* Esmolol for the treatment of hypercyanotic spells in infants with tetralogy of Fallot. *J Cardiothorac Anesth* 1989; **3:** 200–2.
6. Geary V, *et al.* Esmolol in tetralogy of Fallot. *J Cardiothorac Anesth* 1989; **3:** 524–6.
7. Dhir AK, Dhir S. Esmolol in infundibular spasm. *Anaesthesia* 1991; **46:** 998.

Preparations

BP 2008: Prolonged-release Propranolol Capsules; Propranolol Injection; Propranolol Tablets;
USP 31: Propranolol Hydrochloride and Hydrochlorothiazide Extended-

release Capsules; Propranolol Hydrochloride and Hydrochlorothiazide Tablets; Propranolol Hydrochloride Extended-release Capsules; Propranolol Hydrochloride Injection; Propranolol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Inderal; Pirimetan; Propalong†; Propaneitor; Propayerst†; ***Austral.:*** Deralin; Inderal; ***Austria:*** Inderal; Proprahexal; ***Belg.:*** Inderal; ***Braz.:*** Antitensin; Cardiopranol†; Cardix; Hipernolol; Inderal; Neo Propranol†; Polol; Pradinolol; Pranolal; Propacor; Propalol†; Propanox†; Proparil†; Propramed; Propranol†; Propranolil†; Propranolum†; Rebaten; Sanpronol; Uni Propralol; ***Canad.:*** Inderal; Novo-Pranol; ***Chile:*** Coriodal; ***Denm.:*** Inderal†; Propal; ***Fin.:*** Inderal†; Propral; Ranoprin; ***Fr.:*** Adrexan†; Avlocardyl; Hemipralon†; ***Ger.:*** Beta-Tablinen; Dociton; Efektolol†; Elbrol; Obsidan; Propabloc†; Prophylux; propra; Propra-ratiopharm; Propranur; ***Gr.:*** Inderal; ***Hong Kong:*** Becardin†; Hopranolol†; Inderal; Inpanol; Palon†; Prolol†; Propa†; ***Hung.:*** Huma-Pronol; ***India:*** Betabloc; Betaspan; Ciplar; Corbeta; Inderal; Propal; ***Indon.:*** Farmadral; Inderal; ***Irl.:*** Half Inderal; Inderal; Tiperal†; ***Israel:*** Deralin; Inderal; Prolol; Slow Deralin; ***Ital.:*** Inderal; ***Malaysia:*** Inderal; Indon†; Propanol†; ***Mex.:*** Acifol†; Inderalici; Pranoral†; Prochor†; Propalem; Propalgin†; Sintaser; ***Norw.:*** Inderal; Pranolol; ***NZ:*** Angilol; Cardinol; Inderal; ***Philipp.:*** Duranol; Inderal; Phanerol; ***Port.:*** Corpendol†; Inderal; ***Rus.:*** Анаприлин (Anaprilin); Obsidan (Обзидан); ***S.Afr.:*** Cardiblok; Inderal; Prodorol; Pur-Bloka; ***Singapore:*** Inderal; Inpanol; ***Spain:*** Sumial; ***Swed.:*** Inderal; ***Switz.:*** Inderal; ***Thai.:*** Alperol; Atensin†; Betalol; Betapress; Cardenol; Emforal; Inderal; Normpress; Palon; Perlol; Pralol; Prolol; Syntonol; ***Turk.:*** Dideral; ***UAE:*** Cardilol; ***UK:*** Angilol; Bedranol; Beta-Prograne; Half Beta-Prograne; Half Inderal; Inderal; Slo-Pro; Syprol; ***USA:*** Inderal; InnoPran; ***Venez.:*** Algoren; Docitral; Galenol†; Indal†; Inderal; Parinex†.

Multi-ingredient: ***Arg.:*** Propayerst Plus†; ***Austria:*** Inderetic†; ***Belg.:*** Inderetic†; ***Braz.:*** Polol-H; Tenadren; ***Ger.:*** Beta-Turfa; Diutensat comp†; Docidrazin†; Dociretic; Dociteren; Nitro-Obsidan†; Obsilazin N†; Pertenso N; Propra comp; Triamteren tri-comp; ***India:*** Beptazine; Beptazine-H; Ciplar-H; Corbetazine; Zopax Plus; ***Neth.:*** Inderetic; ***S.Afr.:*** Inderetic†; ***Spain:*** Betadipresan Diu†; Betadipresan†; ***Switz.:*** Inderetic†; ***UK:*** Inderetic†; Inderex†; ***USA:*** Inderide†.

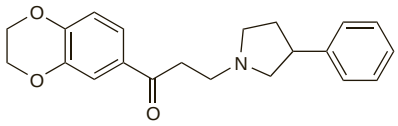
Proroxan *(pINN)*

Proroxano; Proroxanum. 1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-(3-phenyl-1-pyrrolidinyl)-1-propanone.

Пророксан

$C_{21}H_{23}NO_3$ = 337.4.

CAS — 33743-96-3 (proroxan).



Proroxan Hydrochloride *(USAN, pINNM)*

AY-24269; Hidrocloruro de proroxano; Proroxan, Chlorhydrate de; Proroxani Hydrochloridum.

Пророксана Гидрохлорид

$C_{21}H_{23}NO_3HCl$ = 373.9.

CAS — 33025-33-1.

Profile

Proroxan has been used as an antihypertensive and in the treatment of Ménière's disease, motion sickness, and allergic dermatitis.

Proscillaridin *(BAN, USAN, rINN)*

2936; A-32686; Proscilaridina; Proscillaridiini; Proscillaridin A; Proscillaridine; Proscillaridinum; PSC-801. 14-Hydroxy-3β-(α-L-rhamnopyranosyloxy)-14β-bufa-4,20,22-trienolide.

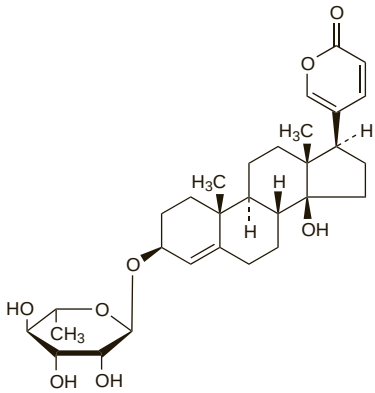
Просцилларидин

$C_{30}H_{42}O_8$ = 530.6.

CAS — 466-06-8.

ATC — C01AB01.

ATC Vet — QC01AB01.



Profile

Proscillaridin is a cardiac glycoside obtained from *Drimia maritima* (Liliaceae). It is a positive inotrope with general properties similar to those of digoxin (p.1259). It is reported to have a rapid onset and a short duration of action.

Proscillaridin is used in the treatment of heart failure (p.1165). It is given orally in usual initial and maintenance doses of 1 to 1.5 mg daily; maintenance doses may range from 0.75 to 2 mg daily as required.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Talusin; ***Pol.:*** Talusin.

Quinapril Hydrochloride

(BANM, USAN, rINNM)

CI-906 (quinapril); Hidrocloruro de quinapril; Kinapril Hidroklorür; Quinapril, chlorhydrate de; Quinaprili hydrochloridum. (3*S*)-2-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid hydrochloride.

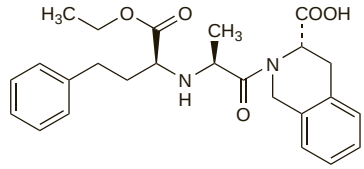
Хинаприла Гидрохлорид

$C_{25}H_{30}N_2O_5$,HCl = 475.0.

CAS — 85441-61-8 (quinapril); 82586-55-8 (quinapril hydrochloride).

ATC — C09AA06.

ATC Vet — QC09AA06.



(quinapril)

Pharmacopoeias. In *US*.

USP 31 (Quinapril Hydrochloride). A white to off-white powder, with a pink cast at times. Freely soluble in aqueous solvents.

Suspension. Extemporaneous formulations of quinapril 1 mg/mL made by adding crushed Accupril tablets (*Pfizer, US*) to the following vehicles were found to be stable for 6 weeks when stored at 5°:

- *Kphos* 15% (*Beach, US*), *Bicitra* 15% (*Draxis Pharma, US*), *OraSweet* 70% (*Paddock, US*)
- *Kphos* 15%, *Bicitra* 15%, *OraSweet SF* 70%
- *Kphos* 15%, *Bicitra* 15%, simple syrup 70%

The suspension containing *OraSweet SF* was considered to be the formulation of choice.[1]

1. Freed AL, *et al.* The development and stability assessment of extemporaneous pediatric formulations of Accupril. *Int J Pharm* 2005;**304:** 135–44.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Breast feeding. After of a single dose of quinapril 20 mg in 6 women, quinapril was detected in the breast milk in a milk to plasma ratio of 0.12; no quinaprilat was detected.[1] It was estimated that the dose received by the infant would only be about 1.6% of the maternal dose.

1. Begg EJ, *et al.* Quinapril and its metabolite quinaprilat in human milk. *Br J Clin Pharmacol* 2001; **51:** 478–81.

Interactions

As for ACE inhibitors, p.1196.

Antibacterials. Quinapril has been reported to reduce the absorption of *tetracyclines* due to the presence of magnesium carbonate in the tablet formulation.

Pharmacokinetics

Quinapril acts as a prodrug of the diacid quinaprilat, its active metabolite. About 60% of an oral dose of quinapril is absorbed. Quinapril is metabolised mainly in the liver to quinaprilat and inactive metabolites. Peak plasma concentrations of quinaprilat are achieved within 2 hours of an oral dose of quinapril. Quinaprilat is about 97% bound to plasma proteins. After an oral dose, quinapril is excreted in the urine and faeces, as quinaprilat, other metabolites, and unchanged drug, with the urinary route predominating; up to 96% of an intravenous dose of quinaprilat is excreted in the urine.

The effective half-life for accumulation of quinaprilat is about 3 hours after multiple doses of quinapril; a long terminal phase half-life of 25 hours may represent strong binding of quinaprilat to angiotensin-converting enzyme.

The pharmacokinetics of both quinapril and quinaprilat are affected by renal and hepatic impairment. Dialysis has little effect on the excretion of quinapril or quinaprilat.

Small amounts of quinapril are distributed into breast milk.

◊ References.

1. Begg EJ, *et al.* The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment. *Br J Clin Pharmacol* 1990; **30:** 213–20.
2. Halstenson CE, *et al.* The pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with various degrees of renal function. *J Clin Pharmacol* 1992; **32:** 344–50.
3. Wolter K, Fritschka E. Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure. *Eur J Clin Pharmacol* 1993; **44** (suppl 1): S53–6.
4. Begg EJ, *et al.* The pharmacokinetics of quinapril and quinaprilat in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; **37:** 302–4.
5. Squire IB, *et al.* Haemodynamic response and pharmacokinetics after the first dose of quinapril in patients with congestive heart failure. *Br J Clin Pharmacol* 1994; **38:** 117–23.
6. Breslin E, *et al.* A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. *J Clin Pharmacol* 1996; **36:** 414–21.

Uses and Administration

Quinapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Quinapril is converted in the body to its active metabolite quinaprilat. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 2 to 4 hours, although the full effect may not develop for 1 to 2 weeks during chronic use. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Quinapril is given orally as the hydrochloride, but doses are expressed in terms of the base. Quinapril hydrochloride 10.8 mg is equivalent to about 10.0 mg of quinapril.

In the treatment of **hypertension** the initial dose is 10 mg of quinapril once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. An initial dose of 2.5 mg daily is recommended in the elderly, in patients with renal impairment, or in those taking a *diuretic*; if possible, the diuretic should be withdrawn 2 or 3 days before quinapril is started and resumed later if necessary.

The usual maintenance dose is 20 to 40 mg daily, as a single dose or divided into 2 doses, although up to 80 mg daily has been given.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Quinapril is given in an initial dose of 2.5 mg daily. Usual maintenance doses range from 10 to 20 mg daily, as a single dose or divided into 2 doses; up to 40 mg daily has been given.

Quinaprilat may be given intravenously in patients unable to take quinapril orally; doses range from 1.25 to 10 mg twice daily.

◊ Reviews.

1. Wadworth AN, Brogden RN. Quinapril: a review of its pharmacological properties, and therapeutic efficacy in cardiovascular disorders. *Drugs* 1991; **41:** 378–99.
2. Plosker GL, Sorkin EM. Quinapril: a reappraisal of its pharmacology and therapeutic efficacy in cardiovascular disorders. *Drugs* 1994; **48:** 227–52.
3. Culy CR, Jarvis B. Quinapril: a further update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 2002; **62:** 339–85.

Preparations

USP 31: Quinapril Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Accupril; ***Austral.:*** Accupril; Acquin; Asig; Filpril; ***Austria:*** Accupro; ***Belg.:*** Accupril; ***Braz.:*** Accupril; ***Canad.:*** Accupril; ***Chile:*** Accupril; ***Cz.:***