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

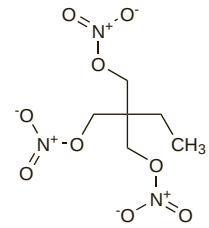
Proprietary Preparations (details are given in Part 3)
Arg.: Normorytmin; ***Austria:*** Asonacor†; Rhythmocor; Rytmonorma; ***Belg.:*** Rytmonorm; ***Braz.:*** Ritmonorm; ***Canad.:*** Rythmol; ***Chile:*** Ritmocor; Rytmonorm†; ***Cz.:*** Prolekofen; Propa-Tabletten†; Propanorm; Rytmonorm; ***Denm.:*** 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

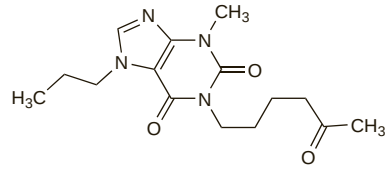
Proprietary Preparations (details are given in Part 3)
Braz.: Sustrate.

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.

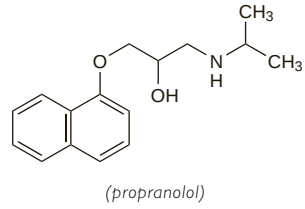
Propranolol Hydrochloride

(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